

Contemporary Endocrinology
Series Editor: Leonid Poretsky

Gabriel I. Uwaifo *Editor*

The Human Hypothalamus

Anatomy, Dysfunction and Disease Management



Contemporary Endocrinology

Series Editor

Leonid Poretsky
Division of Endocrinology
Lenox Hill Hospital
New York, NY, USA

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Gabriel I. Uwaifo
Editor

The Human Hypothalamus

Anatomy, Dysfunction and Disease
Management



Editor

Gabriel I. Uwaifo

Department of Endocrinology, Diabetes, Metabolism and Weight Management

Ochsner Medical Center

New Orleans, LA

USA

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To my parents who have always been my loudest cheer leaders in my pursuit of knowledge and the advancement of clinical science.

To my family who stoically encourage and tolerate my time consuming commitment to academic medicine and gracefully bore with me over the months I turned the family dining table into a “war room” for collating references, hard copy manuscripts, figures, tables etc in the preparation of this volume.

To the patients who have entrusted me with their clinical care, the students who have taught me at least as much as I have imparted to them and to my colleagues and clinical support staff who have made my journey in clinical medicine the ultimate professional adventure.

Thank you all.

Series Editor Foreword

Although the pituitary is often referred to as a “master gland,” reflecting its pivotal role in the regulation of multiple endocrine organs, the pituitary itself functions under tight control exercised by the hypothalamus. In addition to its endocrine function, the hypothalamus regulates certain aspects of autonomic nervous system and behavior, including eating behavior. For these reasons, understanding physiology and pathophysiology of the hypothalamus is extremely important for exploring a multitude of pathologies, with numerous endocrine disorders among them.

The authors of this outstanding volume discuss anatomy, physiology, pathophysiology, imaging, and both endocrine and nonendocrine pathological conditions associated with the hypothalamus. Of particular importance to endocrinologists are multiple chapters addressing not only “standard” endocrine disorders of hormonal excess or deficiency, but also disorders of energy metabolism. All of these are reviewed in immense detail including genetics, clinical presentation, and both medical and surgical therapies.

The authors and the editor are to be congratulated for their collective contribution to this interesting field. The volume that they have produced is extraordinarily successful in reflecting the multidimensional character of their monograph’s subject.

Leonid Poretsky
Lenox Hill Hospital
New York, NY, USA

Foreword

The pituitary has been referred to as the “master gland,” but it does take marching orders from the hypothalamus, a higher center or the “master switchboard.” Located inferior to the thalamus in the vertebrate diencephalon and comprising just 2% of the brain, the hypothalamus is the ultimate regulator and integrator of chronobiology, ingestive behavior, energetics, reproductive function, temperature, neuroendocrine, autonomic, hemodynamic, and homeostatic equilibrium. Indeed, its role in biology is considered critical for survival.

As first described by Galen in the second century AD, the hypothalamus-infundibulum-pituitary unit was functionally characterized as the drainage route for “mucus” passing from the cerebral ventricles to the nasopharynx. Over the ensuing millennium since Galen, knowledge of the role of the hypothalamus has exploded. Hypothalamic anatomical regions have been subcharacterized and linked to specific functions, such as food intake, satiety, and diverse neurotransmitter pathways. For practical reasons, most of our understanding of the critical functions of hypothalamic nuclei has derived from invasive experiments in animals. However, generally supportive findings have been gleaned from experiments of nature or pathological processes in humans.

Along with increased understanding of feedback endocrine regulatory physiology, advances in medicinal chemistry and biotechnology have enabled the synthesis of the secreted products of the hypothalamus. Together, the availability of synthetic or recombinant forms of peripheral hormones (e.g., levothyroxine, glucocorticoid, testosterone, estradiol, progesterone), pituitary trophic hormones (e.g., ACTH, GH, TSH, LH, FSH), and hypothalamic-releasing hormones (e.g., GnRH, CRH, TRH) has expanded the diagnostic and therapeutic armamentarium of the clinical endocrinologist. Thus, the field of neuroendocrinology has advanced from basic science and unravelling of complex regulatory pathways to include a robust component of applied physiology and clinical diagnostics and therapeutics. These advances have created a need for comprehensive texts in the field that would serve as reference sources for researcher and clinicians.

The present volume, *The Human Hypothalamus: Anatomy, Dysfunction and Disease Management*, edited by Gabriel I. Uwaifo, fulfills such a need. The book is well organized, for easier comprehension, and the chapter contributors include current and emerging leaders in the field. The first part, dealing with anatomical structure and function, incorporates clinically relevant

chapters on neuroimaging and neuroendocrinology. The second part, focusing on hypothalamic pathology and dysfunction, is a comprehensive tour de force on the spectrum of genetic, functional, behavioral, neoplastic, and idiopathic disorders that afflict the hypothalamus.

This book offers a depth and breadth of clinical content that sets it apart, consistent with its focus on humans. The information provided here should prove valuable to clinical endocrinologists and other clinicians as well as clinical researchers. Specifically, clinicians involved in the care of patients with hypothalamic and pituitary disorders would have access to a comprehensive spectrum of clinical presentations, current pathophysiological thought, updated diagnostic procedures, and evidence-based therapeutic interventions, all within a single volume. Dr. Uwaifo and his colleagues deserve commendation for bringing this resource to the endocrinology and clinical community.

Sam Dagogo-Jack, MD, DSc
Division of Endocrinology, Diabetes and Metabolism
Clinical Research Center
The University of Tennessee Health Science Center
Memphis, TN, USA

Preface

“The Brain is the principal organ of the body – virtually every other organ can be transplanted, repaired and replaced and the organism lives on but the brain is where the soul of the organism resides. When the brain is irrevocably destroyed the life of the organism ends even if other organs like the heart, kidneys and lungs continue to function.” These words from my esteemed neurology Professor A.O.J. Adeuja left an indelible impression on my mind as a young impressionable medical student decades ago. Though I did not end up being a career neurologist, the primacy of the central nervous system in the functionality of the human organism has remained a lasting theme I have seen in my career as an academic internist and endocrinologist. Of the various components of the brain and the central nervous system though, the hypothalamus is unparalleled in combining the opposites of compact size and yet multiplicity and diversity of functional significance. It truly represents anatomically, physiologically, and pathophysiologically the intersection of the neurological clinical sciences with the rest of clinical medicine and therein lies the great fascination and mystery it has always held for me professionally.

In a time where there are so many “me too” trends be it in pharmacotherapeutics, business ventures, entertainment, etc., it is pertinent to ask if and why we would need a new textbook on the human hypothalamus.

While there are several texts available that provide discussion of the hypothalamus and its related disorders, these broadly fall into the categories of either being huge reference tomes dense in bench and comparative animal and/or translational research or rather more limited summary type texts that often lack the required depth for clinicians involved in the care of patients with the myriad presentations of diseases related to hypothalamic pathology. It is also true that in an area of medicine in which there is such rapid growth in the knowledge base, many of the available comprehensive texts on the subject of human hypothalamic disease have become quite dated.

“The Hypothalamus: Anatomy, Dysfunction and Disease Management” is conceptually intended to serve as a bridge between the all-encompassing comprehensive texts best suited to those heavily invested in hypothalamic research and the more condensed summary texts targeted to professionals with a passing interest in this organ and its pathophysiologic correlates. In that middle space are a broad spectrum of clinicians who have a vested interest in availability of a single volume comprehensive enough in scope and depth and to adequately discuss the current state of the science and clinical

care paradigms related to the human hypothalamus and its various associated disease entities.

The hypothalamus is an anatomically small but functionally immense part of the brain. Much of what we know of its structure and function in humans has been gleaned over generations using comparative neuroanatomy and neurophysiology from various animal models. As our understanding of its numerous structural and functional correlates grows, it has become apparent that fewer structures in the body have such a great dichotomy between physical size and functional significance/importance.

In functional and pathophysiological terms, the hypothalamus represents the intersection of several areas of clinical and medical expertise. The human hypothalamus can be astutely referred to as the crossroad of endocrinology, psychiatry, neurology, and neurosurgery.

Because of its involvement in myriad physiologic functions and the variegated ways disorders involving it can manifest, hypothalamic disease can initially come to medical attention in widely disparate settings and with widely different clinicians. The detection and proper care of hypothalamic dysfunction and disease often thus require carefully coordinated multidisciplinary care.

There is a great need for a single reference source that captures comprehensively the scope of hypothalamic structure, function, dysfunction, and disease to cater to the various clinical, teaching, and research professionals that have a stake in this part of the human brain. There are very few texts currently with this sort of scope and fewer still that are reasonably current and incorporate recent advances in knowledge relevant to various aspects of hypothalamic structure, function, and disease. This textbook intends to capture in one volume all the information that practicing clinicians, clinician scientists, and researchers would need to be adequately informed about various aspects of the hypothalamus in all its complexity. The volume intentionally aims to be comprehensive and broad in scope while not so deeply embedded in basic science and laboratory minutiae to confuse and/or alienate the patient focused clinician. It thus aims to provide relevant reference information for the wide range of professionals involved in the pre- and postmortem detection, diagnosis, characterization, care, and management of various hypothalamic disorders and diseases in addition to providing a sound anatomic and physiologic foundation of the normal human hypothalamus.

The hope and intent is that this volume will fill a significant void in the medical professional community and be frequently referenced and utilized by the wide variety of health professionals with interest in the human hypothalamus. It is expected that the volume will be used to differing degrees by medical professionals and students alike. We hope that it would find utility for interested general clinicians, medical school, and allied health professional teaching faculty as well as subspecialists in domains as wide as neurosurgery, neuroendocrinology, clinical psychiatry, and neuro-oncology.

We understand that in trying to straddle the *Scylla* and the *Charybdis*, we will doubtless have readers on both sides of spectrum who may feel left out. To those who seek more molecular mechanistic depth and discourse of basic science research, we apologize for this volume's inadequacy in this regard and

refer them to the excellent tomes available that have that goal and focus. To those who feel there is way too much breadth and would rather prefer a more condensed summary of the mysteries of the hypothalamus, we again offer our apologies and encourage them to seek out less rigorous and more overview themed publications on the human hypothalamus. If we have succeeded in providing a useful resource for clinicians and clinical researchers with vested interest in the human hypothalamus and its disease then the intent of this effort has been achieved. To all our esteemed readers, thank you so much for investing your valuable time in reading and we hope it serves you well.



Gabriel I. Uwaifo, MD, FACP, FTOS, FACE

June, 2020

New Orleans, LA, USA

Acknowledgments

Any task this ambitious has an army of often unsung heroes that work tirelessly behind the scenes to make the project a polished finished product for the reader. I would like to especially express my profound gratitude to Eugenia Judson who served as my production editor on this project and so did the bulk of the oft-thankless job of reminders and gentle prodding of contributors, collation of various documents, keeping us on schedule, etc. I would also like to acknowledge all the administrative staff at Springer publishers who stuck with this project even in the dark times when it seemed like a “bridge to far to cross.” Finally, I must thank all our contributors who have had to carve out time from their already hectic clinical, academic, and professional schedules to contribute to this effort based essentially out of academic altruism. Thank you all for making this possible and for adding something substantive to the body of work available to clinicians invested in this field of clinical care and investigation.

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Contributors

Nidhi Agrawal, MD Division of Endocrinology, Diabetes and Metabolism, NYU Langone Medical Center, New York, NY, USA

Amjad N. Anaizi, MD Department of Neurosurgery, Medstar Georgetown University Hospital, Washington, DC, USA

Maria J. Barnes, PhD Department of Biochemistry and Nutrition, Des Moines University, Des Moines, IA, USA

Frank Berkowitz, MD MedStar Georgetown University Hospital, Washington, DC, USA

Carmen Bianca Crivii Morphology Department, Anatomy-Embryology, “Iuliu-Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania

Jordan Black, BS Department of Neurosurgery, Medstar Georgetown University Hospital, Washington, DC, USA

Ketan R. Bulsara, M.D., M.B.A. Department of Surgery, Division of Neurosurgery, University of Connecticut Health Center, UConn Health, Farmington, CT, USA

Rebecca Calafiore, BS School of Medicine, University of Connecticut Health Center, Farmington, CT, USA

University of Connecticut School of Medicine, Farmington, CT, USA

David Chachkiani, MD Department of Neurology, Louisiana State University, Health Sciences Center, New Orleans, LA, USA

Roberto Rey Dios, MD Department of Neurosurgery, University of Mississippi Medical Center, Jackson, MS, USA

Arnd Doerfler, M.D., Ph.D. Department of Neuroradiology, University Hospital of Erlangen Medical School, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany

Ehsan Dowlati, MD Department of Neurosurgery, Medstar Georgetown University Hospital, Washington, DC, USA

Amber N. Edinoff, MD Department of Psychiatry and Behavioral Medicine, LSU Health Shreveport, Shreveport, LA, USA

Rima El-Abassi, MD Department of Neurology, Louisiana State University, Health Sciences Center, New Orleans, LA, USA

Dania Felipe, MD Department of Pediatric Endocrinology, Louisiana State University Health Sciences Center, New Orleans, LA, USA

Olinda Verdecie Feria, MD Department of Neurology, Louisiana State University Health Sciences (LSUHSC) Center, New Orleans, LA, USA

Adriana Gabriela Filip Functional Department, Physiology, “Iuliu-Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania

Vishnu Garla, MD, MBBS Department of Internal Medicine/Endocrinology, Diabetes and Metabolism, University of Mississippi Medical Center (UMMC), Jackson, MS, USA

Department of Medicine, Division of Endocrinology, University of Mississippi Medical Center, Jackson, MS, USA

Mississippi Center for Clinical and Translational Research, Jackson, MS, USA

Victoria Habet, DO Department of Pediatric Critical Care Medicine, Yale School of Medicine, New Haven, CT, USA

Nyrene A. Haque, MD Department of Endocrinology, Ochsner Medical Center, New Orleans, LA, USA

Lisa M. Harrison-Bernard, PhD Department of Physiology, LSU Health Sciences Center, New Orleans, LA, USA

Gloria E. Hoffman, Ph.D. Department of Biology, Morgan State University, Baltimore, MD, USA

Susan L. Karam, MD Department of Endocrinology, Ochsner Medical Center, New Orleans, LA, USA

Roger E. Kelley, MD Department of Neurology, Louisiana Health Center, (LSU Health) Shreveport, Shreveport, LA, USA

Hyon Kim, MD Division of Endocrinology, Diabetes and Metabolism, NYU Langone Medical Center, New York, NY, USA

Joshua Knopf, BS School of Medicine, UConn Health, Farmington, CT, USA

University of Connecticut School of Medicine, Farmington, CT, USA

Michael Koban, Ph.D. Department of Biology, Morgan State University, Baltimore, MD, USA

Vaniolky Losada Leon, MD Department of Neurology, Louisiana State University Health Sciences (LSUHSC) Center, New Orleans, LA, USA

Jesus Lovera, MD Department of Neurology, Louisiana State University Health Sciences (LSUHSC) Center, New Orleans, LA, USA

Kunal Maini, MD Department of Psychiatry and Behavioral Medicine, LSU Health Shreveport, Shreveport, LA, USA

Sonal Mehta, MD Department of Medicine, NYU Langone Medical Center, New York, NY, USA

George William Moll Jr[†], MD, PhD, FACE, FAAP Health Sciences Division, Mississippi Academy of Sciences, Jackson, MS, USA

UMMC Pediatrics & Pediatric Endocrinology, Jackson, MS, USA

Anzhela D. Moskalik, MD University of Connecticut School of Medicine, Farmington, CT, USA

Christa O'. Hana S. Nobleza, MD Department of Neurology, Division of Neurosciences Critical Care, University of Mississippi Medical Center, Jackson, MS, USA

Iulian Opincariu Morphology Department, Anatomy-Embryology, “Iuliu-Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania

Max Sosa Pagan, MD Department of Endocrinology, Diabetes, Metabolism and Weight Management, Ochsner Medical Center, New Orleans, LA, USA

Ronak Patel, MD Department of Neurology, Division of Neurosciences Critical Care, University of Mississippi Medical Center, Jackson, MS, USA

Shruti Polu, MD Department of Endocrinology, Ochsner Medical Center, New Orleans, LA, USA

Miana-Gabriela Pop Department of Anatomy and Embriology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Stefany D. Primeaux, PhD Department of Physiology, LSU Health Sciences Center, New Orleans, LA, USA

Joint Diabetes, Endocrinology & Metabolism Program, Pennington Biomedical Research Center, Baton Rouge, LA, USA

Noeен Sarfraz, MD Department of Psychiatry and Behavioral Medicine, LSU Health Shreveport, Shreveport, LA, USA

Juan C. Sarmiento-Ramon, MD Department of Endocrinology, Ochsner Medical Center, New Orleans, LA, USA

Manuel Schmidt, MD Department of Neuroradiology, University Hospital of Erlangen Medical School, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany

Christopher Morgan Smith, MD Department of Neurology, Louisiana State University, Health Sciences Center, New Orleans, LA, USA

Rashmi S. Thakkar, MD MedStar Georgetown University Hospital, Washington, DC, USA

Trung Nam Tran, MD Department of Endocrinology, Diabetes, Metabolism and Weight Management, Ochsner Medical Center, New Orleans, LA, USA

Gabriel I. Uwaifo, MD, FACP, FTOS, FACE Department of Endocrinology, Diabetes, Metabolism and Weight Management, Ochsner Medical Center, New Orleans, LA, USA

The University of Queensland, Brisbane, QLD, Australia

The University of Queensland, Ochsner Clinical School, New Orleans, LA, USA

Simona Valeria Clichici Functional Department, Physiology, “Iuliu-Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania

John Wagner III, MD Department of Psychiatry and Behavioral Medicine, LSU Health Shreveport, Shreveport, LA, USA

Zachary P. Wetsel, MD Department of Neurosurgery, University of Mississippi Medical Center, Jackson, MS, USA

Kyla Wright NYU Grossman School of Medicine, New York, NY, USA

Part I

Structure and Function of the Hypothalamus



Introduction to the Hypothalamus: Correlates From Animal Studies

1

Miana-Gabriela Pop, Carmen Bianca Crivii,
and Iulian Opincariu

The hypothalamus is a small, central portion of the brain, representing about 2% of the structure [1]. The hypothalamus is composed of various nuclei with different functions and a multitude of nervous fibres that ensure its connections with important neighboring areas [2]. The main function of the hypothalamus is to ensure the body's homeostasis [2]. Furthermore, the hypothalamus has a crucial function in the integration of the endocrine system [3]. Other functions for which the hypothalamus is responsible are thermoregulation, energy control, the sleep-wake cycle [1], the memorization process [2], sodium and water balance, growth, and pituitary gland control [1]. The rostral portion of the structure has a role in determining behaviour and reproduction [1].

The hypothalamus is visible on the inferior portion of the brain where it is located between the chiasma optic anteriorly, the optic tracts laterally and the anterior part of midbrain posteriorly [2] (Fig. 1.1). On the sagittal section of the brain, the hypothalamus is located under the thalamus, behind the *lamina terminalis*, and having a poste-

rior extension to the level of the *tegmentum* of the brainstem [2]. Morphologically, the hypothalamus is divided in three regions (supraoptic, tuberal, mammillary) and three areas (periventricular, medial, lateral) whose main contents are specific cellular elements that constitute the hypothalamic nuclei [4].

The hypothalamus is identified in all vertebrates characterized by the presence of a nervous system [4]. According to cadaver studies there are similarities between rodent and human hypothalamic regions, including similarities related to its vascularization [3]. In both humans and animals, the arterial supply for the hypothalamic region is ensured by the terminal branches of the internal carotid artery, anterior communicating artery, and posterior communicating artery, respectively [1]. More, the *rete mirabile* described by Galen in animals are identified nowadays as the hypophyseal portal system that connects the hypothalamus with the anterior pituitary gland [5].

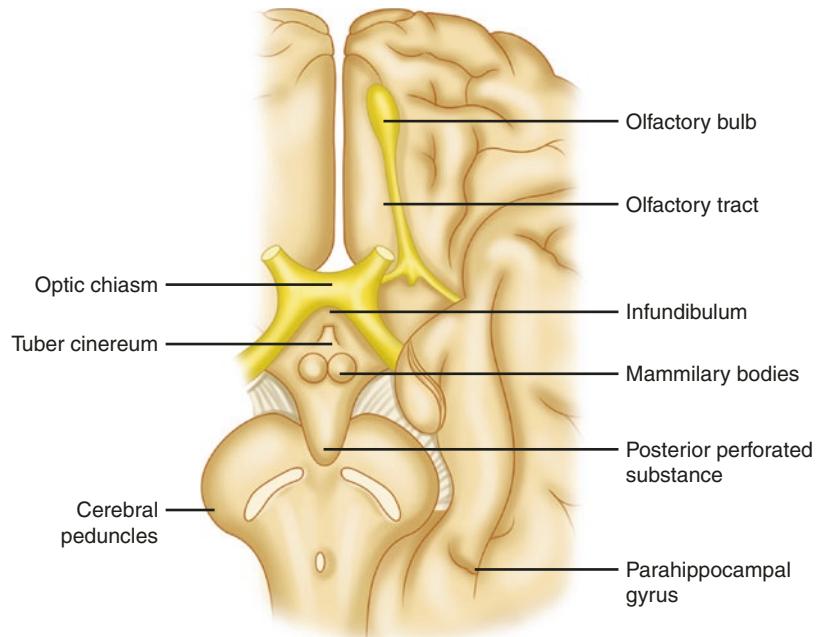
The Hypothalamus and Food Intake

The hypothalamus is involved in the determination of body weight. It controls food intake and has a role in appetite control [6]. Food intake is controlled by various neurons located in the ventromedial nucleus (VMN), dorsomedial nucleus (DMN), paraventricular nucleus (PVN), and lateral hypothalamus (LH) [7, 8]. The extreme lat-

M.-G. Pop (✉)
Department of Anatomy and Embriology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

C. B. Crivii · I. Opincariu
Morphology Department, Anatomy-Embryology, "Iuliu-Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
e-mail: bianca.crivii@umfcluj.ro

Fig. 1.1 The hypothalamus visible on the inferior portion of the brain. (From the author's personal archive)



eral part of the LH is also called “the feeding center” [7]. Some neurons located in the hypothalamus stimulate food intake, such as neuropeptide Y, orexins, ghrelin, or melanin-concentrating hormone, whereas others such as corticotropin-releasing hormone, urocortin III, and glucagon-like peptides decrease the appetite [8].

According to animal studies, bilateral destruction of the lateral hypothalamus determines complete lack of food intake in rats, cats, and monkeys [7]. In the opposite way, experimental electrical stimulation of “the feeding center” leads to increased appetite and food intake with the onset of obesity [7]. Obesity was also observed after VMN injury of the rat hypothalamus [7]. The ventromedial nucleus represents “the satiety center:” its stimulation stops the ingestion of food and determines the sensation of plenitude, whereas its destruction produces hyperphagia [9].

The PVN contains anorexigenic factors (such as oxytocin, corticotropin-releasing hormone, vasopressin), receives projections from the arcuate nucleus, and projects to the nucleus of the solitary tract/dorsal vagal complex, participating in food intake control [10]. Inhibition of the PVN–dorsal

vagal complex circuit with a genetically induced tetanus neurotoxin causes, according to an experimental study, weight gain [10]. Injury of the arcuate nucleus can lead to obesity through ghrelin-induced mechanisms [11]. Ghrelin is produced by the stomach during fasting; its secretion was found to be higher in mice exposed to music compared with a control group, a situation that led to weight gain by the studied rats [12]. The induction of the Huntington disease mutation in hypothalamic nuclei of mice through a genetically engineered virus also led to increased food intake by the rodents and obesity [6].

Anorexia nervosa is defined as an eating disorder characterized by excess production of both orexigenic and anorexigenic hormones in a situation that alters food intake control [13]. Electrical brain stimulation of lateral hypothalamus in an anorexia-induced model of rats led to improved control of food intake and improved the survival of the animals compared with a control group [14]. The use of electrical stimulation of different regions of the brain has been previously used in other psychiatric disorders such as Obsessive compulsive disorder, and thus its usage could also be tested in anorexia nervosa [13].

The Hypothalamus and Sleep-Wake Cycle

The hypothalamus intervenes in regulation of the sleep-wake cycle through neuropeptide-producing hormones synthesized at this level [15, 16]. The sleep-wake cycle is regulated by hypothalamic neurons such as orexin/hypocretin-producing neurons and melanin-concentrating hormone [15, 16]. Hypocretins are neuropeptides (Hcrt 1, Hcrt 2) produced by the hypothalamus [15, 16]. Orexins A and B (hypocretins 1 and 2) neuropeptides have as common precursor the prepro-orexin protein [15, 16]. Both types of orexins A and B are located in the lateral hypothalamus; orexin A (hypocretin 1) has 33 amino acids and is 3.5 kDa and orexin B (hypocretin 2) is composed of 28 amino acids with weights of 2.9 kDa [17]. Hypocretin/orexin neurons function in sleep initiation and maintenance [18]; the lack or absence of orexin neurons alters the sleep-wake cycle [15]. During the awake state, orexin levels are high; their production decreases during sleep [17]. Moreover, hypocretin receptor antagonists are being used for insomnia and the hypocretin receptor agonist for sleep disorders such as narcolepsy [18]. Neurons producing melanin-concentrating hormone (MCH) are located in the

lateral portion of the hypothalamus and are also responsible for the sleep-wake cycle [15].

The Hypothalamus and Water Balance

Thirst sensation is important in fluid-electrolyte homeostasis in both humans and animals. The thirst center is located in the lamina terminalis and is composed of the subfornical organ, organum vasculosum, and median preoptic nucleus [19]. Thirst sensation appears when changes in blood osmolality activates the subfornical organ and organum vasculosum (from the lamina terminalis) [19, 20] (Fig. 1.2). Angiotensin II is also responsible for the balance of water in the body; in rodent models it determines increased water intake, but in humans its effect was less prominent [19, 20].

The Hypothalamus, Reward and Punishment

One important reward pathway in the brain is the mesolimbic dopaminergic pathway [21]. Reward response was studied in many animal models that

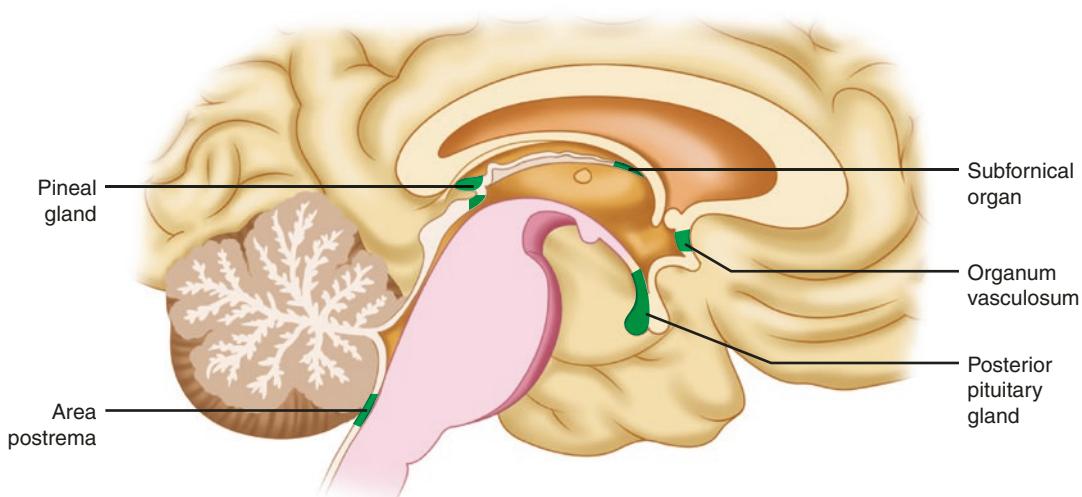


Fig. 1.2 Schematic representation of the subfornical organ and organum vasculosum

revealed a circuit mediated by dopamine between prefrontal cortex and ventral striatum [22]. Dopamine is generally secreted in the presence of a stimulus that is interpreted as a reward. Dopamine was also found to be an important mediator in reward-seeking and reward-learning processes [22]. The mesolimbic reward pathway was found to be altered in children with autism spectrum disorders [21]. More, alteration in the reward dopaminergic pathway was also found in alcohol-dependent patients during their relapse; increased dopamine secretion in nucleus accumbens and prefrontal cortex was associated with alcohol relapse [23].

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Anatomy and Topography of the Hypothalamus

2

Carmen Bianca Crivii, Simona Valeria Clichici,
and Adriana Gabriela Filip

The hypothalamus has a vital role in the regulation of homeostasis, being a fundamental structure for individual and species survival.

The hypothalamus, part of the diencephalon, is located at the base of the brain, hidden by the cerebral hemispheres. Composed of many nuclei, it is involved in the control of endocrine, autonomic, neurological, and behavioural functions.

Gross Anatomy, Anatomical Limits, and Structural Relationships

The hypothalamus occupies the rostral and anterior part of the diencephalon, the lateral walls, and the floor of the third ventricle.

Below the thalamus, being separated by the hypothalamic sulcus (Monro's sulcus), the hypothalamus has boundaries that are not very well defined. Even so, the limits of the hypothalamus can be considered as follows: anterior, the plane that is passing through the *lamina terminalis*;

C. B. Crivii (✉)
Morphology Department, Anatomy-Embryology,
“Iuliu-Hatieganu” University of Medicine and
Pharmacy, Cluj-Napoca, Romania
e-mail: bianca.crivii@umfcluj.ro

S. V. Clichici · A. G. Filip
Functional Department, Physiology,
“Iuliu-Hatieganu” University of Medicine and
Pharmacy, Cluj-Napoca, Romania
e-mail: sclichici@umfcluj.ro;
gabriela.filip@umfcluj.ro

posterior, imprecisely delimited, extends to periaqueductal gray matter, the limit being determined by the mammillary bodies; lateral, the internal capsule; medial, the ependymal layer of the third ventricle.

Situated in the central part of the brain, the hypothalamus is related to several important structures of the forebrain and midbrain.

Anteriorly, the hypothalamus is related to the anterior commissure, from the upper end of the *lamina terminalis*. Beyond the anterior commissure and *lamina terminalis* are the subcallosal area and its gyrus. The *Lamina terminalis*, the former rostral end of the embryological neural tube, contains the vascular organ (VOLT) with osmoreceptors sensitive to the sodium content and osmotic pressure of blood. Therefore, the lamina has a role in regulation of fluid and electrolyte balance by controlling thirst, sodium excretion, blood volume regulation, and vasopressin secretion.

The anterior commissure represents a tract of axons that connect the temporal lobes of the cerebral hemispheres. Most of the axons are concerned with the olfactory pathway; it is also linked to the sensation of pain.

The subcallosal area (paraolfactory area of Broca) is a small triangular field on the medial face of the hemisphere. It is separated by the posterior paraolfactory sulcus from the subcallosal gyrus, which is located behind the subcallosal area and below the rostrum of the *corpus*

callosum. The subcallosal gyrus is continuous with the *indusium griseum* as part of the limbic system.

Posteriorly, the hypothalamus is related to the mammillary bodies, the cerebral peduncles, interpeduncular fossa, and posterior perforated substance. The mammillary bodies are round, paired structures, lying on the inferior and posterior part of the hypothalamus. They are important nuclei of the memory circuit (circuit of Papez). The cerebral peduncles, the frontmost part of the midbrain, connect the brainstem with the upper parts of the brain, the thalamus, and the cerebrum. Between peduncles, there is a depressed area, the interpeduncular fossa, with a layer of gray matter pierced by small blood vessels.

Superiorly, the hypothalamus is related to the thalamus, separated by the hypothalamic sulcus, at the level of the lateral wall of the third ventricle. The thalamus is a large mass of gray matter, part of the diencephalon, relaying information between different subcortical regions and the cerebral cortex.

Medially, the hypothalamus is bound by the ependymal layer of the third ventricle. The ependymal cells (ependymocytes) are involved in the production of cerebrospinal fluid.

Laterally, the hypothalamus is continuous with the thalamus and subthalamic region, flanked by the internal capsule and the optic tracts. The subthalamic region (prethalamus), part of the diencephalon, is involved in the integration of somatic motor function. The internal capsule is a white matter structure separating the thalamus and caudate nucleus from the lentiform nucleus. It is an important structure connecting the cerebral cortex with the subcortical regions by its ascending and descending fascicles.

Inferiorly, the external surface of the hypothalamus coincides with the space between the optic chiasm and mammillary bodies, where the floor of the third ventricle presents a prominence, the *tuber cinereum*, that continues antero-inferiorly with a funnel-like process, the *infundibulum* (the pituitary stalk), with its attachment, the median eminence. The *tuber cinereum* is a gray matter eminence of the floor of the third ventricle

above the optic chiasm. On this area there are two nuclei: tuberomammillary and tuberal nuclei. The first one is the only source of histamine in the brain and is implicated in energy and sleep control, in learning and memory processes, in responses to sexual stimuli, and to stressful situations. The tuberal nucleus, an evolutionary new hypothalamic structure, can only be observed in primates, with a high variability in shape, segmentation, and its population of somatostatin-expressing neurons [1]. Mammillary bodies are two small round bodies on the undersurface of the diencephalon with an important function in memorization.

Blood Supply: Arteries, Veins

The hypothalamus, located at the base of the brain, is surrounded by the circle of Willis, and therefore its blood supply is ensured by branches of the arterial circle. Vascularization is respecting the regional divisions of the hypothalamus. The anterior, suprachiasmatic region is supplied by the branches of the anterior cerebral and anterior communicating arteries. The arterial branches densely penetrate the basal face of the brain, where they are responsible for the formation of the anterior perforated substance. The tuberal region is supplied by the branches of the posterior communicating arteries, which are responsible for the formation of the posterior perforated substance in the interpeduncular fossa [2]. The posterior or mammillary region is supplied by the branches from the bifurcation of the basilar artery and the posterior cerebral arteries close to the origin of the posterior communicating arteries.

Because of the special morpho-functional relationship with the hypophyseal gland, a special vascular network developed between these two structures. The superior hypophyseal artery, a branch of the internal carotid artery or the posterior communicating branch, supplies the pituitary stalk and the adjacent region of the hypothalamus (the median eminence), the anterior part of the hypophyseal gland, and the optic nerve and chiasm.

The superior hypophyseal artery presents an anastomosis with the inferior hypophyseal artery, a branch of the internal carotid artery, up to the level of the hypophyseal gland. From the anatomical point of view, the superior hypophyseal artery can be seen as single or multiple trunks [3].

The hypophyseal portal system is a particular blood distribution with a primary capillary plexus to the level of the hypothalamic arcuate nucleus (from the median eminence) in which the hypothalamic-releasing hormones are discharged in the anterior hypophyseal gland, where the second capillary plexus is formed. Unlike other brain capillaries, these capillaries are fenestrated to allow the easy transfer of the molecules; therefore, the portal system affords a short pathway for hormonal exchange [4].

The hypothalamic venous blood drains via intercavernous sinuses into the superior and inferior petrosal sinuses.

Hypothalamic Topography

The major regions of the hypothalamus are:

- The suprachiasmatic or anterior region (above the optic chiasm) between the *lamina terminalis* and optic chiasm
- The tuberal or middle region (includes the *tuber cinereum*), caudally to the previous
- The mammillary or posterior region, above and including the mammillary bodies.

The anterior columns of the fornix divide each zone into a medial and lateral region. The fornix is a major connector of the limbic system between the mammillary bodies and thalamic, septal, and accumbens nuclei.

Topographically, the hypothalamic nuclei are divided in the mediolateral direction as follows: the periventricular zone, which is inside the ependymal layer of the third ventricle, the medial zone, adjacent to the previous, and the lateral zone.

The periventricular zone contains two distinct nuclei, the paraventricular nucleus (PVN) from the anterior region and the arcuate nucleus from the tuberal region. The PVN runs from anterior to

the tuberal region and the arcuate nucleus extends from the periventricular zone to the medial zone. The periventricular nuclei, along with the supraoptic nucleus from the medial zone, are involved in neuroendocrine regulation. Additionally, the PVN has a role in the control of the autonomic nervous system.

The medial zone contains nuclei in all three hypothalamic regions. In the anterior region, the suprachiasmatic nucleus is involved in the control of the circadian rhythm and the anterior and preoptic nuclei control the autonomic nervous system. In the tuberal region, the dorsomedial and ventromedial nuclei are involved in behavior control, and body weight control (controlling appetite and insulin secretion). The nuclei of the mammillary region are the posterior nucleus, controlling the autonomic nervous system, and more importantly, the mammillary nuclei involved in memory and emotional expression.

The lateral region is a rich zone in fibers and less in nuclei, which belong to the tuberal region. The lateral tuberal complex is involved in the control of appetite.

Autonomic Control

The autonomic nervous system (ANS) regulates the activity of smooth muscles, myocardium, and glands from different systems of the body. The ANS is responsible for the primary mechanism of the fight-or-flight response. Autonomic functions include control of cardiac activity, respiration, vasomotor activity, digestion, urination, and sexual arousal. The hypothalamus has a key role in the integration of autonomic activity. The paraventricular and dorsomedial nuclei, the lateral hypothalamic area, the posterior hypothalamic nucleus, and the mammillary nucleus are the hypothalamic regions implicated in autonomic control. The neurons from these regions have direct or indirect projections through the preganglionic neurons from both sympathetic and parasympathetic systems. In turn, the hypothalamus receives direct sensory inputs necessary to detect rapid internal changes (regarding body temperature, blood sugar, minerals, and hormone levels)

or information from the external environments (via somatosensory, visual, taste, smell, and auditory pathways).

The PVN is identified as crucial to autonomic control [5]. The PVN nucleus has three types of neurons. The magnocellular neurosecretory cells contain vasopressin and oxytocin, which travel through the axons into the posterior hypophysis. Then, these hormones are released directly into the bloodstream. The parvocellular neurosecretory cells project to the median eminence, the neurohemal organ of the brain base. The axons release their hormones at the primary capillary plexus of the hypophyseal portal system [6, 7]. Finally, the central-projecting neurons (the pre-autonomic neurons) project directly onto preganglionic neurons from the autonomic nuclei of the brainstem (including the neurons from the dorsal nucleus of the vagus nerve), and the lateral spinal columns.

The other hypothalamic nuclei involved in the autonomic control have bidirectional connections with the autonomic structures directly or via the PVN. Due to these nuclei, the lateral hypothalamic area is involved in control of feeding, satiety, insulin release, and cardiovascular control.

The hypothalamic connections involve in autonomic control are provided as follows:

1. The dorsal longitudinal fasciculus (DLF) of Schütz, the major autonomic pathway, contains ascending and descending fibers:
 - (a) the descending fibers, originated in the PVN, present a trajectory along the third ventricle, through the periaqueductal gray matter and the reticular formation of the midbrain, then pass near the floor of the fourth ventricle to the level of midline; at the brainstem level, the DLF fibers are projected onto: the periaqueductal gray (for pain modulation), the nuclei of the reticular raphe (for responses to physiological and emotional threats that include integrated activity of spinal cord and brainstem) [8], the parabrachial nucleus, the *locus coeruleus*, the dorsal nucleus of vagus, and the salivatory nuclei; DLF continues to the level of the medulla and

projects to the sympathetic and parasympathetic nuclei of the intermediolateral spinal cord (for sympathetic effects such as hypertension, tachycardia, tachypnea, muscle vasodilation, visceral vasoconstriction, or parasympathetic effects such as hypotension and bradycardia); the DLF projections are bilateral with an ipsilateral domination.

- (b) ascending fibers have their origin in the parabrachial nucleus of the reticular substance; they bring information of taste and general sensation from the nucleus of the *tractus solitarius* to the periventricular and posterior hypothalamic nuclei.
2. The medial forebrain bundle (MFB), with an essential role in reward, motivation, and learning, contains bidirectional fibers between olfactory apparatus and brainstem nuclei, via the hypothalamus. The MFB includes hypothalamic inputs from the septal nuclei, the basal olfactory regions, the peri-amygdaloid region, and different regions of the brainstem. The *stria terminalis* and fornix ensure the hypothalamic projections of the neurons originated into the amygdala and hippocampus [9]. The hypothalamic outputs leave the periventricular nucleus to innervate the parasympathetic nuclei from the brainstem.
3. The mammillotegmental bundle of Guden (part of the mammillotegmental tract of Vicq D’Azyr) controls the autonomic nuclei of the brainstem through the fibers originated in mammillary nuclei, via the tegmental reticular nuclei of midbrain and pons.

Endocrine Control

A particular property of the hypothalamus is its capacity to control the activity of the endocrine system in three ways: the first two are directly related to hormonal secretion, and the third is a nervous control. The neurons of the paraventricular and supraoptic nuclei are involved in the first endocrine control. They secrete oxytocin and vasopressin through the axons into the posterior hypophysis. The second way consists in the con-

trol of the anterior hypophysis by the neurons from the arcuate, paraventricular nuclei that send the axons into the median eminence. They secrete the hypophysiotropic hormones, which are stored and then released into the hypophyseal portal system stimulating the hormonal secretion of the anterior hypophysis. The third way is through the hypothalamic autonomic control of the endocrine system.

Oxytocin and Vasopressin

Oxytocin and vasopressin are hormones of the neurohypophysis released directly from the neurons of the supraoptic and paraventricular nuclei. The magnocellular neurons produce the hormones and send them into the neurohypophysis via the hypothalamo-neurohypophyseal tract. The hormones are released into the blood circulation based on reflexes induced by different neural stimuli.

Oxytocin is released in the milk letdown reflex (milk ejection reflex) as a result of nerve stimulation during breastfeeding. The stimuli are directly transmitted via the spinothalamic tract to the pre-optic and paraventricular nuclei to excite the magnocellular neurons, which release oxytocin into circulation. Traveling through the bloodstream, the hormone acts on the mammary glands, causing milk release.

During parturition, the tension from the uterine wall and cervix pressure are transmitted to the hypothalamus; oxytocin is released in the bloodstream and enhances the frequency and strength of contractions. Oxytocin also acts on the male and female reproductive tract to support sperm transport.

Vasopressin (antidiuretic hormone, ADH; arginine vasopressin, AVP) is transported by the axons to the posterior hypophysis and is released for the control of the osmotic balance, blood pressure, and kidney function of the body. It is secreted in response to high plasma osmolarity or low plasma volume. The effect is to increase the water reabsorption to the level of the distal tubule and collecting duct. Therefore, the amount of urine decreases, and it becomes more concentrated. The water absorption in the distal tubule

and collecting duct is supported by the increase of sodium absorption across the loop of Henle.

Another effect of vasopressin is to increase the permeability of the collecting duct for urea, facilitating its reabsorption. Besides the kidney effects, vasopressin has several effects on the central nervous system. It is involved in the circadian rhythm, in aggressive reactions, in blood and temperature control, and in analgesia [10].

The Hypophysiotropic Hormones

Thyrotropin-releasing hormone (TRH) is produced in the PVN by the parvocellular neurons. The synthetizing neurons project their axons to the external layer of the median eminence from where the TRH circulates through the hypophyseal portal system into the anterior hypophysis. They are stimulating the receptors to release the thyroid-stimulating hormone (TSH) from the thyrotropic cells (3–5% of the anterior hypophyseal cells), and prolactin from lactotrophic cells (20% of the anterior hypophyseal cells). TSH stimulates the thyroid gland to produce triiodothyronine (T3) and thyroxine (T4) with major implications in the way the body uses energy. More than that, they have a role in regulation of weight, muscle strength, body temperature, and, most importantly, they act on nervous system development and maturation. Prolactin has an important role in the maturation of the mammary glands and, in association with other hormones (like oxytocine, estrogen, progesterone, glucocorticoids) acts on milk secretion. Corticotropin-releasing hormone (CRH) or corticoliberin is released in the PVN by the parvocellular neurons and is involved in stress response. It follows the same way as TRH to the anterior lobe of the hypophysis, where it stimulates corticotrophic cells (15–20% of the anterior hypophyseal cells) and the cells responsible for the pro-opiomelanocortin (POMC) synthesis. Opiomelanocortin (POMC). POMC, a complex precursor protein, is cleaved to give several important biologically active molecules such as adrenocorticotrophic hormone (ACTH), α -, β -, γ -melanotropins (MSH), and β -endorphin [11].

The principal effect of ACTH is to increase production and secretion of cortisol by the corticoadrenal gland. It has also an effect on the circadian rhythm [12].

Growth hormone-releasing hormone (GHRH) or somatocrinin is a releasing hormone of the growth hormone (GH) produced in the arcuate nucleus. Via the hypophyseal portal system, the GHRH is carried to the anterior hypophysis where it stimulates GH secretion. GH or somatotropin is a hormone that stimulates growth, cell reproduction, and cell regeneration.

Growth hormone-inhibiting hormone (GHIH), or somatostatin, is produced in the ventromedial nucleus of the hypothalamus. The neuroendocrine neurons project to the median eminence. GHIH travels through the neuronal axons into the adenohypophysis where it inhibits the secretion of the somatotropic cells, responsible for the secretion of growth hormone [13].

Gonadotropin-releasing hormone (GnRH) is activated at puberty, being responsible for the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior hypophysis. GnRH travels through the hypophyseal portal system between the median eminence and anterior hypophysis where it activates the gonadotroph cells (about 10% of the hypophyseal gland). These cells synthesize and release the gonadotropins (FSH and LH) in a low amount prior to puberty and in high amount following puberty. Gonadotropins have an increase of serum concentration during the menstrual cycle.

Circadian Timing

Circadian timing represents an indispensable adaptation of living organism. The circadian timing system describes a network that regulates the timing of daily and seasonal physiological cycles. The leading nucleus involved in setting the circadian rhythms is the suprachiasmatic nucleus (SCN) of the hypothalamus. The nucleus lies on the anterior part of the hypothalamus, superior to the optic chiasm, on each side of the third ventricle.

SCN presents two parts, the core (ventrolateral) and the shell (dorsolateral). The shell receives

stimuli from the core and sends the information to other hypothalamic nuclei. The SCN core has inputs from the bilateral retina (retinohypothalamic tract) with a moderate contralateral predominance. Thus, SCN has increasing activity under the control of light and, in turn, via the PVN, activates the spinal intermediolateral column, especially the sympathetic preganglionic neurons of the thoracic region [14, 15].

Temperature Control

The homeostatic control of the body temperature is essential for survival, the mammals maintaining the body temperature by self-regulation, no matter the temperature of their surroundings. Human beings have an internal temperature of around 36.5–37.5°C necessary for the metabolic processes.

The preoptic anterior hypothalamus (POAH), consists of the medial preoptic and anterior hypothalamic nuclei, together with the posterior hypothalamus regulates the body temperature. POAH contains neurons that are sensitive to local temperature changes. They change their discharge rate related to the warming or cooling of the POAH. The warm-sensitive neurons (30% of the POAH neurons) react especially to the temperature rise above 37°C by increasing the rate of discharge. The result is the activation of the PVN and lateral hypothalamus responsible for the parasympathetic stimulation, promoting the heat dissipation.

The cold-sensitive neurons (5% of the POAH neurons), more prevalent in the posterior hypothalamic nucleus, react especially to a decrease in temperature below 37°C by increasing the rate of discharge. They increase sympathetic outflow via PVN and the posterior hypothalamus, promoting the heat generation and conservation (even by shivering) [16].

The temperature-insensitive neurons (more than 60% of the POAH neurons), not sensitive to changes in temperature, these neurons play a role in heat generation/conservation. Additionally, these neurons receive somatosensory information from the thermoreceptors of the skin through the lateral spinothalamic tract. The collaterals of the

ascending temperature pathway project into the reticular substance of the brainstem, intermediary synaptic station on the way to the hypothalamus. Thus, POAH becomes an integration center for the central and peripheral information [17].

Appetite and Body Weight

The balance between energy expenditure and dietary intake is a target to maintain the body weight within physiological limits. The arcuate nucleus of the hypothalamus has a key role in the regulation of appetite, receiving information of energy balance directly from the circulating molecules, from the median eminence, or from the molecules that are able to cross the blood–brain barrier.

The median eminence is one of the brain regions unprotected by the blood–brain barrier, being sensitive to the circulating signals of energy balance. From here, the information is sent to the arcuate nucleus. The molecules that are able to cross the blood–brain barrier are the gut hormones (peptide YY and glucagon-like peptide 1), leptin, and insulin.

In response, the arcuate nucleus has two circuits to control the energy balance. The first circuit stimulates food intake by neuropeptide Y (NPY) and agouti-related peptide (AgRP), both molecules are increasing the appetite and are decreasing the metabolism and the energy expenditure. The second circuit involves the neuropeptides pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) with an inhibitory response to food intake [18, 19].

The Hypothalamo–Neuroendocrine–Immune System Axis

Hans Selye introduced the term ‘stress’—“the nonspecific response of the body to any demand” [20]. Now we know that any real or perceived threat to homeostasis represents a state of stress. The stress response is mediated by the hypothalamic PVN, the anterior lobe of the hypophysis, and the adrenal gland, structures known commonly as the hypothalamo-pituitary-adrenal

(HPA) axis. PVN has afferents projections from different regions of the brain regulating the HPA axis. These regions are the brainstem nuclei (the solitary tract), the *lana terminalis* region (the subfornical organ, the median preoptic nucleus, the vascular organ of the *lamina*), the other hypothalamic nuclei (arcuate nucleus), and the limbic structures (hippocampus, prefrontal cortex, amygdala) [21]. In response to stress, corticotropin-releasing factor (CRF) induces the release of ACTH into the systemic circulation. ACTH stimulates the synthesis and the secretion of glucocorticoids from the adrenal cortex, responsible for the suppression of immune responses. Another pathway is mediated by the direct action of neuropeptides on the immune cells that are activated or suppressed. The immune cells possess receptors for neuropeptides, neuromediators, or hormones. Consequently CRH, ACTH, steroids, β-endorphin, or growth hormone induce production of inflammatory cytokines, TNF-α (tumor necrosis factor-α), and IL-1 and IL-6 (interleukins), molecules which act on the HPA axis and sympathetic system [22]. Therefore, a bidirectional relationship between the central nervous system and the immune system is established.

Memory and Emotional Expression

Memorization is a mental process to store information related to all kind of personal experiences to be reminded or evoked. The process of memorization seems to be influenced by emotions.

The limbic system is the neuronal network involved in emotion and memory. The limbic system comprises the hippocampal formation, amygdaloid complex, hypothalamus, nucleus accumbens, cingulate cortex, and ventral tegmental area.

The hypothalamus is the main output node for the limbic system. At the same time, the hypothalamus activates the sympathetic system as a part of an emotional reaction.

The mammillary bodies have direct connections with the hippocampus (via the fornix), with the anterior thalamic nuclei (via the mammillo-

thalamic tract), and the tegmental nuclei of the midbrain (via the mammillotegmental tract). These connections provide the possibility to transfer the information between hippocampus and anterior thalamic nuclei inducing the memory consolidation.

The thalamus represents the connection between the sensory pathways and the higher cortical regions and amygdala. The amygdala processes the emotional information and sends the information to the cortex [23]. To this end, the hippocampus is an integrator of all emotional experiences with cognition [24].

To conclude, the hypothalamus, an extremely small structure of the brain, participates in the control of almost all the processes, having an integrative role of the body activities.

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Neuroimaging of the Human Hypothalamus

3

Rashmi S. Thakkar and Frank Berkowitz

Introduction

The hypothalamus is the ventralmost part of the diencephalon which is located below the thalamus. It surrounds the anterior inferior portion of the third ventricle. It is a small but highly complex structure in the brain that controls many important body functions [1–3]. It functions primarily as an integrative mechanism for various anatomic and neuroendocrine activities including temperature regulation, water balance, appetite, and behavior.

Magnetic resonance (MR) imaging is the modality of choice in evaluating the hypothalamic region [4, 5]. With the help of high-resolution T1- and T2-weighted imaging, hypothalamic structures including its nuclei and white matter tracts can be evaluated. The mammillary bodies, anterior commissure, posterior commissure, mammillothalamic fasciculus, and post-commissural fornix can be identified.

In this chapter we will review the anatomy of the hypothalamus at MR imaging and discuss the imaging findings of various hypothalamic lesions.

MR Imaging of the Hypothalamus

Standard clinical MR imaging studies most commonly use T1-weighted, T2-weighted, proton density-weighted, and intravenous contrast-enhanced T1-weighted images. For detailed evaluation of hypothalamic anatomy, sagittal and coronal spin-echo T1-weighted sequences can be performed with thin sections ($\leq 2\text{--}3$ mm) and a small field of view (16–20 cm). The same sequence can be obtained after the administration of the intravenous gadolinium contrast with a standard dose (0.2 mmol/kg) [6]. Alternatively, a high-resolution three-dimensional spoiled gradient-echo volume acquisition can be obtained resulting in thinner sections (1–1.5 mm) which can be reconstructed in all three planes. In addition to these sequences, heavily T2-weighted MR images can depict cisternal, as well as neural, structures.

Axial T2-weighted, axial fluid-attenuated inversion recovery (FLAIR), and axial diffusion-weighted images (DWI) can be obtained selectively either for the hypothalamic-pituitary axis or for the whole brain. MR angiography is not routinely incorporated; however, the sequence can provide necessary vascular information. In addition to these MR imaging sequences, MR spectroscopy may be performed for further evaluation of hypothalamic lesions [7].

R. S. Thakkar (✉) · F. Berkowitz
MedStar Georgetown University Hospital,
Washington, DC, USA
e-mail: fxb10@gunet.georgetown.edu

MR Imaging Anatomy of the Hypothalamus

Sagittal MR imaging clearly demonstrates the hypothalamic structures. In the midsagittal section, the human hypothalamus is bounded anteriorly by the lamina terminalis, posteriorly by a plane drawn between the posterior commissure and the caudal limit of the mammillary body, and superiorly by the hypothalamic sulcus. Ventrally, the hypothalamus encompasses the floor of the third ventricle. Inferiorly the hypothalamus forms the tuber cinereum, a tubular structure composed of gray matter, that lies between the optic chiasm anteriorly and mammillary bodies posteriorly. The median eminence is a small bulge in the tuber cinereum that continues downward to form the infundibular stalk, which is attached to the posterior lobe of the pituitary gland [8, 9]. Figure 3.1 shows the boundary of the hypothala-



Fig. 3.1 *MR anatomy* of boundaries of the hypothalamus on sagittal enhanced T1-weighted image. IS infundibulum stalk, OC optic chiasm, AC anterior commissure, PC posterior commissure, MB mammillary bodies, TC tuber cinereum, PP hyperintense posterior pituitary

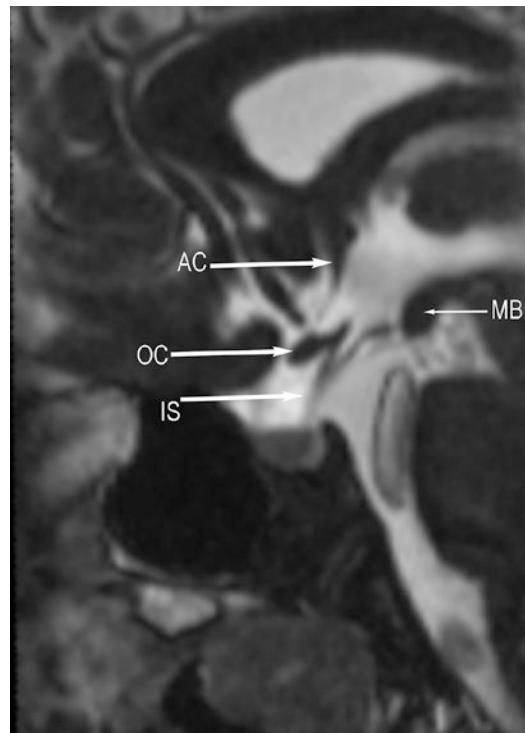


Fig. 3.2 *MR anatomy* of boundaries of the hypothalamus on high-resolution sagittal T2-weighted image. IS infundibulum stalk, OC optic chiasm, AC anterior commissure, MB mammillary bodies

mus on sagittal enhanced T1-weighted MR images through the sella. Figure 3.2 shows the boundary on high-resolution T2-weighted image.

The hypothalamus is commonly divided into regions along its anteroposterior axis. Rostral to the optic chiasm and extending dorsally to the anterior commissure and its bed nucleus is the preoptic region. The supraoptic region lies above the optic chiasm. The tuberal region lies above and includes the tuber cinereum. The mammillary region includes the mammillary bodies and the posterior hypothalamic nuclei [10, 11].

MR Imaging Characteristics of Lesions Involving the Hypothalamus

The hypothalamus is susceptible to involvement by a wide variety of pathologic processes. Hypothalamic lesions can be classified as devel-

opmental abnormalities, primary tumors of the CNS, secondary tumors of the CNS, and inflammatory and granulomatous disease [12].

Patient age, clinical findings, and MR imaging features are helpful in developing the differential diagnosis.

Congenital and Developmental Lesions

Congenital Hormone Deficiency

Congenital growth hormone deficiency is an important cause of short stature in childhood. It is characterized by low growth velocity in childhood and, if left untreated, severe short stature in adulthood [13].

MRI is the best tool in delineating pituitary anatomy and pathology. On MRI, patients with congenital hypopituitarism have an absent, interrupted, or thin pituitary stalk. The abnormal stalk prevents antidiuretic hormone and oxytocin from traveling to the posterior aspect of the sella. Ectopic storage of these hormones is often manifested as a T1-hyperintense focus at the median eminence. The anterior pituitary may be small or absent [14, 26] (Fig. 3.3).

Hypothalamic Hamartoma

Hypothalamic hamartomas (HH) are developmental malformations associated with a range of neurological and endocrine problems including intractable seizures, cognitive impairment, pervasive developmental disorders, behavioral disturbances and psychiatric disorders, and central precocious puberty [15].

HH are ectopic foci of gray matter typically originating in the region of the tuber cinereum and mammillary bodies, although they may arise anywhere along the base of the hypothalamus. Histologically they are composed of well-differentiated neurons and glial cells [16].

On MR imaging HH is isointense relative to gray matter on T1-weighted sequence and isointense or slightly hyperintense on T2-weighted sequence. The lesion does not enhance on post-contrast images [17] (Fig. 3.4).

Lipoma

Intracranial lipomas are uncommon lesions of developmental origin. They are generally asymptomatic; however, they may occasionally produce neurological symptoms such as seizures. Surgical treatment is rarely indicated.

Lipomas are benign fatty lesions resulting from a congenital malformation located at or near midline. They occur along the surface of the infundibulum, floor of the third ventricle, or adjacent to the cranial nerves. On MRI they are isointense to subcutaneous fat on all sequences (Fig. 3.5). Usually fat-suppressed sequences can help to distinguish lipomas from hemorrhagic/proteinaceous cysts. They may contain calcifications and/or traversing blood vessels [18, 19].

Epidermoid Cyst

Epidermoid cysts are developmental epithelial inclusion cysts, most commonly located along the petrous apex and cerebellopontine angle or in the juxtasellar region. Although they are congenital lesions, they become symptomatic only in adulthood as a result of accumulation of desquamated cell debris deriving from the capsule. Suprasellar lesions can cause visual disturbances and DI [20].

MRI shows a well-circumscribed multilobulated extra-axial cystic lesion with low-intermediate signal on T1-weighted sequence and high signal on T2-weighted sequence without postcontrast enhancement. High signal intensity on FLAIR and DWI, with corresponding low signal on apparent diffusion coefficient (ADC) images, can help to distinguish them from arachnoid cysts (Fig. 3.6) [21].

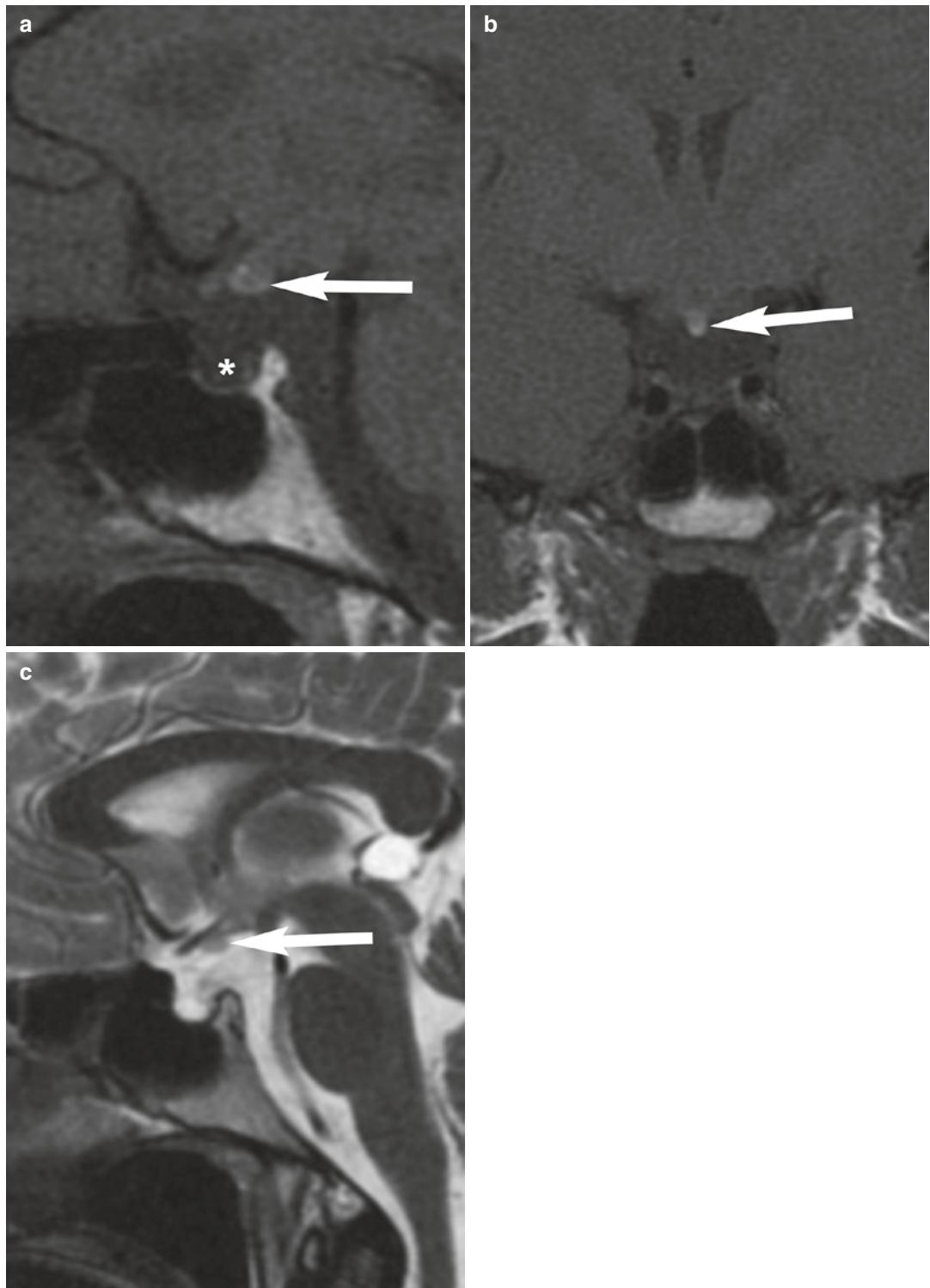


Fig. 3.3 Congenital hormone deficiency. A 25-year-old male with panhypopituitarism. Sagittal unenhanced (a) and coronal unenhanced (b) T1-weighted and sagittal (c) T2-weighted MR images show absence of the pituitary

stalk and absence of pituitary tissue in the sella (*). A 5 mm nodule at the median eminence, which is hyperintense on T1-weighted images and isointense on T2-weighted images (white arrow), represents ectopic posterior pituitary tissue

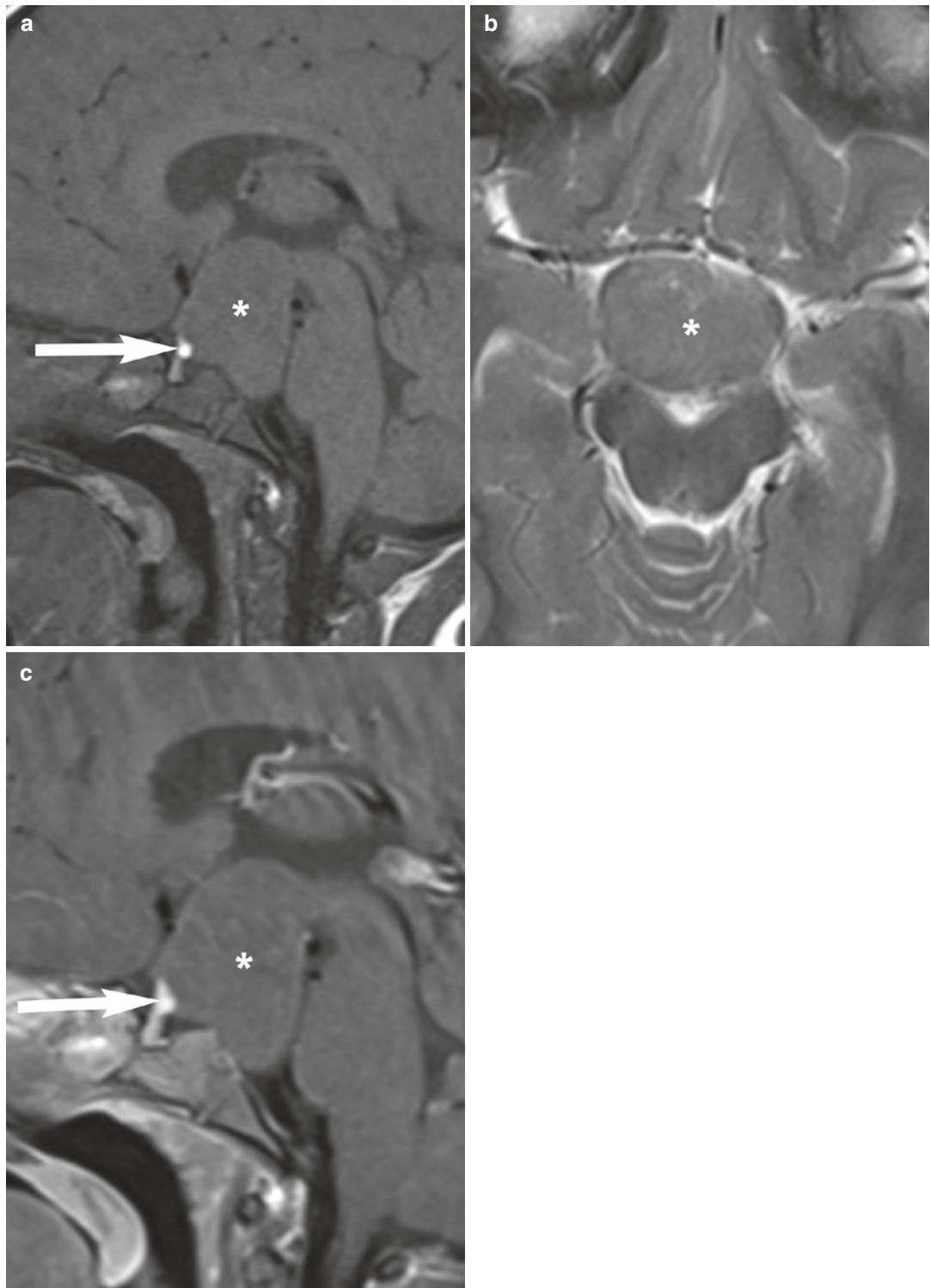


Fig. 3.4 Hypothalamic hamartoma. A 14-month-old male with uncontrollable seizures. Sagittal unenhanced T1-weighted (a) and axial unenhanced T2-weighted (b) show lobulated mass (*) in the hypothalamus which is

isointense to gray matter. On sagittal enhanced T1-weighted image (c), there is no enhancement in the hypothalamic mass. Note the hyperintense focus of ectopic posterior pituitary (white arrow), which is often associated with HH

Fig. 3.5 Lipoma. Sagittal unenhanced T1-weighted image shows normal infundibular stalk and pituitary gland in the sella. Incidental 3 mm hyperintense nodule in the interpeduncular cistern (white arrow) is consistent with lipoma



Fig. 3.6 Epidermoid cyst. Coronal T2-weighted (a) and contrast-enhanced T1-weighted (b) images show a T2 hyperintense, T1 hypointense suprasellar mass (*) with a rim of enhancement. The lesion is hyperintense on axial DWI (c)

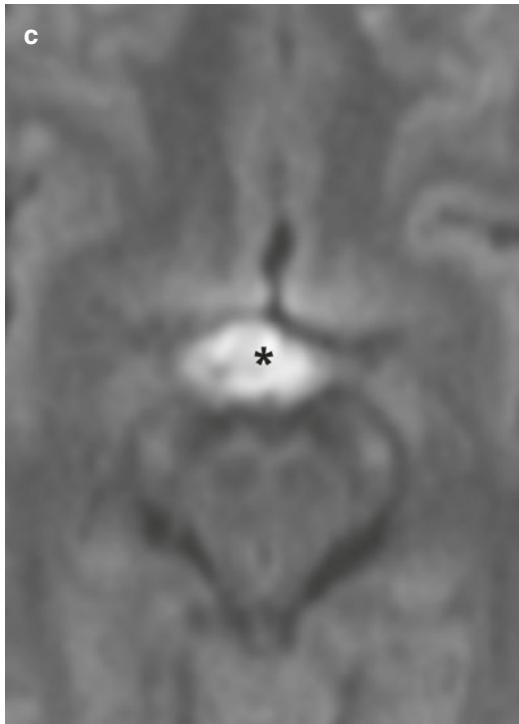


Fig. 3.6 (continued)

Dermoid Cyst

Dermoid cysts are similar to epidermoid cysts as they are rare developmental epithelial inclusion cysts. These are most commonly located along the tentorium. The MR imaging characteristics depend on the contents of the lesion such as lipid material, cholesterol granules, or desquamated epithelium. They are hyperintense on T1WI, have variable signal on T2WI, and do not enhance with contrast. Fluid-fluid or fluid-debris levels may be present. They can cause chemical meningitis if the dermoid cyst ruptures into the subarachnoid space [22].

Rathke Cleft Cyst

Rathke cleft cysts are benign sellar/suprasellar lesions derived from Rathke's pouch remnants. Rathke's pouch is an extension of the embryonic oral cavity. Rathke cleft cyst is lined with epithe-

lium and contains variable amount of protein, mucopolysaccharide, and/or cholesterol. In 71% of cases, the cysts are partially intrasellar and partially suprasellar in location [23]. Purely suprasellar Rathke cleft cyst with a normal pituitary gland has also been reported [24]. Usually they are asymptomatic, but they may produce symptoms due to their mass effect on the pituitary gland.

MR imaging shows a well-circumscribed lesion with variable low, intermediate, or high signal on T1WI and T2WI. On T2WI, a small low-signal nodule may be seen within the predominant high signal of the lesion (Fig. 3.7). The incidence of these intracystic nodules varies from 17% to 78% [25]. There is no contrast enhancement centrally; occasionally there may be thin peripheral rim of enhancement due to associated inflammation [26].

Primary Tumors

Craniopharyngioma

Craniopharyngiomas are intracranial epithelial neoplasms that occur in an intrasellar and/or suprasellar location in both children and adults [27, 28]. The prevalence of craniopharyngioma peaks between 10 and 14 years of age, with a second peak occurring between 40 and 60 years of age. Males are more commonly affected than females [29]. Typical symptoms include headache, visual field defects, and hypothalamic dysfunction, most commonly diabetes insipidus (DI). Histologically craniopharyngiomas are divided into two types: adamantinomatous (pediatric) and papillary (adult) types. Some tumors have mixed histologic features.

Typical MR features of a squamous-papillary craniopharyngioma include predominantly solid or mixed solid-cystic spherical tumor in a suprasellar location in adults. The cystic component of the tumor is hypointense on T1-weighted sequence and hyperintense on T2-weighted sequence. The solid tumor parts demonstrate intense enhancement on postcontrast sequence with or without small necrotic areas (Fig. 3.8) [30, 31].

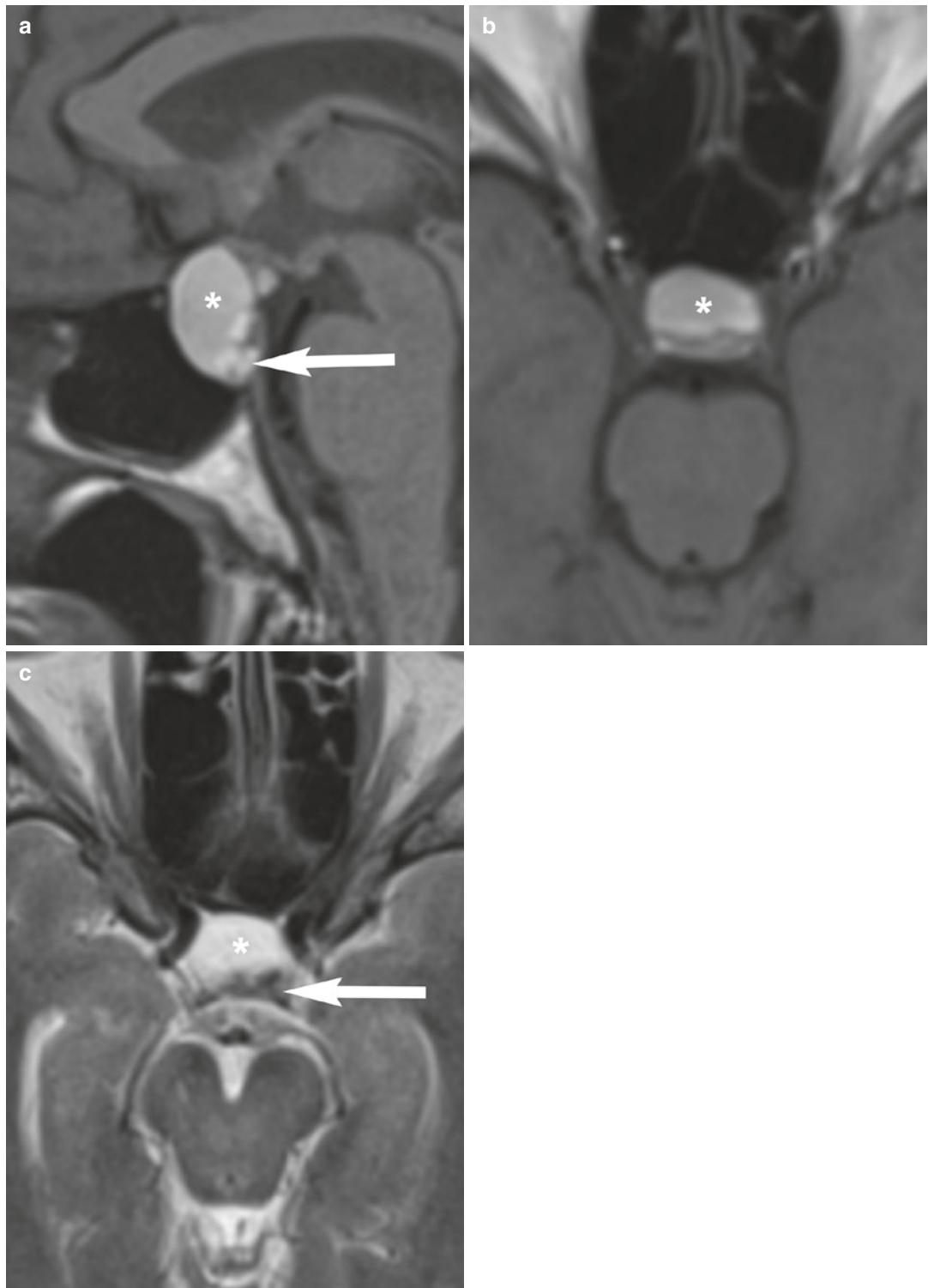


Fig. 3.7 Rathke cleft cyst. A 30-year-old female with headache. Sagittal (a) and axial (b) unenhanced T1-weighted images show a hyperintense mass in the sella and suprasellar region (*) with variable signal in its poste-

rior aspect. Axial unenhanced T2-weighted (c) image shows the cyst to be predominantly hyperintense with small hypointense intracystic nodules in the posterior aspect (white arrow)

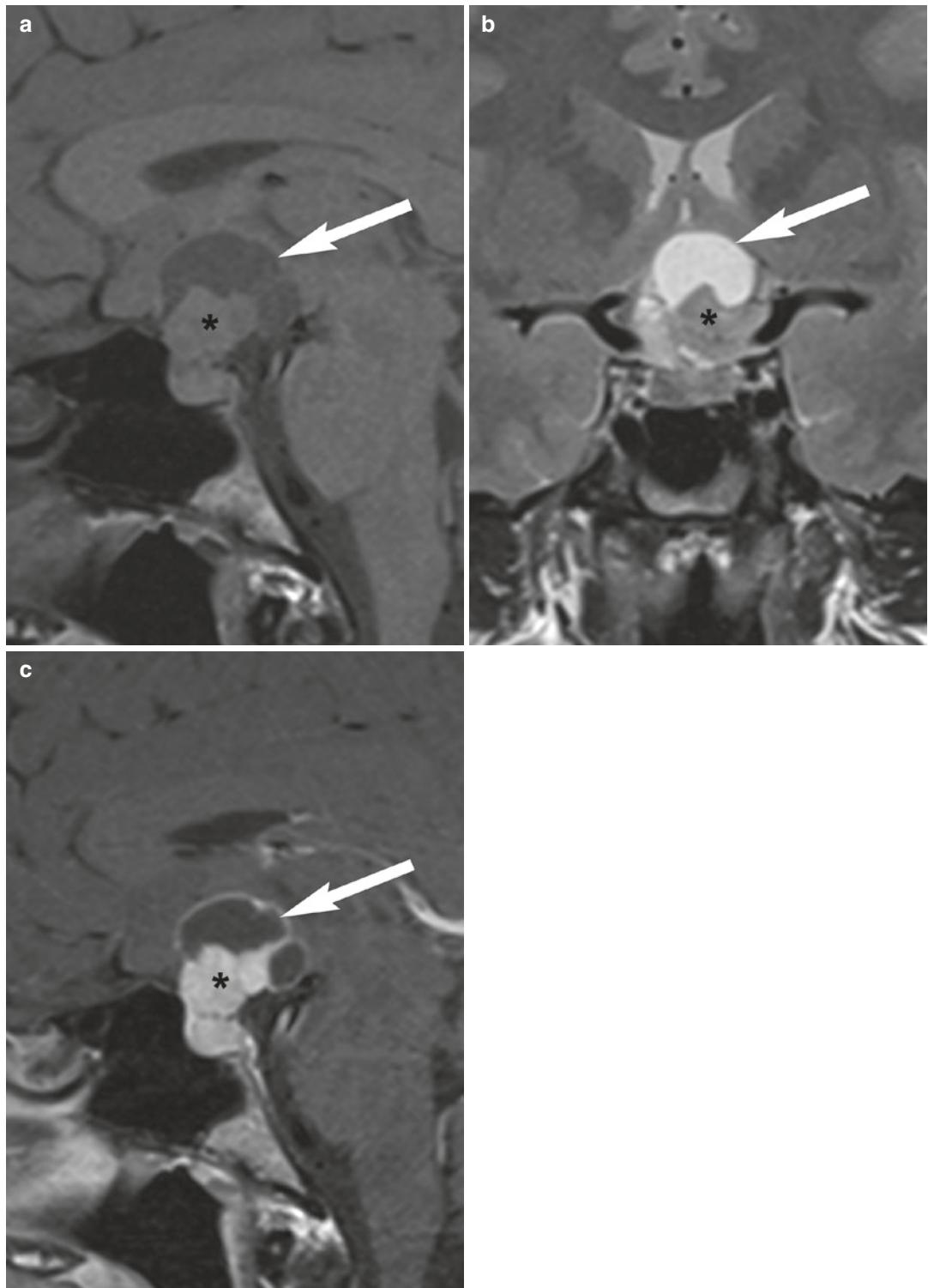


Fig. 3.8 Craniopharyngioma, squamous-papillary. A 25-year-old male with headache and diplopia. Sagittal unenhanced T1-weighted (a), coronal unenhanced T2-weighted (b), and sagittal contrast-enhanced T1-weighted (c) images show a mixed solid and cystic

mass. The cystic component of the tumor (white arrow) is hypointense on T1-weighted image and hyperintense on T2-weighted image and has a rim of enhancement. The solid component (*) has homogenous enhancement

The adamantinomatous craniopharyngioma is a cystic or predominantly cystic lobulated tumor centered in the suprasellar region in children. On pre-contrast T1-weighted images, single or multiple hyperintense cysts are identified. These cysts are either hypointense or hyperintense on T2-weighted images. On postcontrast images, the cysts have thin peripheral rim of enhancement. These cysts contain various amounts of cholesterol, triglyceride, methemoglobin, protein, and desquamated epithelium [32]. The signal intensity of these cysts is mainly influenced by the protein concentration and the presence of free methemoglobin. The hypointense areas within the solid tumor on T2-weighted sequences represent hemosiderin and keratin nodules. Encasement of the adjacent arterial vessels within the suprasellar cistern is very characteristic of the adamantinomatous tumor (Fig. 3.9) [28].

MR imaging has an important role in the evaluation of the extent of the lesion for pre-operative planning and in detection of tumor recurrence. Computed tomography is useful to identify tumoral calcifications which are often coarse calcifications.

Germinoma

Germinomas are tumors arising from the germ cells and most frequently occur during childhood and young adulthood. Intracranial germinomas occur most frequently in the pineal region, most often in male patients. The suprasellar/hypothalamic region is the second most common location, with equal frequency in both sexes [33]. Patients with hypothalamic germinomas present with visual or pituitary axis dysfunction such as diabetes insipidus or panhypopituitarism [34].

MR imaging features include homogenous, well-margined round solid masses that involve the infundibular stalk and floor of the third ventricle. Typically, they are iso- to hypointense on

T1-weighted sequence and iso- to slightly hyperintense on T2-weighted sequence with homogeneous postcontrast enhancement (Fig. 3.10). Suprasellar germinomas are characterized by homogeneity with lack of cystic or calcific component [29]. Additionally, there will be loss of high signal of the posterior pituitary lobe on sagittal T1-weighted sequence due to blockage of the infundibulum with the mass. This is very important imaging sign to recognize as the child will present with symptoms of diabetes insipidus [35].

Hypothalamic-Chiasmatic Glioma

Hypothalamic-chiasmatic gliomas represent a distinctive group of cerebral neoplasms, most characteristic of pediatric age group. Histologically, the vast majority of these neoplasms are pilocytic astrocytomas, more rarely fibrillary astrocytomas. The association between optic pathway glioma (OPG) and neurofibromatosis type 1 (NF1) is well known. The vast majority of these tumors are indolent, particularly in the NF1 population. Tumors may grow more slowly and occasionally regress spontaneously [36]. Males and females are equally affected. Surgical resection may be considered for exophytic OPGs, causing obstructive hydrocephalus or mass effect in the neighboring brain structures. Chemotherapy can delay its growth.

On MRI, there is fusiform and/or nodular enlargement of the optic chiasm and/or optic nerves with thickening of the third ventricular floor and hypothalamus. They are low-intermediate signal on T1WI and intermediate-high signal on T2WI with variable contrast enhancement (Fig. 3.11). Larger lesions may have cystic components and can grow directly into the pituitary stalk [37].

Other primary tumors that can affect the hypothalamus are very rare. These include hemangioblastoma and ganglioglioma.

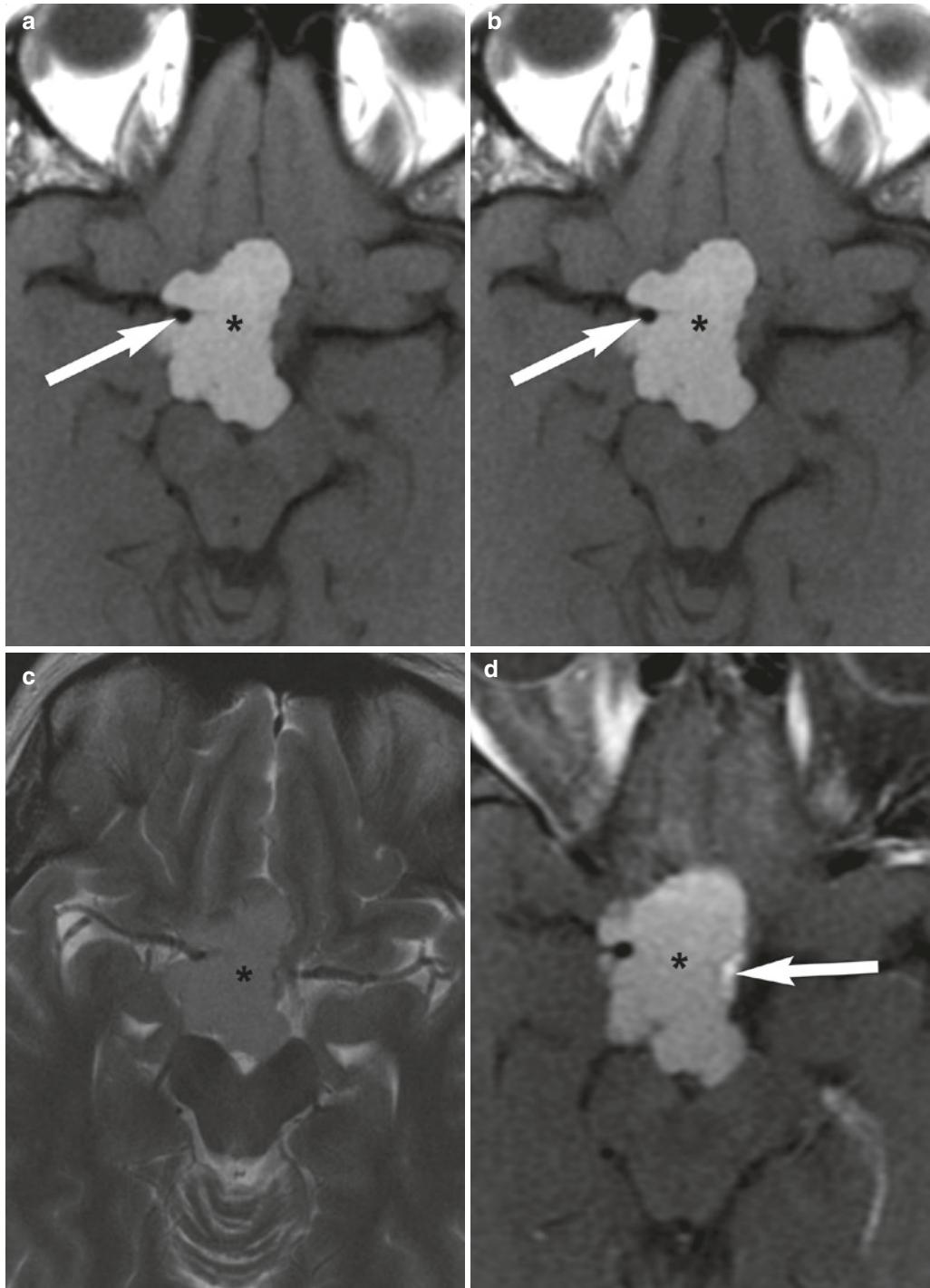


Fig. 3.9 Craniopharyngioma, adamantinomatous. A 15-year-old male with altered mental status. Sagittal (a) and axial (b) unenhanced T1-weighted and axial unenhanced T2-weighted images (c) show lobulated suprasellar mass (*) which is hyperintense on T1-weighted

sequence and mildly hyperintense on T2-weighted sequence. The mass encases the right internal carotid artery (white arrow). On axial contrast-enhanced T1-weighted image (d), the lobulated mass (*) shows a small focus of enhancement (white arrow)

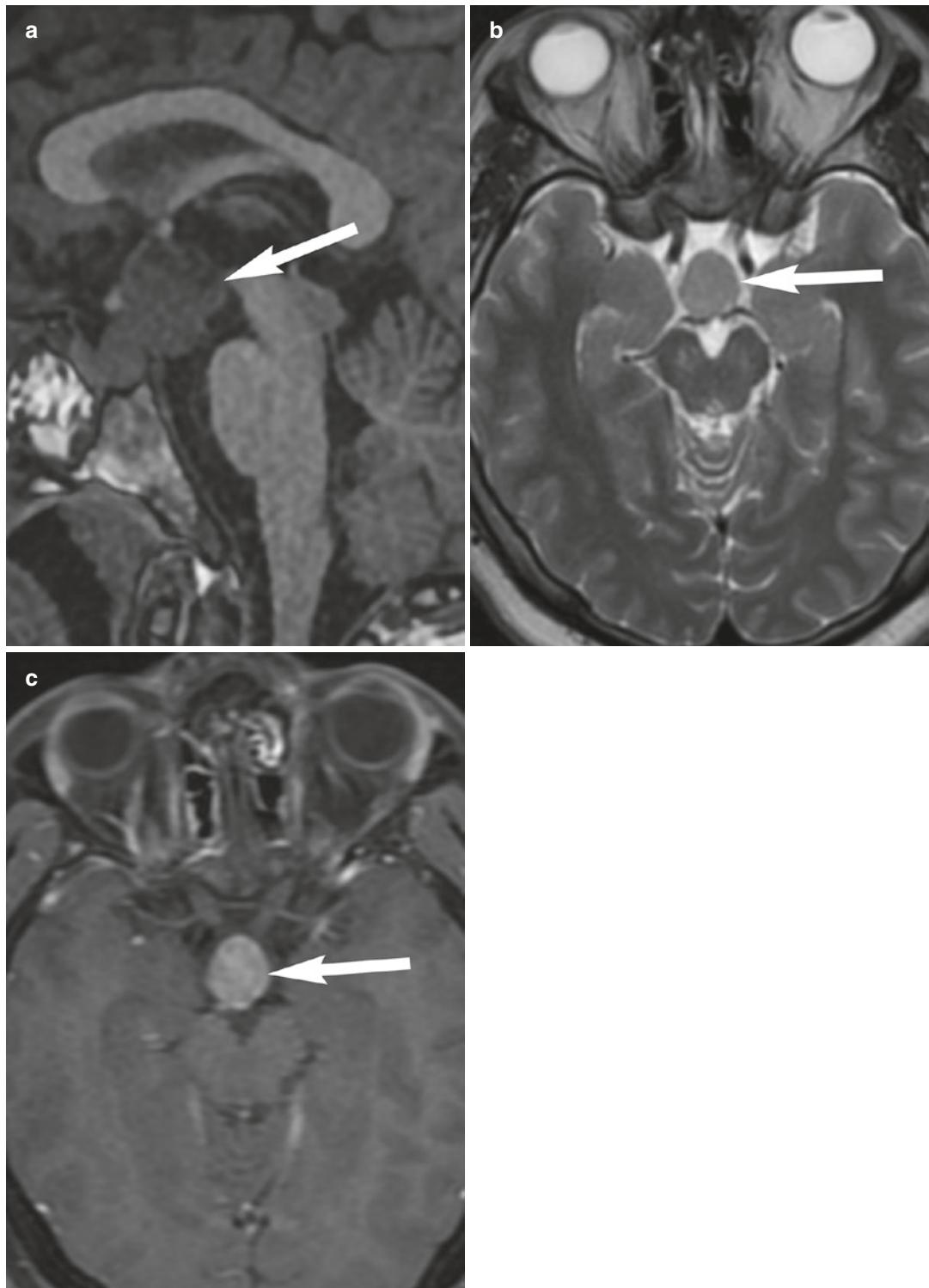


Fig. 3.10 *Germinoma*. A 15-year-old male with headache and diabetes insipidus. Sagittal (a) unenhanced T1-weighted and axial (b) unenhanced T2-weighted images show a circumscribed suprasellar mass causing infundibular thickening. It is isointense to gray matter on

T1- and T2-weighted sequences. Note the absence of posterior pituitary hyperintense signal on the T1-weighted image. On axial contrast-enhanced T1-weighted image (c), the mass shows homogenous enhancement

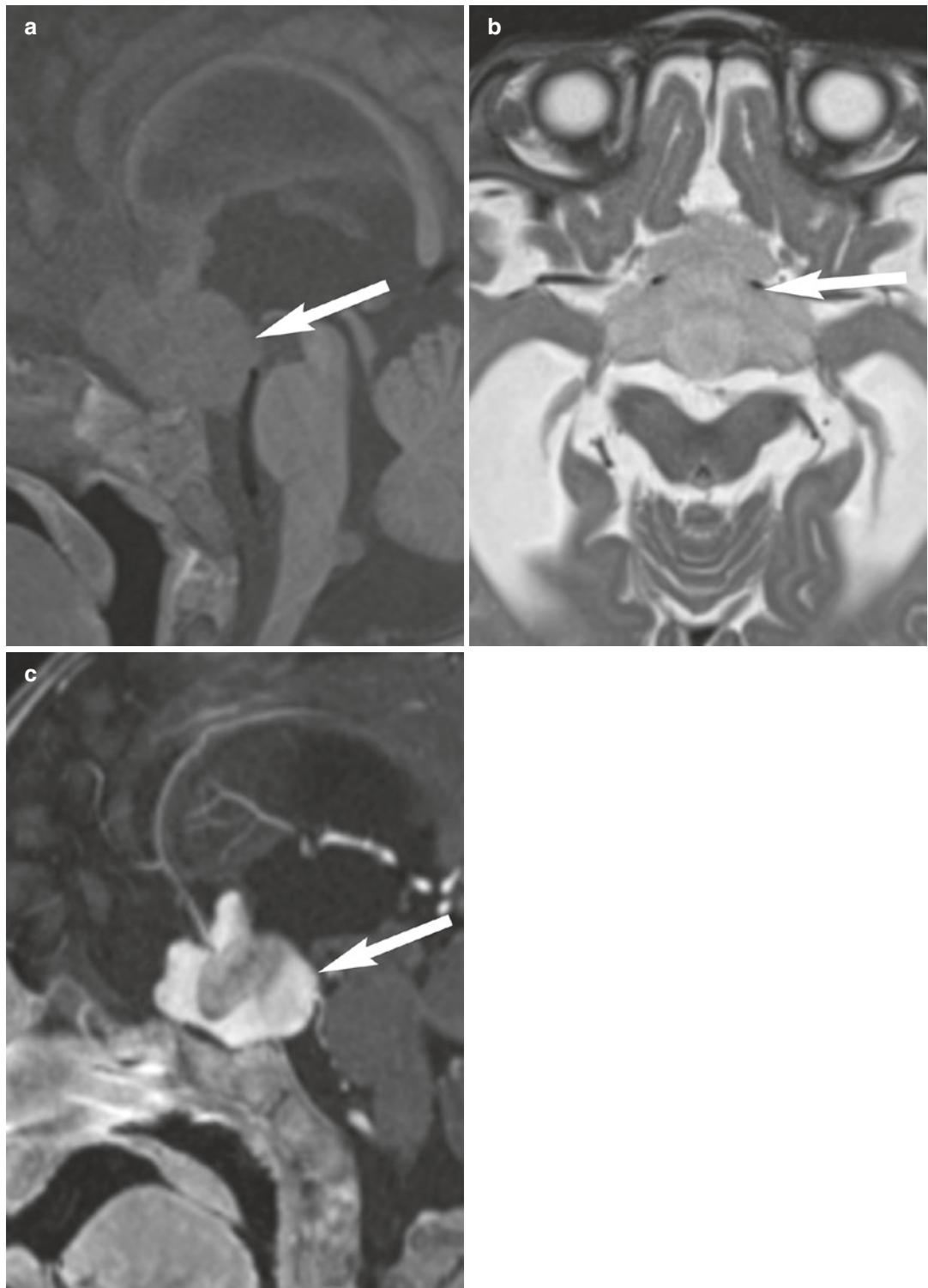


Fig. 3.11 Hypothalamic-chiasmatic glioma. A 7-year-old male with NF-1. Sagittal (a) unenhanced T1-weighted and axial (b) T2-weighted images show large lobulated mass centered in the suprasellar region with extension into

bilateral optic pathways. It is isointense on T1-weighted images and mildly hyperintense on T2-weighted images. On sagittal (c) contrast-enhanced T1-weighted image, there is heterogenous enhancement of the mass

Metastatic Tumors

Hematogenous metastasis to tuber cinereum, infundibular stalk, and neurohypophysis is common due to its lack of blood-brain barrier. The normal brain parenchyma has inherent protection due to intact blood-brain barrier [38]. The most frequent tumor to metastasize in women is breast cancer, followed by the lung, stomach, and uterus. In men, it is the lung followed by the prostate gland, urinary bladder, stomach, and pancreas.

On MR imaging there is marked thickening of the infundibular stalk. They are usually isointense on T1WI and have post-contrast enhancement. Unlike pituitary adenoma, metastases to the hypothalamic-pituitary axis show bone destruction without sellar remodeling [39].

Inflammatory and Granulomatous Disease

The most common cause of infectious encephalitis is viral encephalitis. Viral hypothalamic encephalitis may manifest with fever, DI, and the syndrome of inappropriate ADH secretion (SIADH) [40]. MR imaging shows the extent of inflammation in the hypothalamus and helps differentiate encephalitis from other hypothalamic conditions manifesting as masses.

Another infectious etiology that can affect hypothalamus is tuberculosis which presents as nodular, granulomatous enhancement along the leptomeninges as well as parenchymal lesions.

The causes of non-infectious inflammation of the hypothalamus include Langerhans cell histiocytosis (LCH), lymphocytic hypophysitis, and sarcoidosis.

Langerhans Cell Histiocytosis (LCH)

LCH is a disorder of the reticuloendothelial system in which bone-marrow-derived dendritic Langerhans cells infiltrate various organs as focal lesions or in diffuse patterns. Prevalence of 2 per

100,000 in children less than 15 years, with only one third of the lesions occurring in adults [41]. Manifestations of LCH at MR imaging include (1) lesions of the craniofacial bones and skull base with or without soft-tissue extension; (2) intracranial, extra-axial involvement of hypothalamic-pituitary region and meninges; (3) intracranial, intra-axial changes (white matter and gray matter); and (4) cerebral atrophy.

In hypothalamic involvement, MR imaging shows a fusiform or lobulated lesion with intermediate signal on T1WI and T2WI involving the pituitary stalk. The pituitary stalk is usually >3 mm in thickness and is often associated with loss of posterior pituitary high signal on T1WI. Lesions may also cause enlargement of the pituitary gland.

Lymphocytic Hypophysitis

Lymphocytic hypophysitis is an autoimmune inflammatory condition caused by the infiltration primarily of the hypothalamus, infundibulum, and neurohypophysis by lymphocytes and plasma cells. It is more prevalent in women (80%) particularly in peripartum period, but it can also occur in children. Clinical findings include headaches and pituitary dysfunction, with deficiency of ACTH in adults and growth hormone in children [42].

MRI shows slightly lobulated lesions with intermediate signal on T1WI, heterogeneous low-intermediate and high signal on T2WI involving the pituitary with thickened pituitary stalk and prominent heterogeneous or homogenous enhancement of the pituitary gland, pituitary stalk, and dura (Fig. 3.12). Following treatment with steroids, there is complete resolution of the imaging features [43].

Sarcoidosis

Sarcoidosis is a multisystem granulomatous disorder of unknown cause that most commonly affects young adults of both sexes. Clinical

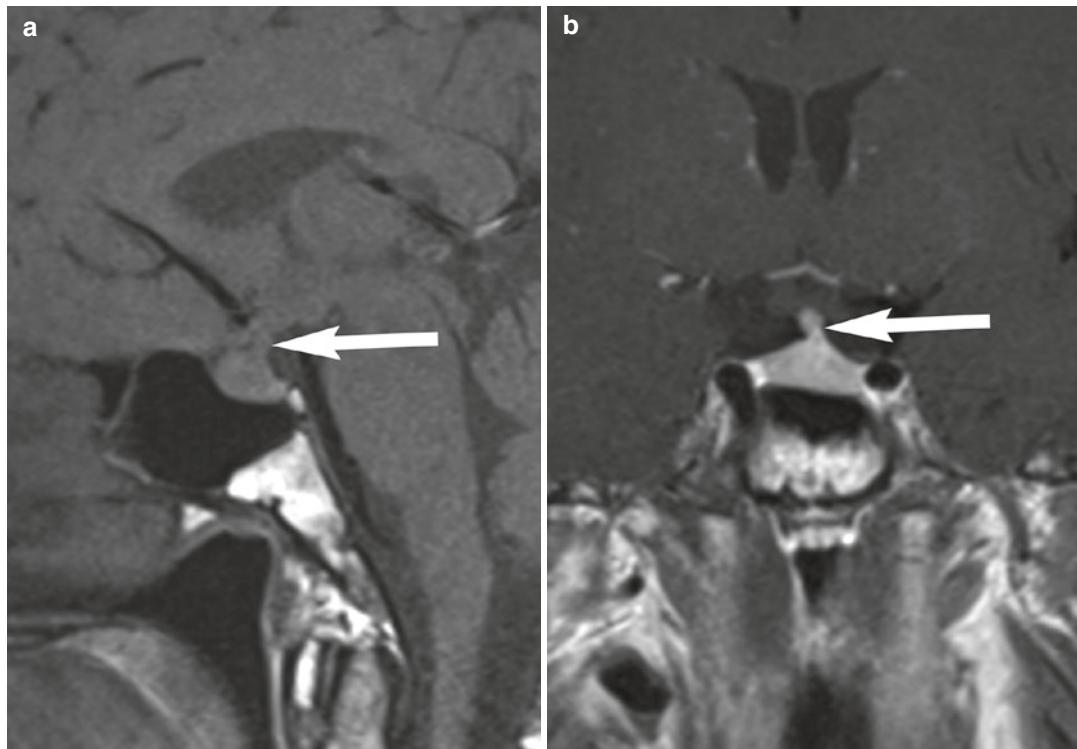


Fig. 3.12 Lymphocytic hypophysitis. A 32-year-old post-partum female with symptoms of hypopituitarism. Sagittal (a) unenhanced T1-weighted image shows thickening of the infundibular stalk (white arrow). On coronal (b)

contrast-enhanced T1-weighted image, there is homogeneous enhancement of the thickened infundibular stalk measuring 4 mm (white arrow)

involvement of the CNS (neurosarcoidosis) occurs in about 10% of affected patients during the course of the disease. Neurosarcoidosis develops primarily in the leptomeninges and may spread along the Virchow-Robin spaces to form intraparenchymal masses. The disease has a predilection for the base of the brain, particularly the hypothalamus and pituitary gland, although any portions of the brain and spinal cord can be affected.

On MR imaging, granulomatous infiltration causes plaque-like or nodular thickening of the pituitary stalk and the gland. These lesions are isointense to gray matter on T1WI and hypointense on T2WI with intense post-contrast enhancement of the leptomeninges (Fig. 3.13).

One of the most typical manifestations is a thick, enhancing infundibulum [44].

Lesions Arising From Surrounding Structures

Large pituitary adenomas may extend into the suprasellar cistern, invading the hypothalamus. At MR imaging, large pituitary adenomas have a bilobed configuration with a waist-like configuration at the dorsum sella. The large pituitary adenomas can be homogeneous or may show variable signal intensity depending on the necrotic, cystic, or hemorrhagic components.

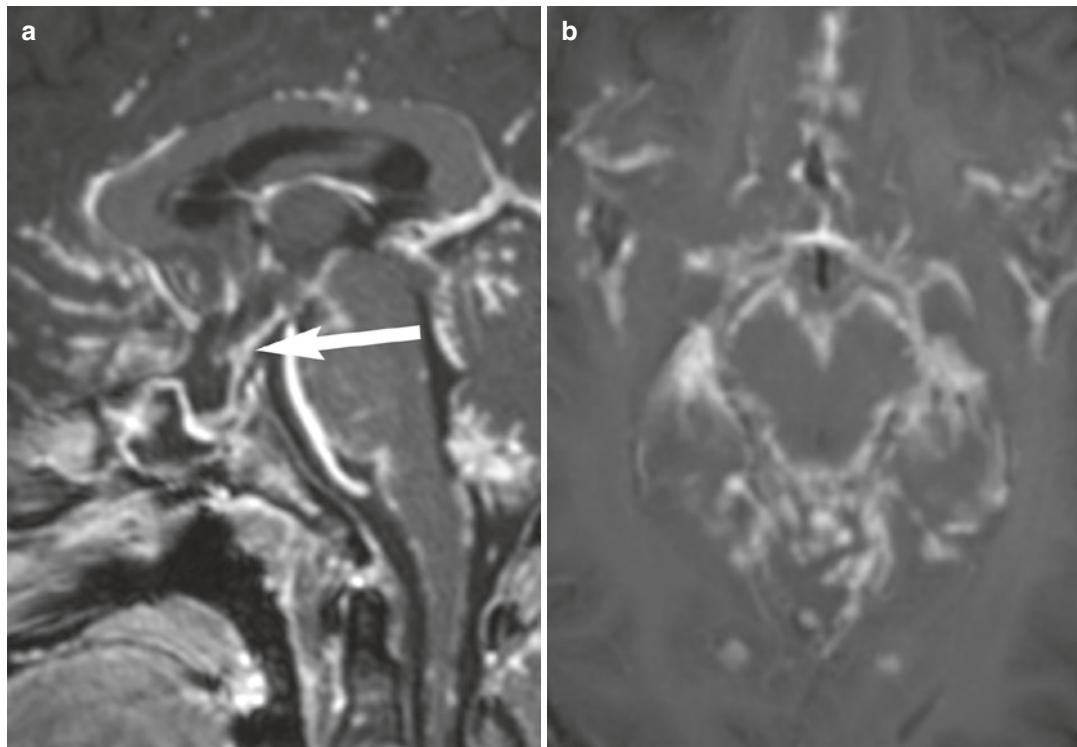


Fig. 3.13 *Neurosarcoidosis*. A 35-year-old female with systemic sarcoidosis presented with altered mental status. Sagittal (a) and axial (b) contrast-enhanced T1-weighted

images show diffuse nodular leptomeningeal enhancement involving the base of the skull with nodular thickening and enhancement of the infundibular stalk (white arrow)

Summary

Imaging of the hypothalamus is ideally performed with MRI and relies on a strong knowledge of the neuroanatomy and signal characteristic of the normal pituitary gland and surrounding structures. The knowledge of key differentiating MRI characteristics in common and uncommon disease entities involving the hypothalamus, in conjunction with the clinical findings, aids in guiding the clinician to the appropriate path of management. MR imaging is considered the gold standard for accurately characterizing hypothalamic lesions.

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Neurophysiology of the Hypothalamus

Stefany D. Primeaux, Lisa M. Harrison-Bernard,
and Maria J. Barnes

Hypothalamic Regulation of Food Intake

A series of complex central and peripheral systems are needed to maintain energy homeostasis in order to have enough energy intake to maintain a stable body weight. The hypothalamus exerts central control on feeding and energy expenditure by integrating information from peripheral signals reflecting hunger and satiety levels and adiposity stores and from higher brain signals regulating reward. Information is processed in hypothalamic neural circuits which project to limbic and autonomic brain regions, which then send efferent signals to the body to regulate food intake. Receptors located on hypothalamic neurons are sensitive to changes in food homeostasis, energy balance, glucose metabolites, and adipos-

ity, and activation of these receptors regulate the expression of and response to various hypothalamic neuropeptides (Fig. 4.1).

Hypothalamic Feeding Circuitry The hypothalamus is composed of multiple nuclei that are critical in relaying afferent signals from the gut and brainstem and processing efferent signals that modulate food intake and energy expenditure. Several groups of interconnecting neurons in the hypothalamus are involved in the coordination of feeding behavior, the arcuate nucleus (ARC), the paraventricular nucleus (PVN), the ventromedial nucleus (VMH), the dorsomedial nucleus (DMH), and the lateral hypothalamus (LatH). These hypothalamic nuclei stimulate food intake through orexigenic circuits and inhibit food intake through anorexigenic circuits [1–3]. In early studies, lesions to specific hypothalamic nuclei resulted in either extreme overeating and obesity or extreme undereating and wasting and were instrumental in establishing the hypothalamus as a key brain region in the regulation of food intake [1, 4, 5]. Subsequent studies reported that the hypothalamus became highly active immediately prior to eating and during times of hunger and food seeking [6, 7].

The ARC is a crucial hypothalamic region involved in the regulation of appetite. The ARC receives hormonal and nutrient signals from the periphery through the median eminence, a region

S. D. Primeaux (✉)
Department of Physiology, LSU Health Sciences Center, New Orleans, LA, USA

Joint Diabetes, Endocrinology & Metabolism Program, Pennington Biomedical Research Center, Baton Rouge, LA, USA
e-mail: sprime@lsuhsc.edu

L. M. Harrison-Bernard
Department of Physiology, LSU Health Sciences Center, New Orleans, LA, USA
e-mail: lharris@lsuhsc.edu

M. J. Barnes
Department of Biochemistry and Nutrition Des Moines University, Des Moines, IA, USA
e-mail: Maria.Barnes@dmu.edu

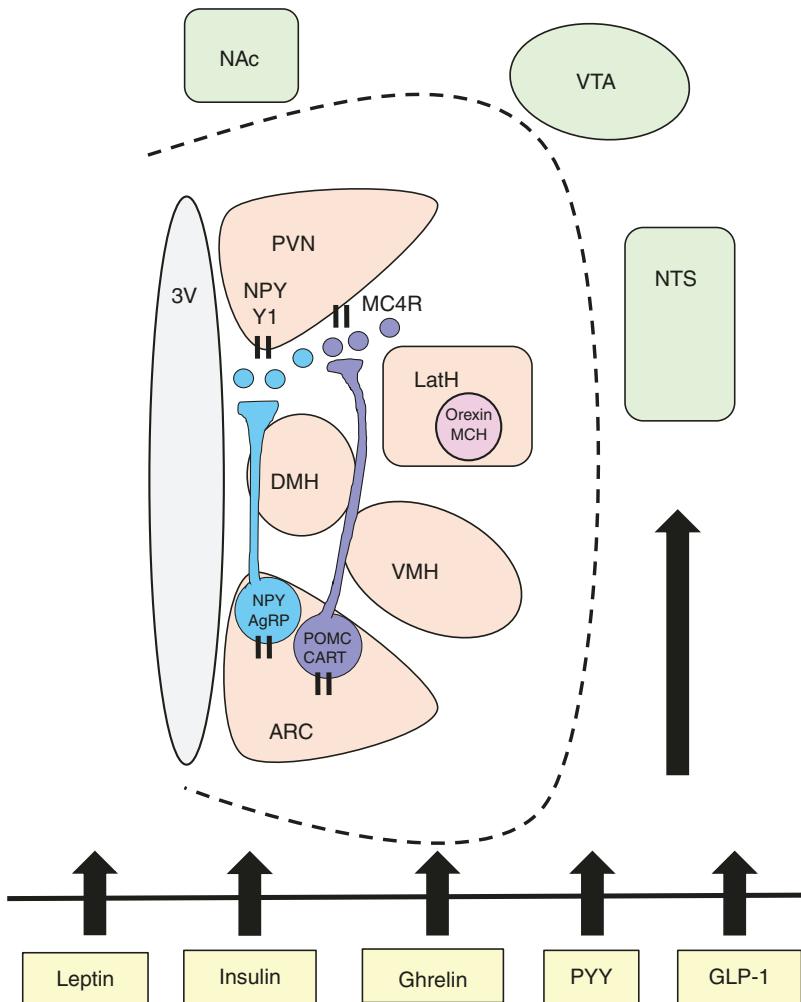


Fig. 4.1 Hypothalamic Regulation of Food Intake. The hypothalamus integrates information from peripheral signals like leptin, insulin, ghrelin, peptide YY (PYY) and glucagon-like peptide (GLP-1), and extra-hypothalamic regions (nucleus of the solitary tract (NTS), nucleus accumbens (NAc), and ventral tegmental area (VTA)) to exert central control over feeding and energy expenditure. Primary feeding neural circuitry in the hypothalamus involves the expression of orexigenic (neuropeptide Y (NPY) and agouti-related peptide (AgRP)) and anorexi-

genic (proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART)) neuropeptides in the arcuate nucleus (ARC) and their binding to receptors (NPY Y1 and melanocortin receptor 4 (MC4R)) at the paraventricular nucleus of the hypothalamus (PVN). Ventromedial nucleus of the hypothalamus (VMH), dorsomedial nucleus of the hypothalamus (DMH), lateral hypothalamus (LatH), third ventricle (3V), melanin-concentrating hormone (MCH)

associated with a “leaky” blood-brain barrier [8–10]. Integration of these peripheral signals and afferent inputs from the periphery (via the vagus nerve) and other brain nuclei is coordinated in the ARC and initiates a feedback response. In the ARC, two primary types of neurons are important for the feeding response: the orexigenic (appetite-stimulating) neuropeptide Y (NPY) and agouti-related peptide (AgRP)-expressing neu-

rons and the anorexigenic (appetite-suppressing) proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART)-expressing neurons. Neuronal projections from these two populations communicate with other hypothalamic areas involved in appetite regulation, such as the PVN, DMH, and LatH. Activation of neural projections from the ARC to the PVN strongly influences feeding behavior [11].

Neuropeptide Y/Agouti-Related Peptide NPY, a 36-amino-acid peptide, is widely expressed in the central nervous system. NPY-expressing neurons are found primarily in the hypothalamus where NPY serves as a potent orexigenic neuropeptide and an important regulator of body weight. NPY acts at five different receptors (Y1-Y5), though NPY is a potent stimulator of food intake via activation of NPY Y1 and Y5 receptors. NPY reduces energy expenditure by Y1 receptor-mediated reduction in tyrosine hydroxylase expression in the PVN and brainstem, leading to decreased sympathetic output to brown adipose tissue, an adipose depot involved in energy expenditure. Most neurons expressing NPY in the hypothalamus are found in the ARC and also express AgRP, a 132-amino-acid protein. Deletion of NPY/AgRP neurons in mice reduces food intake and body weight. Fasting or food deprivation leads to overexpression and secretion of NPY and AgRP. AgRP is able to increase food intake by acting as an endogenous inverse agonist of the melanocortin receptors, MC3R/MC4R, and by preventing the anorexigenic effect of α -melanocortin-stimulating hormone (α -MSH, a product of the POMC gene) on second-order neurons. NPY/AgRP neurons directly inhibit anorexigenic POMC neurons via inhibitory action on POMC expression neurons in the ARC. NPY/AgRP neurons have extensive projections within the hypothalamus including the PVN, DMH, and LatH and receive activating glutamatergic input from the VMH and PVN. PVN neurons receive inhibitory innervation from neurons in the LatH that promote feeding, resulting in a highly coordinated feeding response [10].

Proopiomelanocortin A separate population of neurons in the ARC express POMC mRNA, a 241-amino-acid pro-protein, which is cleaved into α -MSH and released from POMC axons to activate G-protein-coupled MC3R/MC4R on downstream neurons, including neurons in the PVN. Binding of α -MSH to MC3R/MC4R results in a decrease in food intake and an increase in energy expenditure. Under fasting conditions, the expression of POMC is reduced, while an increase in food consumption stimulates POMC

expression. MC4R is highly expressed within the hypothalamus, in particular the PVN, which is considered the predominant energy regulating MC4R population in the central nervous system. Targeted deletion of MC4R results in hyperphagia, reduced energy expenditure, obesity, and disruptions in glucose homeostasis [10, 12]. The coordination of food intake by MC4R suggests that melanocortin neurons may exert a “tonic” inhibition on feeding, which is relaxed following AgRP binding to MC3R/MC4R, ultimately resulting in stimulation of feeding [3]. The majority of POMC neurons in the ARC also co-express CART mRNA. In animal studies, CART administration and altered CART expression have both orexigenic and anorexigenic effects. POMC/CART neurons project mainly to second-order neurons in the PVN, but also to the DMH, the LatH, and the VMH. These second-order neurons process the received information and project to multiple extra-hypothalamic regions leading to an integrated response on energy intake and expenditure (Roh, 2016).

The LatH and VMH are hypothalamic regions involved in food intake regulation, monitoring internal homeostasis, and motivating a feeding response. The LatH expresses the orexigenic neuropeptides melanin-concentrating hormone (MCH) and orexin. NPY, AgRP, and α -MSH projections from the ARC are extensive in the LatH and are in contact with MCH- and orexin-expressing neurons. MCH-immunoreactive fibers project to the cortex, brainstem, and spinal cord. Two MCH receptors have been cloned, MCHR1 and MCHR2 [13]. Administration of MCH increases food intake, and fasting increases the expression of *Mch* mRNA. Orexin acts via two receptors OX1R and OX2R, and administration of orexin increases food intake, though this effect on food intake may be confounded by increased arousal [3]. The LatH is also a regulator of the rewarding aspects of food, and this region becomes highly active in response to rewarding food items [14]. In contrast, activation of the VMH is aversive, and animals will work to reduce stimulation in this region [15]; therefore, the coordination of these regions suggests that

when caloric or weight limits are met, activation of VMH may lead to the cessation of further intake. The DMH also contains a high number of NPY and α -MSH terminals originating from the ARC. Destruction of the DMH induces hyperphagia and obesity. The PVN serves as the primary outflow from the NPY/AgRP- and POMC-expressing neurons in the ARC. Microinjections of almost all known orexinergic peptides into the PVN will stimulate feeding. Additionally, neurons within the PVN control sympathetic outflow to peripheral organs and secrete a variety of regulatory neuropeptides.

Extra-hypothalamic projections Hypothalamic nuclei involved in food intake regulation send and receive information from various extra-hypothalamic brain regions, such as the nucleus of the solitary tract (NTS) in the brainstem. Signals from the periphery bind to receptors on the nodose ganglia of the vagus nerve and project to the NTS, where extensive neuronal pathways exist between brainstem structures and hypothalamic appetite circuits. These extra-hypothalamic circuits provide an alternative pathway for the communication of peripheral satiety factors to act on the hypothalamus to coordinate the “homeostatic” aspects of food intake. Hypothalamic neural circuits are also directly connected to the mesolimbic reward system, comprising the ventral tegmental area (VTA) and the nucleus accumbens (NAc), which control the “hedonic” aspects of food intake. Integration of homeostatic inputs from the hypothalamus with hedonic feeding signals from the mesolimbic pathway is further influenced by signals from decision-making regions of the brain (i.e., amygdala, prefrontal cortex). The coordination of these brain regions generates an orchestrated response to signals regulating feeding and energy homeostasis. Recent studies using fMRI have begun to shed light on the complex feeding-reward mechanism and brain structures and their ability to be impacted and directed by cognition [10].

Peripheral signals acting on the hypothalamus: *Leptin* Leptin, an adipose tissue-derived adipokine, is released into the plasma in propor-

tion to whole-body fat stores and plays a crucial role in the central regulation of food intake. In the hypothalamus, circulating leptin crosses the blood-brain barrier and binds to leptin receptors (Ob-Rb) expressed on neurons in the ARC, VMH, DMH, and LatH. In the ARC, *Ob-Rb* mRNA is expressed on both NPY/AgRP and POMC/CART neurons and directly impacts expression of these neuropeptides. Leptin induces POMC expression while exerting an inhibitory effect on NPY/AgRP expression. Thus the net effect of leptin action within the hypothalamus is an inhibition of food intake. The exact mechanism regulating leptin’s actions on NPY/AgRP and POMC neurons is not fully understood, though several hypotheses have been proposed. Leptin may directly inhibit NPY gene transcription by activating SOCS3, by hyperpolarizing NPY/AgRP neurons and inhibiting secretion, or by inactivating NPY/AgRP synthesis by increasing STAT3 activation. Leptin induces *c-fos* activation in POMC-expressing neurons and may increase POMC expression by depolarization of the neuronal membrane or by altering STAT3 or PI3K activation [16].

Insulin Insulin is secreted from pancreatic β -cells and plays an important role in the regulation of energy homeostasis. Upon nutrient ingestion, circulating insulin rises and crosses the blood-brain barrier via receptor-mediated transport. POMC neurons express insulin receptors, and binding of insulin to these receptors increases POMC expression. On NPY/AgRP neurons, insulin induces membrane hyperpolarization and decreased firing rate of AgRP neurons, thus reducing the release of AgRP.

Gastrointestinal hormones Gastrointestinal hormones are important regulators of food intake and are sensitive to gut nutrient content. Short-term feelings of hunger and satiety are believed to be partly mediated by changes in circulating gut hormone concentrations. Ghrelin, which is secreted from the stomach during hunger and fasting, stimulates feeding by activating hypothalamic NPY/AgRP neurons. Upon nutrient ingestion, glucagon-like peptide 1 (GLP-1), peptide YY (PYY), and cholecystokinin (CCK) are released from the

intestines and exert anorexigenic effects in hypothalamic feeding regions and in the NTS by modulating vagal afferents. GLP-1 also acts as a neurotransmitter in the brain and is produced in the NTS and centrally affects food intake by binding to GLP-1 receptors, which are densely expressed in the ARC and primarily located on POMC neurons. PYY is relatively selective for NPY Y2 receptors, which are highly expressed in the ARC on NPY neurons, and activation of these receptors inhibits NPY expression. Administration of CCK into the DMH reduces food intake and downregulates NPY expression [3].

Hypothalamic Control of Reproduction

Hypothalamic control of reproduction involves a coordinated effort between the hypothalamus, pituitary gland, and gonads (i.e., ovaries and testes) to regulate gonadal and reproductive function in males and females. A relatively small number of neurons (~1500) located in the preoptic area (POA) and the arcuate nucleus (ARC) of the hypothalamus are required for the coordination of reproductive function via the hypothalamic-pituitary-gonadal (HPG) axis.

Hypothalamic-Pituitary-Gonadal (HPG) Axis In the hypothalamus, gonadotropin-releasing hormone (GnRH) neurons release the hormone, GnRH, into the portal vasculature via the median eminence, where it is transported to the anterior pituitary gland located just below the hypothalamus. The GnRH neurons are the central initiator of reproduction, and GnRH is released by two distinct modes: pulsatile and surge. The pulsatile mode refers to the episodic release of GnRH, in which there are pulses of GnRH secretion, followed by periods of undetectable levels of GnRH. The surge mode of GnRH secretion occurs in females during the pre-ovulatory phase, in which the presence of GnRH in the portal circulation appears to be consistently elevated. GnRH binds to GnRH receptors on gonadotropes in the anterior pituitary gland to stimulate the release of the gonadotropins, luteinizing hor-

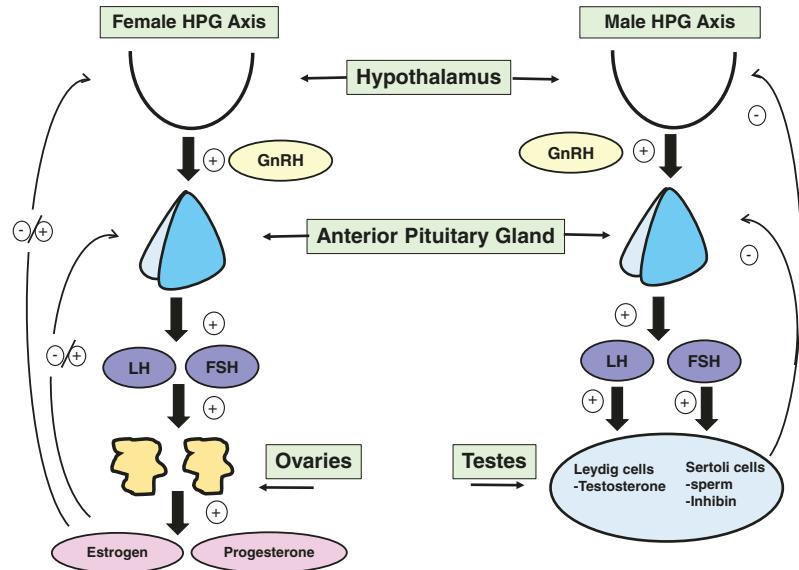
mone (LH), and follicle-stimulating hormone (FSH). Upon release, LH and FSH are delivered into the general circulation and bind to receptors on the male and female gonads. In humans, LH pulse frequency is used as a surrogate of GnRH pulsatility. Binding of LH and FSH to the male and female gonads stimulates the release of steroid hormones (i.e., estrogens, progestins, androgens). Following release, these sex steroid hormones are transported through the general circulation and feedback to the anterior pituitary gland and the hypothalamus to modulate further release (Fig. 4.2).

Neuroanatomy and Neurocircuitry of GnRH neurons

GnRH cell bodies are located in the POA and in the ARC, forming a neuronal network with projections to the median eminence. The distribution pattern and activity of hypothalamic GnRH neurons are established and functionally mature before birth. GnRH neurons are intermingled among a large number of neurons and glia and have neuroprocesses that span several millimeters in length. These neurons contain multiple synaptic spines, have dendritic and axonal characteristics, and are capable of making numerous axo-somatic, axo-axonal, and dendrodendritic synapses, which allows them to be influenced by a range of neuroendocrine and metabolic inputs. Receptors for multiple neurotransmitters and neuromodulators are expressed on GnRH neurons; however, interestingly, receptors for sex steroid hormones are absent. Due to their long processes, synaptic and non-synaptic inputs can occur throughout the entirety of the neuron to modulate GnRH release [17].

GnRH neurons send the majority of their projections to the median eminence and the pituitary stalk, where GnRH peptide is released to stimulate synthesis and secretion of LH and FSH. Numerous neuropeptides and neurotransmitters converge at the median eminence, including thyrotropin-releasing hormone, corticotrophin-releasing hormone, growth hormone-releasing hormone, somatostatin, and dopamine, and have the potential to interact with GnRH neurons. Considerable research has been conducted on the regulation of

Fig. 4.2 Hypothalamic-Pituitary Gonadal Axis. Reproduction is regulated by a coordinated effort between the hypothalamus, which releases gonadotropin-releasing hormone (GnRH); the anterior pituitary gland, which secretes luteinizing hormone (LH) and follicle-stimulating hormone (FSH); and the male and female gonads. Feedback from the released sex steroids is required to modulate HPG axis



GnRH release by kisspeptin and neurokinin B and indicates that these neuropeptides regulate the release of GnRH into the portal circulation and add to the complexity of the GnRH pulse generator. Kisspeptin and neurokinin B interact with GnRH neurons to regulate the release of GnRH into the portal circulation.

KNDy neurons A population of neurons in the ARC expresses kisspeptin, neurokinin B, and the opioid peptide, β -dynorphin. These neurons have been termed KNDy neurons, are upstream of GnRH neurons, and provide a major synaptic input to GnRH neurons. A high percentage of KNDy neurons is thought to express steroid hormone receptors, such as estrogen and progesterone receptors, metabolic hormone receptors, such as leptin, and GABA and glutamine receptors. Activation of ARC KNDy neurons stimulates pulsatile LH release, and studies suggest that kisspeptin and neurokinin B stimulate LH release, while β -dynorphin inhibits LH/GnRH release, supporting the hypothesis that KNDy neurons are responsible for pulsatile GnRH release. A differential response to kisspeptin on the HPG axis has been reported in men and women. In men, kisspeptin potently stimulates the release of LH, even at modest doses. However, in women, the effect of kisspeptin is variable and

dependent on the phase of the menstrual cycle, with the greatest effect occurring during the pre-ovulatory phase. This suggests that fluctuations in sex steroid milieu, as well as other mechanisms, such as changes in pituitary sensitivity to GnRH or the responsiveness of GnRH neurons to kisspeptin, affect the sensitivity to kisspeptin across the menstrual cycle [18, 19].

Hypothalamic-Pituitary-Gonadal Axis: **Puberty** Pubertal maturation and reproductive function rely on the appropriate regulation of LH pulse frequency. LH and GnRH release during the perinatal period is elevated and is often termed the perinatal surge. A sex difference has been reported in the perinatal surge, with males having a larger surge than females. In infants and children (<5 years), higher basal levels of GnRH and LH are detectable. However, this is transient, and GnRH and LH levels are subdued in mid-childhood (5–11 years). This suppression during mid-childhood is attributed to a central inhibition and thought to be mediated by GABA transmission. Precocious puberty is caused by early maturation of the HPG axis resulting in pulsatile secretion of GnRH and activation of the gonads. Puberty is initiated by an increase in the frequency and amplitude of GnRH release from the hypothalamus, presumably due to a loss of central inhibi-

bition. In females, between early puberty (prior to first menstruation) and mid-puberty (between first menstruation and first ovulation), GnRH release gradually increases due to a change in the amplitude and frequency of GnRH pulsatility. During this progression, the pattern of GnRH release begins to more closely mimic patterns seen in adulthood. In males, increased GnRH release stimulates LH release from the anterior pituitary, which increases testosterone secretion from the testes. Testosterone is responsible for the development of secondary sex characteristics in males (i.e., voice change, hair growth). GnRH-stimulated FSH release in males during puberty leads to spermatogenesis. Stimulatory neuromodulators (e.g., glutamate, kisspeptin) amplify pubertal GnRH release. Glutamate and kisspeptin levels increase during puberty, and the sensitivity of GnRH neurons to stimulatory signals increases after puberty onset. GnRH release during puberty appears to require the actions of the kisspeptin and neurokinin B networks [20].

Hypothalamic-Pituitary-Gonadal Axis

Reproductive Age: Females In females, gonadotropins control the function of the ovaries, including folliculogenesis, steroidogenesis, ovulation, and luteolysis. Estrogens and progestins synthesized from the ovaries provide a feedback mechanism to the hypothalamus and anterior pituitary to regulate the release of GnRH and gonadotropins resulting in the menstrual cycle. The frequency and amplitude of GnRH pulses during a 24-hour period vary in accordance with the stage of the menstrual cycle and production of estrogen and progesterone by the ovaries. The responsiveness of the anterior pituitary to GnRH and the ovaries to FSH and LH also varies across the menstrual cycle. Slower pulsatile release of GnRH leads to FSH secretion, while a faster GnRH pulse rate of one per hour stimulates LH release. FSH stimulates estrogen synthesis and the development of multiple follicles, while an increase in LH, known as the “LH surge,” triggers ovulation. In females, the HPG axis is under both negative and positive feedback control, which provides flexibility for the production of different ovarian environments necessary for folliculogen-

esis, ovulation, and pregnancy. Immediately prior to ovulation, during the late follicular phase of the menstrual cycle, estrogen-induced negative feedback changes to positive via mechanisms that are not completely understood, but likely involve steroid-sensitive inputs to GnRH neurons. Rising levels of estrogen increase the pulsatile release of GnRH which leads to an increase in LH and results in the LH surge. There is a corresponding increase in the sensitivity of the anterior pituitary to GnRH at this time. In the early and mid-follicular phase, in which the follicles in the ovary mature, and in the luteal phase, the phase that starts with the formation of the corpus luteum and ends in pregnancy or menses, low levels of estrogen inhibit GnRH release from the hypothalamus and LH release from the anterior pituitary. Progesterone levels are elevated during the luteal phase of the menstrual cycle, and the frequency of the pulsatile release of GnRH is reduced (~3–5 hours), which leads to FSH synthesis. Inhibin is released from follicular granulosa cells in response to stimulation by FSH and inhibits further FSH release [17, 21, 22].

Males In males, the hypothalamic GnRH release stimulates the anterior pituitary to release LH and FSH in a pulsatile manner. However, unlike in females, the GnRH pulse is relatively constant in frequency (every 90 minutes), amplitude, and duration, and regulated variations in GnRH pulsatile release do not play a significant role. The actions of LH and FSH on the testes are distinct. LH stimulates testosterone synthesis in Leydig cells of the testes. FSH acts on Sertoli cells in the testes to promote spermatogenesis. The Sertoli cells also produce inhibin, a hormone that is a potent and selective inhibitor of FSH release from the anterior pituitary. Testosterone exerts negative feedback control over hypothalamic GnRH. With rising levels of testosterone, GnRH release from the anterior pituitary is inhibited (decreased frequency and amplitude) and subsequently inhibits LH and FSH release. Testosterone also directly inhibits the release of LH by the anterior pituitary gland, and inhibin acts at the anterior pituitary to inhibit the secretion of FSH [17, 21–24].

Hypothalamic Regulation of Body Temperature

Temperature regulation is dependent on signals that are received externally and internally. External signals come from the environment and are detected through our skin, while internal signals are those that come from our brain, spinal cord, and viscera [25, 26]. The physiological responses to changes in body temperature (e.g., sweating, shivering, vasoconstriction, and vasodilation of arteries) are controlled by a sophisticated communication system that relies on signals from thermoreceptors located throughout the body. The signals that are transmitted by the thermoreceptors converge upon neurons located in the hypothalamus, specifically within the preoptic area (POA). The POA has been identified as the primary regulator of temperature homeostasis in the central nervous system [27, 28].

Preoptic area (POA): Synaptic inputs Neuronal populations within the POA that control body temperature homeostasis receive ascending synaptic signals from thermoreceptors that are located in the skin, viscera, and the spinal cord [29]. The efferent pathways from the periphery project to the central nervous system, which ascends into the lateral parabrachial nucleus prior to terminating in the POA. The lateral parabrachial nucleus is an essential relay site for the transmission of external thermoregulatory signals [30, 31]. Lesions in the lateral parabrachial nucleus will prevent the signals from reaching the POA and thus attenuate the responses sent by external signals to either warm or cool.

Thermosensitive neurons The temperature-sensitive neurons in the POA can be divided into two categories: warm or cold sensitive [32]. The majority of temperature-sensitive neurons in the POA are comprised of warm-sensitive neurons [25, 33]. The warm-sensitive neurons have been identified primarily in the ventromedial (vmPOA) and median (mPOA) area of the POA [34, 35]. At thermoneutral temperatures, warm-sensitive neurons are tonically active. However, changes in activity, above or below baseline level, can occur

when temperatures are warmed or cooled in the brain, skin, or spinal cord [36, 37].

The cold-sensitive neurons have been reported to receive GABAergic input from warm-sensitive neurons. Tan et al. [27] demonstrated that a majority of the warm-sensitive neurons investigated were GABAergic. Administering a GABA antagonist, such as bicuculline, resulted in a cold-defensive response. In addition, in response to cold challenges, the expression of GABA in the mPOA is reduced and results in an increase in activity of the cold-sensitive neurons [38]. Increased activation of this population of neurons results in an increase in brown adipose tissue thermogenesis and shivering [39–41]. Taken together these data demonstrate the significant role of these populations of neurons and their location within the POA that is responsible for body temperature homeostasis.

Synaptic outputs Once the POA receives thermal information from external and/or internal signals, neurons within the POA integrate these signals and dispense information that results in the maintenance or reestablishment of body temperature homeostasis. The POA uses a descending pathway which results in the signal exiting the central nervous system, traveling through the spinal cord, and ultimately activating circuits which can influence somatic motor neurons, sympathetic output, and parasympathetic output [42]. When generating heat via brown adipose tissue thermogenesis or shivering, data suggest that information leaves the POA and travels initially to the dorsal medial hypothalamus (DMH). Cold exposure activates DMH neurons. However, if the activity of these same neurons is blocked, the shivering and brown adipose tissue thermogenesis that occur during cold exposure are attenuated [43–45]. These data suggest that DMH neurons play a significant role in transmitting the cold-defensive response that is initiated by the POA. However, the DMH is not required to mediate the cooling signals that are initiated by the POA. The POA projects directly upon neurons located in the rostral ventral lateral medulla (RVLM) or the rostral ventral medial medulla. These locales then project into the intermediolateral nucleus (IML) of the spinal cord (Fig. 4.3).

Fig. 4.3 Hypothalamic Regulation of Temperature (Cold). Descending pathway from the preoptic area (POA) warms the body to maintain or reestablish body temperature homeostasis. Dorsal medial hypothalamus (DMH), rostral ventral lateral medulla (RVLM), third ventricle (3V)

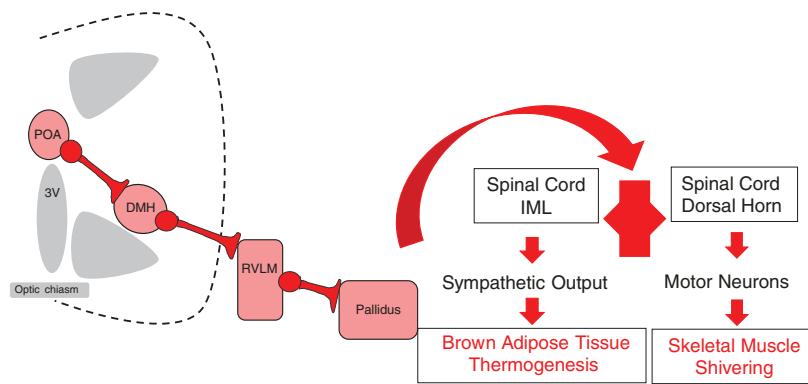
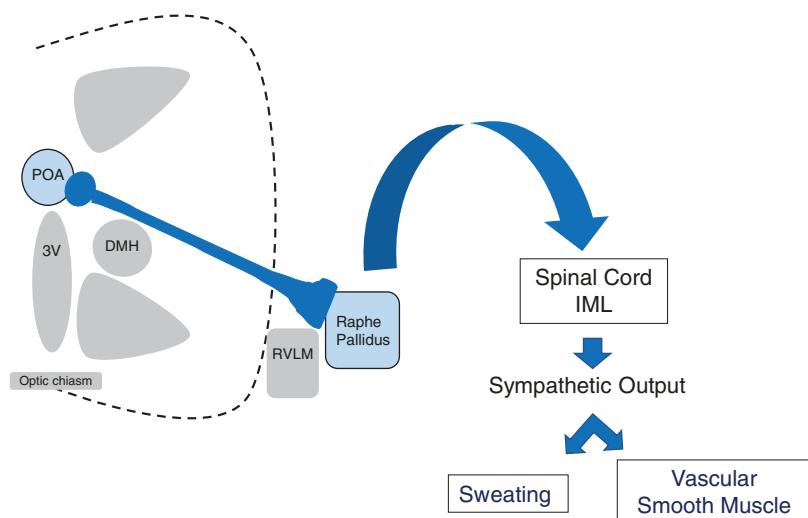


Fig. 4.4 Hypothalamic Regulation of Temperature (Warm). Descending pathway from the preoptic area (POA) cools the body to maintain or reestablish body temperature homeostasis. Dorsal medial hypothalamus (DMH), rostral ventral lateral medulla (RVLM), third ventricle (3V)



The signal to warm leaves the DMH and travels to the raphe pallidus (RPA) [46]. The rostral RPA has been described to be the final site within the central nervous system that receives thermoregulatory signals from the POA prior to descending into the spinal cord. The rostral RPA can receive signal via the DMH or directly from the POA. Signals from the rostral RPA activate preganglionic neurons in the ILM of the spinal cord which ultimately increase sympathetic activity (Fig. 4.4).

Hypothalamic Regulation of Water/Fluid Balance

The hypothalamus plays a pivotal role in maintaining homeostasis of water and fluid balance through the regulation of intake (thirst and salt

appetite) and output (renal excretion via neuroendocrine and autonomic function) relationships to determine body fluid homeostasis, blood volume, and blood pressure. Hypothalamic structures, including the lamina terminalis, supraoptic nuclei (SON), and paraventricular nuclei (PVN), are important in the regulation of thirst, salt appetite, and arginine vasopressin (AVP) secretion. Magnocellular neurosecretory neurons (MNCs) of the hypothalamic SON and PVN synthesize and secrete AVP and oxytocin (OXT) in response to peripheral signals generated by osmoreceptors and baroreceptors. There are over 100,000 MNCs in the human hypothalamus [47–55].

Hypothalamus and Neurohypophysis The posterior pituitary lies below the hypothalamus, with which it forms a structural and functional

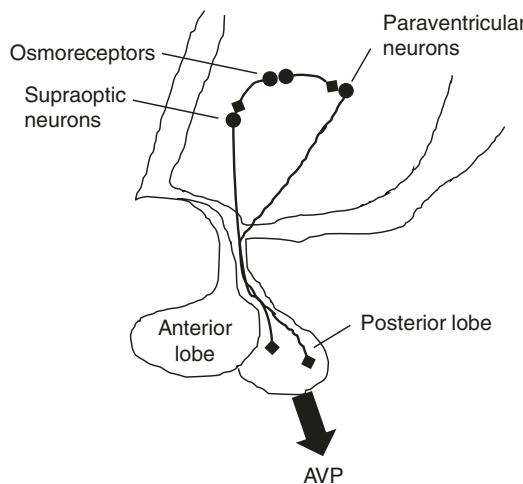


Fig. 4.5 Hypothalamic Regulation of Fluid Balance. Anatomy of the hypothalamus and pituitary gland depicting the pathways for arginine vasopressin (AVP) secretion

unit – the neurohypophysis. The neurohypophysis consists of three parts: SON and PVN of the hypothalamus, supraopticohypophyseal tract, and the posterior pituitary. The SON is situated along the proximal part of the optic tract. It consists of the cell bodies of discrete vasopressinergic and oxytotic MCN projecting to the posterior pituitary along the supraopticohypophyseal tract. The MNCs send axons to the posterior pituitary, where each axon branches into approximately 1800 neurosecretory terminals that abut fenestrated capillaries. The PVN also contains discrete vasopressinergic and oxytotic MCN, also projecting to the posterior pituitary along the supraopticohypophyseal tract. Vasopressinergic neurons of the PVN and SON are known to receive projections from the subfornical organ (SFO) and organum vasculosum of the lamina terminalis (OVLT) (Fig. 4.5).

Vasopressinergic neurons possess the intrinsic capacity to respond to changes in circulating osmolarity. The electrical activity of MNCs acutely isolated from the SON of adult rats or mice is increased by hypertonicity and inhibited by hypotonicity. Hyperosmotic stimuli excite the cells by increasing the activity of nonselective cation channels and thus causing membrane

depolarization, whereas hypoosmotic solutions inhibit MNCs through a hyperpolarization caused by a reduction in the basal activity of the nonselective cation channels. Unlike many other types of cells that partly regulate their volume when exposed to osmotic stress, OVLT neurons and MNCs have been shown to display passive osmometry in that they display changes in soma volume varying as an inverse function of extracellular fluid osmolality and can be maintained without adaptation during perturbations lasting ≥ 60 min.

Osmoreceptors The process of systemic osmoregulation is of vital importance for the organism because significant changes in cell volume caused by acute changes in extracellular fluid osmolality can cause severe organ injury. Notably, changes in plasma osmolarity ($p\text{Osm}$) are mirrored by changes in cerebrospinal fluid (CSF) osmolality and can therefore induce lethal neurological trauma. The hypothalamus contains neurons that function as osmoreceptors that are important in the thirst mechanism and the regulation of AVP release. The lamina terminalis is located along the median rostral border of the third ventricle. The lamina terminalis, consisting of the component nuclei of the SFO, OVLT, and median preoptic nucleus (MnPO), is considered to seat central osmoreceptors that can detect elevations in plasma or CSF osmolality by dehydration or high dietary NaCl to stimulate thirst and AVP secretion and regulate blood pressure. All three regions of the lamina terminalis are involved in osmoregulation. Many different factors (e.g., reduced arterial pressure, temperature, pain) can influence the release of AVP from the posterior pituitary, but the osmotic regulation of AVP secretion is one of the most finely tuned homeostatic mechanisms.

The SFO and OVLT are distinguished as sensory circumventricular organs. These nuclei contain dense capillary cores characterized by a fenestrated endothelium that results in an incomplete blood-brain barrier and increased vascular permeability. Specialized third ventricular ependymocytes, known as tanycytes, project pro-

cesses that surround these fenestrated vessels and express tight junction proteins that are thought to regulate vascular permeability within these structures. Alongside the vascular core of these structures reside astrocytes and the neuronal soma responsible for downstream neurotransmission. The SFO, MnPO, and OVLT project to hypothalamic SON and PVN to subsequently regulate AVP secretion and central sympathetic neurocircuitry. Downstream projections from the SFO and OVLT through thalamicocortical circuits and the bed nuclei of the stria terminalis are thought to regulate thirst and salt appetite.

The primary set of central osmoreceptors resides in the OVLT. Systemic hyperosmolality is associated with an increase in thirst and AVP release to increase the intake and retention of water. Lesions of OVLT blunt thirst and AVP secretion in response to hypernatremia, whereas hyperosmotic stimuli activate OVLT neurons. OVLT neuron osmoreceptor function is thought to be mediated by the mechanosensitive transient receptor potential vanilloid 1 (TRPV1) and/or TRPV4 expressed on the surface of these neurons that conduct a nonselective cationic current upon cell shrinkage or elevations in temperature. Increases in pOsm increase plasma AVP concentrations in a linear manner. SON neurons become depolarized when exposed to hyperosmolar solutions. Hyperosmolality stimulates AVP synthesis via TRPV cation channels, localized in the OVLT, SFO, AP, and NTS, that are able to convert pOsm changes into electrical signals enhancing action potential discharge and generating a current transported to SON and PVN.

An increase in water intake will lower pOsm and suppress thirst to reduce water intake and inhibit AVP release to promote water excretion by the kidney. Hypoosmotic stimuli were found to cause hyperpolarization because of the suppression of a nonselective cation current. All cells respond to dehydration or to hyperhydration by changing volume, but cells of the SFO, OVLT, and MnPO of the hypothalamus are “perfect” osmoreceptors; that is, their changes in volume are maintained as long as the osmotic stimulus persists. Cell shrinking during dehydration is mechanically coupled to the activation of TRPV1

channels through a densely interwoven microtubule network present only in osmosensitive cells, including excitatory thirst neurons from the SFO bearing angiotensin II receptors. This coupling allows dehydration and decreased systemic volume stimuli to be integrated because SFO neurons are outside of the blood-brain barrier. Systemic hypoosmolarity might be perceived by TRPV4 channels. These neurons integrate osmolar status with additional endocrine signals reflecting circulating volume status through the action of angiotensin II, relaxin, and atrial natriuretic peptide (ANP) via peptide-specific receptors in the SFO and OVLT. Angiotensin II and relaxin excite both OT and AVP MCNs. In contrast, ANP inhibits AVP neuron activity. Studies that combined neuroanatomical tracing and detection of *c-fos* expression in response to angiotensin II or relaxin suggest that both of these circulating peptides act on neurons within the dorsal cap of the OVLT and the periphery of the SFO to stimulate AVP release. AVP neurons themselves have independent osmosensing properties, and AVP receptors are present on vasopressinergic neurons of both the PVN and SON, highlighting the potential for auto-control of AVP release through direct osmoregulation and short loop feedback.

Peripheral signals controlling AVP secretion originate from cardiac and aortic baroreceptors and are carried to the central nervous system via the glossopharyngeal and vagus nerves, which project to, and synapse in, the nucleus tractus solitarius (NTS) of the dorsal medulla oblongata. Neurons in this nucleus are closely connected with cardiovascular function and may affect the electrical activity of hypothalamic vasopressinergic neurons of SON and PVN. Cardiopulmonary and arterial baroreceptor afferents projecting to the NTS act tonically to inhibit AVP release. Thus, the ablation of NTS removing this inhibition induces AVP release. There is evidence that SON and PVN receive dopamine (DA)-ergic inputs from pathways that originate in the arcuate and periventricular nuclei. These data indicate that DA induces AVP release by hypothalamic neurosecretory neurons acting through D2 receptors. Noradrenergic (NA)-ergic projections origi-

nating in the locus coeruleus and in the lateral tegmental area, which ascend together in the dorsal NAergic bundle, modulate the AVP response to hypovolemia. Electrophysiological studies on the role of the A1 and A2 NAergic cell groups of the caudal medulla in regulating the activity of hypothalamic AVPergic neurons showed that stimulation of A1 and A2 region enhanced the activity of AVP-secreting neurons. The A1 pathway transmits hemodynamic information to hypothalamic AVP cells by releasing several neurotransmitters and/or neuropeptides as ATP, NA, NPY, and substance P. There is evidence that serotonin (5-HT) may play a role in the mechanisms controlling thirst and water balance. This suggests that central 5-HT transmission is necessary for the hormone response to osmotic stimuli. Electrophysiological studies suggest that a GABAergic pathway arising from the diagonal band of Broca of the limbic system innervates AVP-secreting neurons of the SON. In fact, stimulation of the diagonal band evokes a reduction in the excitability of AVP-secreting neurons. AV3V region, a forebrain area subserving salt-water balance, might be also involved in GABA-AVP interaction. Cholinergic neurons gained through the immunohistochemical application of antibodies against the ACh biosynthetic enzyme (choline acetyltransferase (ChAT)) have been observed in the SON and PVN, among the axons of the hypothalamic-neurohypophysial tract and among pituicytes of the posterior pituitary. Several data indicate that the integrity of CVOs is essential for the transmission of information, concerning pOsm, from the periphery to vasopressinergic neurons of SON and PVN. These data might indicate that CVOs inform SON and PVN to synthesize AVP in response to dehydration, whereas MVS nuclei might regulate axoplasmic transport of AVP to posterior pituitary; therefore, AVP release might be under the synergistic control of CVOs and MVS nuclei.

Isolated rat MNCs respond to increases or decreases in external $[Na^+]$ by generating depolarizing and hyperpolarizing receptor currents, respectively. Thus, physiologically relevant increases in external $[Na^+]$ enhance the relative permeability of stretch-induced cation channels to

Na^+ . The findings indicate that MNCs are endowed with mechanisms to allow local detection of changes in either extracellular $[Na^+]$ or osmolality. Osmotic stimuli delivered in the absence of changes in external $[Na^+]$ effectively modulate the activity of stretch-induced cation channels and yield proportional osmoreceptor potentials and changes in firing rate in MNCs. Analogously, in the absence of osmotic perturbation, changes in $[Na^+]$ can provoke receptor currents as a result of changes in driving force and relative Na^+ permeability through stretch-induced cation channels. Although AVP secretion depends on synaptic inputs originating from other osmo-regulatory neurons, MNCs themselves currently provide a comprehensive model for signal detection and integration at the cellular level.

Arginine Vasopressin: AVP Peptide AVP is a mammalian peptide that has been evolutionarily conserved and appears to precede the bifurcation of the vertebrate and invertebrate lineages. The nonapeptide, AVP, is a small hormone (MW – 1080), also known as antidiuretic hormone (ADH), is synthesized by the MCNs chiefly in the SON and PVN of the hypothalamus. AVP production within the hypothalamus is encoded, along with two associated proteins, neurophysin II, and a glycopeptide, copeptin. The AVP gene, composed of three exons (coding for AVP and neurophysin II), and the OXT gene (coding for oxytocin and neurophysin I) are located in the same chromosome region 20p13, at a very short distance from each other. AVP is produced as the precursor prepro-AVP, composed of 164 amino acids, packaged into neurosecretory granules and transported axonally in the stalk to the posterior pituitary. The synthesis of AVP involves precursor peptides prepro-AVP and provasopressin (proAVP) that are enzymatically cleaved into the AVP, NPII, and glycopeptide copeptin and stored for secretion. These three products are all released into the circulation in equal ratios (Table 4.1).

AVP Synthesis Synthesis of the AVP and OXT precursors occurs in the cell bodies of discrete vasopressinergic and oxytotic MCN within the SON and PVN of the hypothalamus. MNCs each

Table 4.1 Parameters and effects of arginine vasopressin (AVP), antidiuretic hormone (ADH)

Origin	Hypothalamic neurons Released from posterior pituitary
Chemical nature	9-amino acid peptide
Transport in the circulation	Dissolved in plasma
Half-life	15 min
Factors affecting release	↑ Osmolarity (hypothalamic osmoreceptors) ↓ Blood pressure or volume (carotid, aortic, atrial receptors)
Target cells or tissues	Renal collecting duct
Receptor/second messenger	V ₂ receptor/cAMP
Tissue action	Increases renal water reabsorption
Action at cellular-molecular level	Inserts AQP2 water pores in apical membrane

project a single axon caudally and medially to collect in the hypothalamic-neurohypophysial tract, which courses through the internal zone of the median eminence to the posterior (neural lobe of the) pituitary gland (the neurohypophysis) where OXT and AVP are secreted into the general circulation.

Increased firing frequency of vasopressinergic and oxytotic neurons opens voltage-gated Ca²⁺ channels in these nerve terminals. This, in turn, leads to transient Ca²⁺ influx, fusion of the neurosecretory granules with the nerve terminal membrane, and release of the hormone and its neprilysin into the systemic circulation in equimolar quantities. Secretion of OXT and AVP from axon swellings and terminals in the posterior pituitary gland occurs by exocytosis of dense-core vesicles in response to action potential invasion of the neurosecretory membrane. Once released into the extracellular space, the hormones enter the general circulation by diffusion through fenestrated capillaries in the posterior pituitary gland. Because the neurohypophysis lacks a blood-brain barrier, secreted peptides gain immediate access to the systemic circulation.

AVP secretion Plasma AVP secretion is regulated by two physiological parameters – pOsm

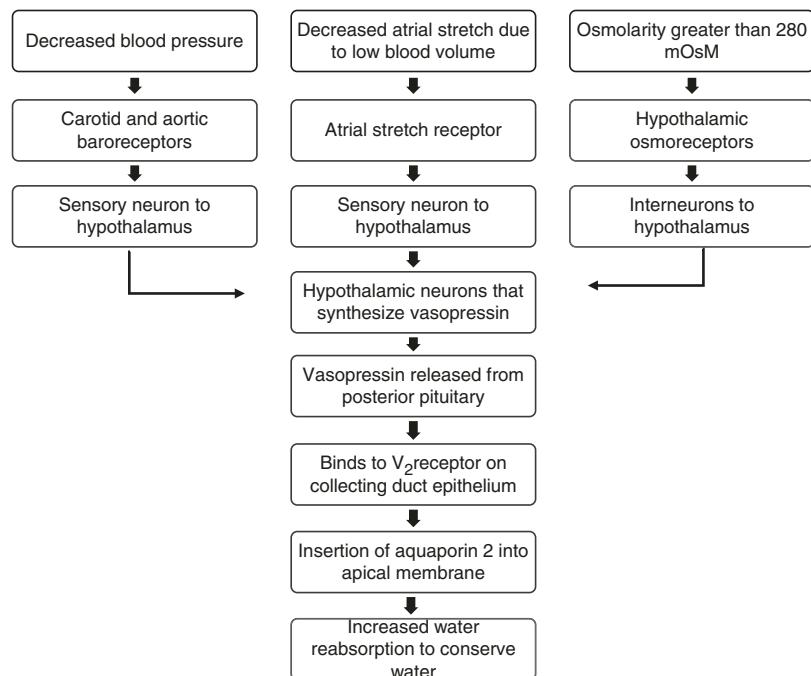
and blood volume. An increase in pOsm or a loss of blood volume leads to the activation of both MNC and presynaptic PVN neurons, resulting in the concurrent systemic release of OXT and AVP, along with an increase in sympathetic outflow to the kidneys. These two complementary PVN outputs act in concert at the level of the kidneys to properly modulate water and Na⁺ reabsorption/excretion, restoring fluid and electrolyte homeostasis.

AVP is packaged into vesicles and shipped via fast axonal transport to nerve endings. MNC axon terminals are tightly packed with dense-core (neurosecretory) vesicles that contain AVP, as well as a distinct population of microvesicles that contain glutamate. Hormone secretion is controlled by changes in electrical activity. The control of AVP secretion is achieved primarily through the regulation of the rate at which action potentials are discharged by MNC somata. The axon terminals of MNCs cannot fire repetitively in response to sustained depolarization, but can be excited at high frequencies by repetitive axon stimulation.

Various factors can modulate stimulus-secretion coupling at MNC terminals in the posterior pituitary gland, including ionic conditions purines and neuropeptides. Frequency facilitation of AVP release is maximal at approximately 13 Hz, and sustained higher-frequency stimulation results in less AVP release. Frequency facilitation of hormone release has been ascribed to increased calcium entry through voltage-gated channels to enhance exocytosis, as a consequence of action potential broadening during high-frequency firing, depolarization as a result of the accumulation of potassium in the extracellular space, and a progressively more extensive invasion of the neurosecretory terminal field in the posterior pituitary gland.

The osmotic control of AVP release is an integrated process, and there are a variety of extrinsic and intrinsic factors involved in the osmotic modulation of firing rate and AVP secretion by MNCs. The osmotic control of MNCs results from an interplay between intrinsic properties, paracrine actions of surrounding glia, and the influence of extrinsic synaptic inputs. Therefore, changes in AVP release induced during changes in pOsm are mediated via

Fig. 4.6 Control of Vasopressin Secretion. There are three stimuli that control vasopressin secretion: plasma osmolarity, blood volume, and blood pressure. Vasopressin released from the posterior pituitary acts on V_2 receptors in the collecting duct of the kidney to cause insertion of aquaporin 2 into the apical membrane to increase water permeability



the control of action potential discharge by MNC somata. Under basal (isotonic) conditions, MNCs fire action potentials at a slow rate, and this activity is inhibited by hypoosmotic and enhanced by hyperosmotic conditions (Fig. 4.6).

AVP Plasma Levels The osmotic control of AVP secretion plays a key role in systemic osmoregulation because of its ability to stimulate water reabsorption by the kidney. AVP has a very short biological half-life (about 3 min), and it is cleared mostly by filtration in the kidneys. Accordingly, its effects are very prompt and promptly reversible. The relationship between pOsm and plasma AVP concentrations has been determined. The concentration of AVP in the blood rises in proportion with pOsm above a threshold of ~280 mosmol kg⁻¹. At pOsm of 280 mOsm/kg, plasma AVP levels are in the range of 0.5–1.5 pg/ml, which is sufficient to promote significant water reabsorption from the kidney. Changes in pOsm of only 1% (about 2.8 mOsm/kg) are sufficient to increase plasma AVP concentration by about 1 pg/ml. On the other hand, the “threshold” at which volume depletion stimulates AVP release is about 3% of plasma volume reduction.

The concentration of AVP in the circulation is reduced when pOsm declines, thereby promoting diuresis and a regulatory enhancement of pOsm. Conversely, increases in pOsm enhance the concentration of AVP, thereby increasing water reabsorption and promoting a homeostatic reduction in pOsm. Together with adaptive changes in thirst, feedback adjustments in AVP secretion mediated by changes in pOsm provide the core mechanisms responsible for systemic osmoregulation in mammals.

AVP Functions AVP is the principal endocrine regulator of renal water excretion, facilitating adaptive physiological responses to maintain plasma volume and pOsm. The primary function of AVP is to maintain body fluid balance by keeping pOsm within narrow limits and allowing the kidneys to adapt water excretion to the body’s needs, in conjunction with thirst. AVP regulates water homeostasis via a dual effect: regulating the fast shuttling of aquaporin 2 (AQP2) to the cell surface and stimulating the synthesis of mRNA encoding AQP2.

Although AVP has multiple actions, its principal physiological effect is in the regulation of

water resorption in the distal nephron, the structure and transport processes of which allow the kidney to both concentrate and dilute urine in response to the prevailing circulating AVP concentration. Following binding to AVP V2 receptor in the kidney, AVP increases the water permeability of the principal cells of the late distal convoluted tubules and the entire collecting ducts (CD), thereby enhancing water reabsorption. AVP increases water permeability by promoting the insertion of AQP2-rich vesicles in the luminal membrane of the CD cells and is the water channel responsible for AVP-dependent water transport from the lumen of the nephron into the CD cells. The presence of AQP2 in the wall of the distal nephron allows resorption of water from the duct lumen along an osmotic gradient and excretion of concentrated urine. This allows an increase in water reabsorption when a favorable osmotic driving force is present. In addition, AVP exerts two other effects on the CD through V2R. (i) In the cortical and outer medullary CD, AVP stimulates sodium reabsorption by its action on the luminal sodium channel (ENaC). This drives water isoosmotically and thus helps concentrate all other solutes in the lumen. (ii) In the terminal inner medullary CD, AVP increases the permeability to urea by activating the facilitated urea transporters UT-A1 and UT-A3. This allows concentrated urea to diffuse in the medullary interstitium and thus maintain in the interstitium a high urea concentration that favors water reabsorption. In the thick ascending limb, AVP stimulates the Na-K-2Cl cotransporter, NKCC2, and thus promotes sodium reabsorption. But, this effect requires a higher concentration of the hormone than that on the CD. Altogether, these combined effects on several membrane transporters and channels contribute jointly to urine concentration.

AVP-dependent blood pressure regulation is multimodal. Reductions in circulating volume stimulate AVP release. Falls in arterial blood pressure of 5–10 per cent are necessary to increase circulating AVP concentrations in man. Progressive reduction in blood pressure produces an exponential increase in plasma AVP, in contrast to the linear increases of osmoregulated

signals due to hypovolemic stimuli originating from baroreceptors located in the carotid sinus, aortic arch, and left atria, which are carried to SON and PVN via the glossopharyngeal and vagus nerves that synapse in the NTS. Ascending projections are via the NTS in the brainstem.

AVP Receptors The actions of AVP are mediated by the activation of specific G-protein-coupled receptors currently classified into three types: V1, vascular smooth muscle cells (V1); V2, renal collecting duct (V2); and V3, pituitary (V3) AVP receptors. Renal V2 receptors mediate AVP-induced water permeability. V2 receptors are localized in the principal cells of the CD and, to a lesser extent, in the thick ascending limb of the loop of Henle. The kidney V2R is exquisitely sensitive. AVP is also a potent vasoconstrictor agent, and it is involved in the control of affective behavior, memory process, and thermoregulatory mechanisms. The biological effects of arginine AVP are mediated by three receptor subtypes: the V1a and V1b receptors that activate phospholipases via Gq/11-mediated phospholipase C activation (Ca^{2+} , inositol triphosphate & diacylglycerol mobilization) and the V2 receptor with Gs-mediated adenylate cyclase activation (cAMP production & protein kinase A stimulation).

Hypothalamic Regulation of Blood Pressure

The hypothalamus plays an integral role in regulating the homeostasis of several physiological systems. To date, we know that the primary region within the hypothalamus that plays a role in regulating blood pressure is the paraventricular nucleus (PVN). The neuronal network that exists within this locale receives and sends signals within the central nervous system, the spinal cord, and the kidneys. This transmission of information through the PVN plays an integral role in regulating blood pressure homeostasis (Fig. 4.7).

Paraventricular Nucleus and Blood Pressure Regulation The PVN consists of presympa-

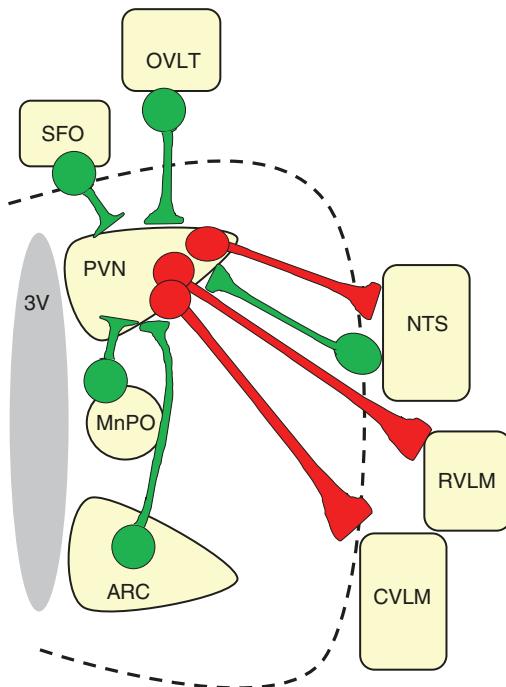


Fig. 4.7 Hypothalamic Control of Blood Pressure. Communication received by (green) and sent from (red) the paraventricular nucleus (PVN). The PVN receives neural signals from the subfornical organ (SFO), organum vasculosum lamina terminalis (OVLT), arcuate nucleus (ARC), nucleus tractus solitarius (NTS), and the median preoptic nucleus (MnPO). Information is integrated in the PVN and relayed to the rostral ventral lateral medulla (RVLM), caudal ventral lateral medulla (CVLM), and NTS. This relay of information controls sympathetic outflow to the periphery and augments blood pressure

thetic neurons that regulate sympathetic output to the heart, the kidneys, and the adrenal medulla [56]. Retrograde and anterograde tracings have demonstrated that this population of neurons utilizes an intricate communication system [57–59]. Synaptic projections allow neurons within the PVN to receive and coordinate signals from the subfornical organ (SFO), organum vasculosum lamina terminalis (OVLT), arcuate nucleus (ARC), nucleus tractus solitarius (NTS), and the median preoptic nucleus (MnPO). After receiving communication from these locales within the central nervous system, PVN neurons can integrate these signals and relay this information to the rostral ventral lateral medulla (RVLM), caudal ventral lateral medulla (CVLM), and to the NTS [56, 60, 61]. This relay of communication

allows these presynaptic neurons within the PVN to regulate sympathetic outflow to the periphery, which ultimately influences blood pressure.

The intricacy of the communication that exists among neurons within the PVN is further enhanced by the responsibility that each subgroup of presynaptic neurons have in regulating blood pressure. Subpopulations of presynaptic neurons within the PVN are organized based on their ability to regulate sympathetic activity to the kidneys, regulate sympathetic activity to the heart, or regulate the release of hormones such as vasopressin, oxytocin, and corticotrophin-releasing hormone [62, 63].

Neurotransmitters play a role in controlling blood pressure by regulating, in part, the activity of presynaptic neurons within the PVN. The impact that these neurotransmitters have on PVN neurons results in a tonic level of inhibitory and excitatory inputs that helps in blood pressure maintenance.

GABA and glutamate GABA and glutamate are the predominate inhibitory and excitatory neurotransmitters in the brain [64, 65]. The influence of each of these neurotransmitters on presynaptic neurons within the PVN has been demonstrated. Although excitatory (i.e., glutamatergic) and inhibitory (i.e., GABAergic) inputs to PVN neurons are ubiquitous [66–70], the tonic influence that GABAergic synaptic inputs have on these neurons exceeds that of glutamatergic inputs in basal conditions [71, 72]. This observation was determined by blocking GABA_A receptors with bicuculline which significantly increased the excitability of presynaptic PVN neurons [73, 74]. These data suggest that PVN neurons are inactive under basal conditions due to the inhibitory influence of the GABAergic tone. Once removed (i.e., GABAergic tone), the underlying excitatory input from glutamate can augment the activity of these neurons which increases sympathetic activity and ultimately causes blood pressure to increase. Utilizing hypertensive animal models, studies demonstrate that GABAergic influence on presynaptic

neurons in the PVN is diminished in these models [67, 75–77]. These data suggest that the lack of GABAergic inhibition on presynaptic neurons in the PVN is contributing to the elevated blood pressure.

Nitric Oxide Nitric oxide (NO), a gas, has been described as a “nonconventional neurotransmitter” in the central nervous system [78]. Neurons that contain nitric oxide synthase (nNOS), an enzyme that synthesizes NO, are highly populated in the PVN [79, 80]. Li et al. [81] demonstrated that NO plays an important role in augmenting the transmission of GABA from the PVN. When inhibitors of NO were administered into the PVN, it resulted in an increase in neuronal activity. Activation of these neurons initiated steps which resulted in an increase in renal sympathetic nerve activity, blood pressure, and heart rate [82, 83]. These studies suggest that NO augments the release of GABA in the PVN by binding to GABA_A receptors. Nitric oxide’s ability to increase GABA release resulted in its ability to inhibit the release of the excitatory neurotransmitters glutamate and angiotensin II within the PVN.

Arcuate Nucleus and Blood Pressure Regulation In addition to the PVN, the ARC is a hypothalamic site containing neurons which project to and receive synaptic input to the kidneys and cardio-regulatory sites within the central nervous system including the PVN, SFO, NTS, and the RVLM [84, 85]. The ARC contains several neuronal populations that are identified by the neuropeptides and neurotransmitters they express. These neuronal populations are involved in numerous physiological functions that are discussed in greater details in other sections of this book.

Neuronal Activity Chemical stimulation of neuronal populations within the ARC can invoke an increase or decrease in blood pressure and sympathetic activity [86, 87]. The physiological responses that occurred were dependent on the baseline blood pressure of the model used and whether their baroreceptors were intact. The cardiovascular responses that occur in response to

stimulation of neurons within the ARC are mediated by signals that are received from the PVN [86]. This relay of information from the PVN to the ARC appears to rely on the GABAergic tone. Neurons within the ARC contain GABA receptors [88, 89], and neurons which project from the PVN to the ARC are GABAergic. When GABA_A receptors were inhibited or activated in the ARC, changes in blood pressure were also elicited. Administering a GABA_A receptor antagonist in the ARC increased, while administering a GABA_A receptor agonist, decreased blood pressure, sympathetic activity, and heart rate [90]. However, the decrease in blood pressure, sympathetic activity, and heart rate was attenuated when GABA_A receptors in the PVN were blocked [86]. Taken together, these data suggest an integral role of neurons in the ARC to sense and relay cardiovascular signals directed by presynaptic neurons located in the PVN. Although data have not been reported, one can postulate that the ARC also senses and relays information from other cardiovascular sites that project onto neurons located in the ARC. The signals that are relayed by the ARC could play an integral role in blood pressure maintenance.

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Neuroendocrinology of the Hypothalamus and Pituitary Axes

5

Trung Nam Tran, Max Sosa Pagan,
and Gabriel I. Uwaifo

Introduction

Neuroendocrinology is the scientific discipline that encompasses the interactions and interrelationships between neural and endocrine systems. While this interaction is now appreciated to occur in various organ systems of the human body, nowhere else is this interplay more intimate than in the hypothalamus and pituitary axes. This process involves at least two distinct processes:

1. The neural regulation of hormonal secretions in classic endocrine, paracrine, eccrine, and autocrine fashions
2. The effects of peripheral hormones on various neurophysiologic, neurobehavioral, and neuropsychiatric processes. While this is by no means exhaustive in its depth and scope, this

T. N. Tran (✉) · M. S. Pagan

Department of Endocrinology, Diabetes, Metabolism and Weight Management, Ochsner Medical Center, New Orleans, LA, USA
e-mail: trung.tran@ochsner.org;
max.sosapagan@ochsner.org

G. I. Uwaifo

Department of Endocrinology, Diabetes, Metabolism and Weight Management, Ochsner Medical Center, New Orleans, LA, USA

The University of Queensland,
Brisbane, QLD, Australia

The University of Queensland, Ochsner Clinical School, New Orleans, LA, USA
e-mail: gabriel.uwaifo@ochsner.org

chapter aims to provide a global look at the major aspects of the neuroendocrine functions and interactions of the human hypothalamus and pituitary axes.

Neuroendocrinology as a discipline is relatively young and developed as an offshoot from traditional endocrinology and classic neurology in the mid-twentieth century from a growing appreciation of the multiplicity of neurohormones produced by various neurons, nuclei, and areas of the brain that have both local and systemic effects essentially elevating the brain to the status of being an endocrine organ. Furthermore, the increasing appreciation of the effects of various peripheral and systemic circulating hormones on brain function, neural development, and behavior similarly has seen the growth and recognition of the nascent field of behavioral neuroscience. This will be delved into in more depth and scope in the chapter on the neuropsychiatric and neurobehavioral syndromes of the hypothalamus.

Neuroendocrine systems include the unique endocrine glands, neurosecretory neurons, adjunctive non-endocrine tissues, neurochemicals, neurocircuits, hormones, and other humoral signals that in coordinated integrated fashion provide regulatory and functional control of defined physiologic and behavioral processes.

Neurosecretion: Central to an understanding of neuroendocrinology as a whole is an understanding of neurosecretion as a unique form of endocrine functionality distinct to neurologic systems. Neurosecretion entails the production and secretion of hormones by neurons (so-called neurohormones) and their consequent action on target tissues and organ systems. This novel concept was first firmly demonstrated by Scharrer and colleagues in work they did in fish but has since been demonstrated to be virtually universal in various animal- and plant-based species [1].

These neurosecretory cells are distinct and different from the more typical neuronal cells that communicate via local neurotransmitters across neuronal terminal junctions as the central basis for more traditional communication across central neuronal systems of the brain and between the peripheral neuronal system and its various effector cells, tissues, and organ systems. The hypothalamus is the major relay coordinating hub for the brain-based neurosecretory systems, while the pituitary gland is its major effector target organ. The neurosecretory cells distinct from the traditional neuronal cells secrete their hormonal products at neurovascular junctions, and these have two major final effector pathways mediated via the pituitary: the adenohypophysis (the anterior pituitary) and the neurohypophysis (the posterior pituitary) [2, 3].

The adenohypophyseal system as will be further described below entails the release of neurohormones which are hypothalamic releasing and inhibitory factors from the median eminence of the hypothalamus into the hypothalamo-hypophyseal portal circulatory system that then ferries them to their target effector endocrine cells in the adenohypophysis from where various other effector hormones are secreted into the systemic circulation for various end-organ effects.

For the neurohypophyseal system as further described below, the neurohormonal neurosecretion of mainly oxytocin and vasopressin again occurs at neurovascular junctions, but here the neurosecretion occurs directly into the neurohypophyseal systemic circulation to again result in systemic effects at various target organ systems.

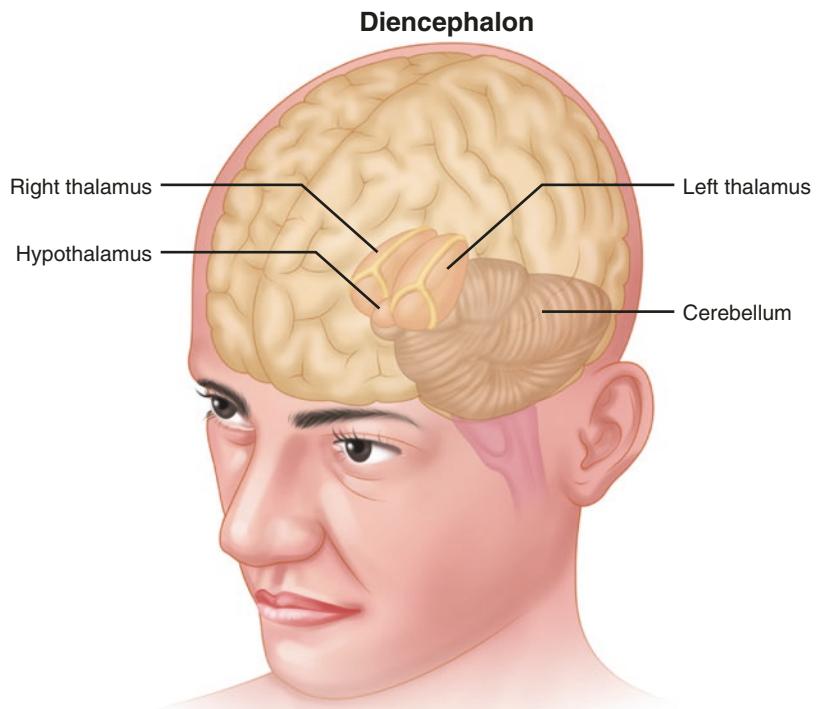
Neuroendocrinology of the Hypothalamic Axis

While the details of the neuroanatomy and topography of the hypothalamus and pituitary will be discussed in other chapters, some basic familiarity with this is important to an understanding of the neuroendocrinology of both the hypothalamic and pituitary axes. Suggestions regarding the integrative role of the hypothalamus in endocrine, autonomic, neuronal, and behavioral responses date to the second to eighteenth centuries A.D. Though in actual mass the hypothalamus constitutes ~2% of the total brain volume, its importance to normal physiology is underlined by the marked morbidity and mortality known to be associated with diseases that disrupt its normal function and interactions with the brain and other organ systems. The range of physiologic processes the hypothalamus is involved in regulation is extensive and includes (but is not restricted) autonomic, neurosecretory, and motor regulation of metabolism, energy balance, reproductive behavior and function, food and fluid intake regulation, lactation, aggression and social behavioral modulation, pregnancy modulation, thermoregulation, circadian and internal clock rhythmicity and regulation, as well as the sleep-wake cycle among others.

As the name implies, the hypothalamus is broadly meant to include the portion of the forebrain (diencephalon) below the thalamus. Its Greek derivative translates to hypo (below) the thalamus (bed). Figure 5.1 shows the spatial relationship of the hypothalamus to the thalamus and rest of the major brain structures. The diencephalon includes broadly all the brain structures on either side of the third ventricle including the thalamus, hypothalamus, epithalamus, and subthalamus. Because of the close neuronal interaction between the nuclei in all these structures, many include all of them in discussions of functional neuroanatomy and neurophysiology of the hypothalamus.

To better understand the place of the hypothalamus in the organization and spatial arrangement of the brain, it is important to remember that human brain embryologically begins as an ectodermally derived neural tube which orga-

Fig. 5.1 Spatial schematic of the diencephalon relative to the rest of the brain



nizes into three main vesicles at ~ the third week of embryologic development. These are the forebrain (prosencephalon) which ultimately develops into the telencephalon (cerebral hemispheres) and the diencephalon; the midbrain (mesencephalon) which includes the tectum, the cerebral aqueduct, corpora quadrigemina, the tegmentum, and the cerebral peduncles; as well as the hindbrain (rhombencephalon) which includes metencephalon (that develops to become the pons and cerebellum) and the medulla oblongata.

The epithalamus includes the anterior and posterior paraventricular nuclei, the medial and lateral habenular nuclei, the stria medullaris thalami, the posterior commissure, and the pineal gland.

As applies to the pituitary gland, the embryologic development of the hypothalamus is a complex carefully orchestrated process with highly regulated sequential events that are mediated and propelled by a series of transcription factors. The details of this intricate process are beyond the scope of this chapter, but it is important to be aware of the major transcription factors involved

in this process. The expression of these factors is also known to be epigenetically modulated by various environmental stimuli prominent among which are sex steroids and peripheral satiety signals such as the hormone leptin [4, 5]. There are also several recognized clinical examples that demonstrate both paternal and maternal differential epigenetic imprinting of the expression of some of these genes in the developing hypothalamus.

Among the major genes and transcription factors thus far identified are BM-1, BM-2, and BM-4 (involved in development of the paraventricular nucleus, the supraoptic nucleus, the periventricular nucleus, the preoptic area, mamillary nuclei, and the posterior hypothalamus). DLX-1 is involved in the development of the tuberal hypothalamus, while VgII2, SF-1, Sox14, and Satb2 are involved in the development of the ventromedial nucleus. Gsh-1 and Mash 1 are involved in the development of the arcuate nucleus and the ventromedial nucleus, while OTP is involved in the development of the paraventricular nucleus and supraoptic, periventricular, anterior hypothe-

lamic, and arcuate nuclei as well as the preoptic area. rPtx-2 is involved in the development of the tuberal hypothalamus and mamillary nuclei, while Sim-1 involved in the development of the paraventricular and supraoptic nuclei. Fkh5 is also involved in the development of the mamillary nuclei, while Tst-1 is involved in the development of both the mamillary nuclei and the posterior hypothalamic nucleus. Other genes and their transcription factor products like Fezf-1, Nkx2-2, COUP-TFII, etc. are also involved in this very complex process, but their exact topographic localization is still not fully elucidated [4–7].

The hypothalamus can be topographically subdivided into the anterior (ventral), mid, posterior (dorsal), medial, lateral, and paraventricular zones/regions with distinctive nuclei present in each of these regions.

The hypothalamus is strategically located as an intermediate coordinating hub that mediates homeostatic control over endocrine, autonomic, and behavioral processes. It achieves this via its extensive connections to the pituitary gland, the limbic system, and the cortical system and structures.

The anterior portion of the hypothalamus includes the supraoptic (SON), paraventricular (PVN), suprachiasmatic (SCN), and anterior hypothalamic nuclei (AHN). The periventricular nucleus (PeVN) begins anteriorly but extends caudally.

The middle portion of the hypothalamus includes the arcuate (AN), ventromedial (VMN), dorsomedial (DMN), and lateral hypothalamic nuclei (LHN). The posterior portion of the hypothalamus includes the posterior hypothalamic (PHN) and premamillary nuclei (PMN).

The broad anterior to posterior spatial relationships of these nuclei are depicted in Figs. 5.2 and 5.3.

The medial to lateral orientation of the hypothalamic nuclei is best visualized in coronal views of the brain and underlines the duality of each of the respective nuclei in each of the brain hemispheres with the third ventricle as the defining central divider. The periventricular zone

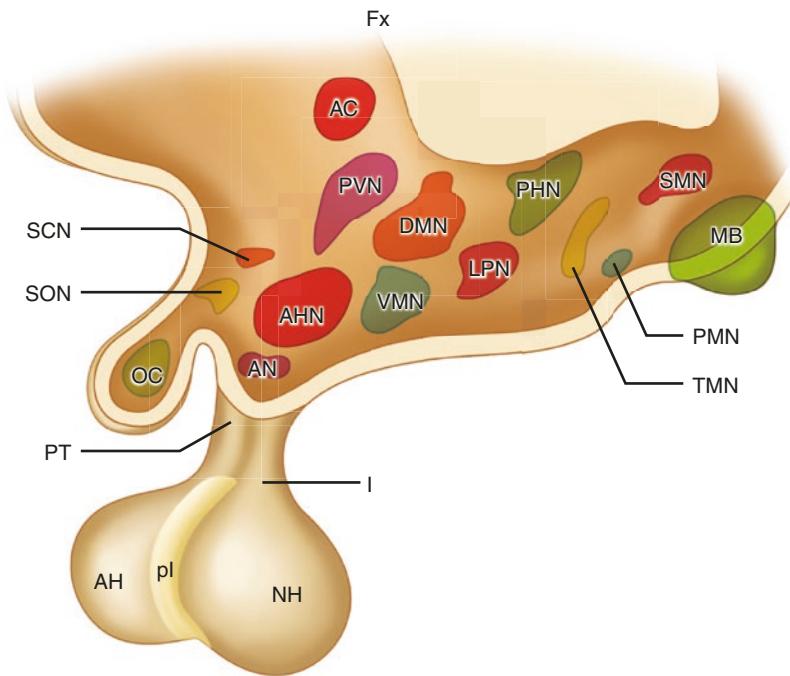
includes the PeVN, SCN, PVN, and AN. The medial zone area includes the medial preoptic nucleus, AHN, DMN, VMN, PMN, MBs, and PHN, while the lateral zone includes the lateral preoptic nucleus, lateral hypothalamic nucleus (LHN), and the SCN. Figures 5.4 and 5.5 illustrate these spatial relationships.

The understanding of the functional significance of the various nuclei has been gradually accrued over the decades by first documenting their neuronal connections and then lesional and electrical stimulation experiments mostly performed initially in animals but with the growth of neurosurgical techniques now more commonly extended to human patients as well. Figure 5.6 is a depiction of the most salient neuronal connections thus far established between hypothalamic nuclei and the rest of the brain [8–20].

The hypothalamic and pituitary axes are found in virtually all vertebrate nervous systems, and Table 5.1 highlights the major functional effects and chemical mediators (neurotransmitters, neuropeptides, and neurohormones) that have presently been identified in mediating these effects [8–20].

While the functional significance of some of the hypothalamic nuclei and areas remains unclear and the subject of intense ongoing investigation as well as controversy, others have fairly well-defined roles and significance. The magnocellular (cytologically large) portions of the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) are intricately involved in salt, electrolyte, intravascular volume, and water balance. This is largely mediated by the production and release of the antidiuretic hormone: vasopressin. Further details of the functional significance of these and other hypothalamic-pituitary hormones will be provided in the neurophysiology chapter.

On the other hand, parvocellular (cytologically small) portions of the PVN produce and secrete corticotropin-releasing hormone (CRH) and by this means modulate neuronal, autonomic, and hormonal responses to endogenous and environmental stress [21–24].

**Fig. 5.2** Sagittal schematic of hypothalamic nuclei

Key: SCN suprachiasmatic nucleus, SON supraoptic nucleus, OC optic chiasm, AN arcuate nucleus, PT pars tuberalis, AH adenohypophysis, PI pars intermedia, NH neurohypophysis, I infundibulum, AHN anterior hypothalamic nucleus, VMN ventromedial nucleus, LPN lateral posterior hypothalamic nucleus, TMN tuberomamillary nucleus, PMN pre-mamillary nucleus, MB mamillary body, SMN supramamillary nucleus, PHN posterior hypothalamic nucleus, DMN dorsomedial nucleus, PVN paraventricular nucleus, AC anterior commissure, FX fornix

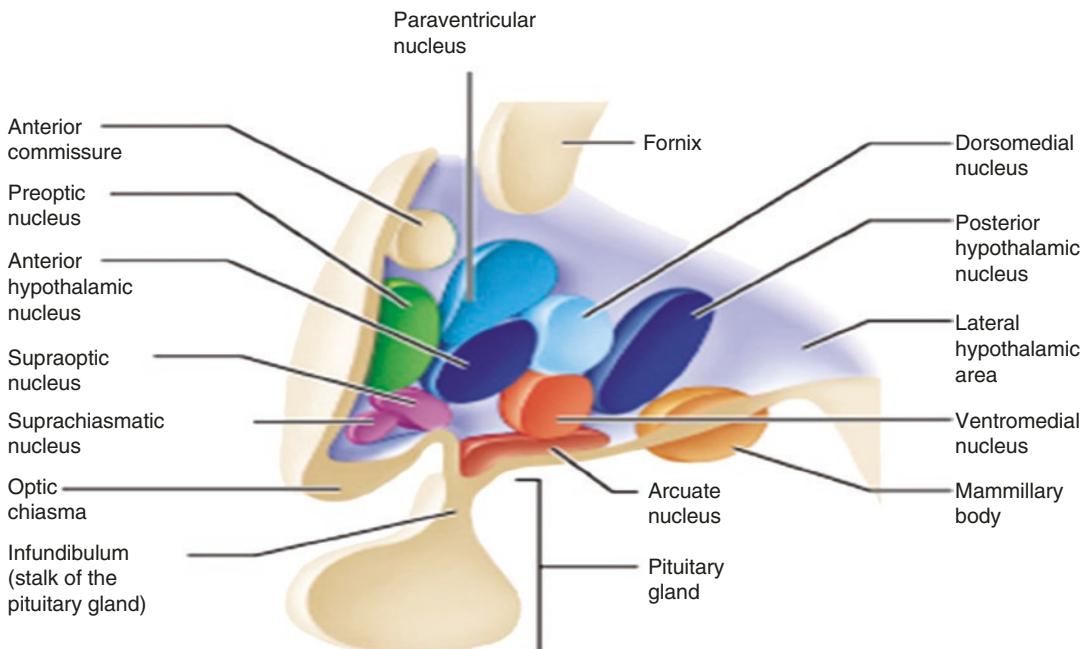
**Fig. 5.3** 3D schematic of hypothalamic nuclei-sagittal view

Fig. 5.4 Coronal spatial view of the thalamus and hypothalamic zones

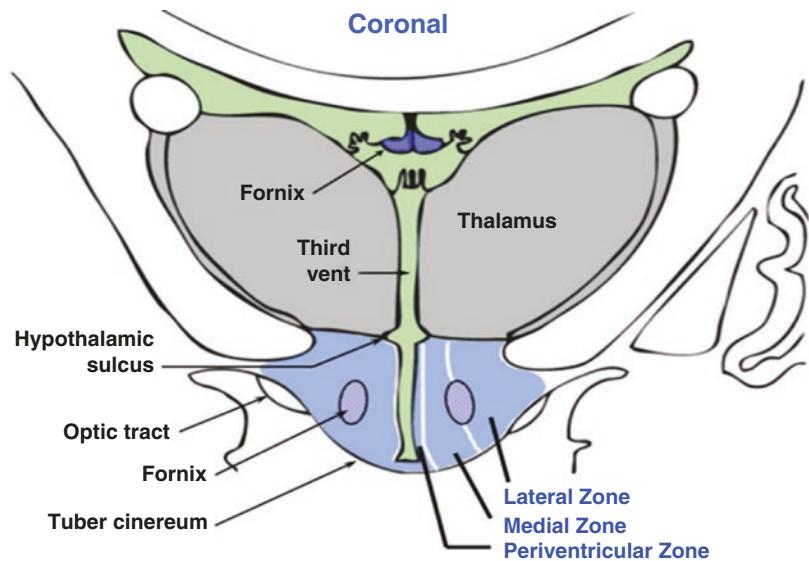
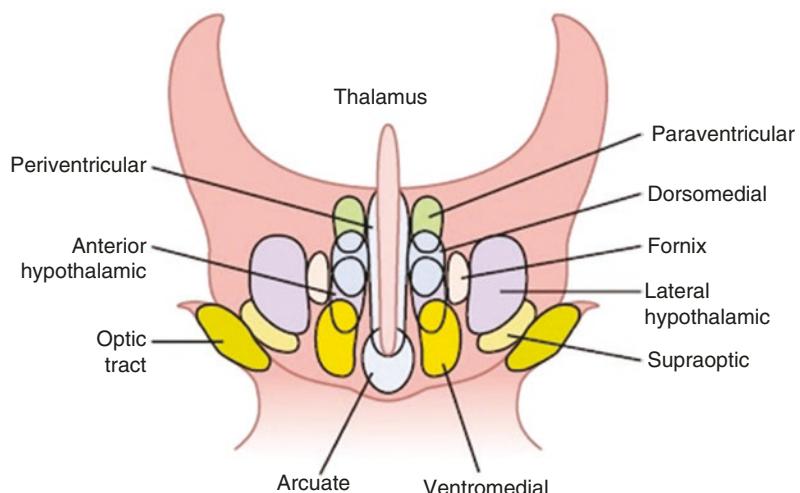


Fig. 5.5 Coronal schematic of the mediolateral relationships of the hypothalamic nuclei



The preoptic nucleus (PON) is a major producer of gonadotrophin releasing (GnRH) which is central to the normal regulation of gonadal function and development [25–27].

The arcuate nucleus (AN) has myriad cells that produce both orexigenic and anorexigenic factors that are central to control of feeding behavior and energy balance which are then also central to body habitus and weight management as is further elucidated in the chapter on

hypothalamic-mediated wasting and obesity syndromes [8, 14, 28, 29].

The ventromedial nucleus (VMN) expresses receptors for various ovarian hormones including estradiol and progesterone and by this means modulates female sexual behavior.

The suprachiasmatic nucleus (SCN) has neurons with circadian clock pacemaking ability that controls various circadian rhythms including but not restricted to sleep-wake cycling [30–32].

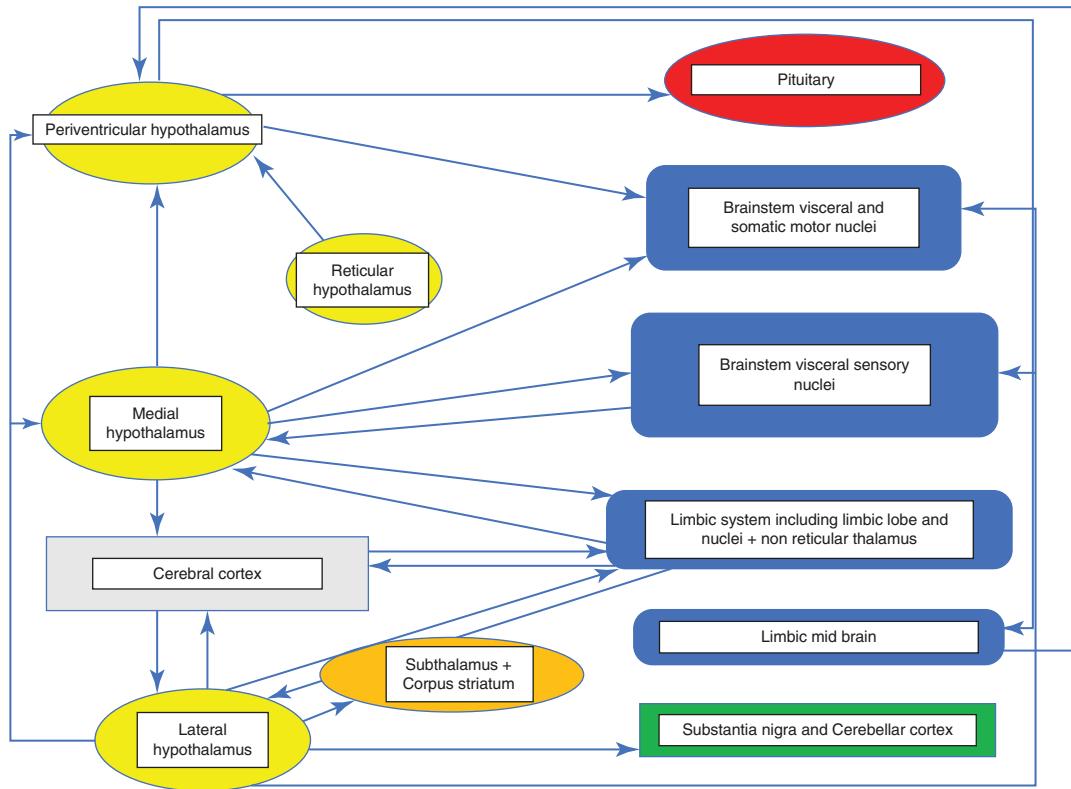


Fig. 5.6 Neuronal connections between hypothalamic nuclei and the rest of the brain

Table 5.1 Summary of functional roles and chemical mediators of main hypothalamic nuclei

Region/zone	Nucleus	Functional role	Chemical mediators
Anterior	Preoptic	Thermoregulation Regulation of HPG axis Regulation of HPT axis Modulation of male sex behavior	GnRH, TRH, ER alpha ER beta, ProgR, AR
Anteromedial	Supraoptic (magnocellular)	Salt and water balance Intravascular volume modulation Blood pressure modulation Modulation of parturition Emotional attachment Lactation and milk let-down reflex	Vasopressin, oxytocin
	Paraventricular (magnocellular)	Salt and water balance Intravascular volume modulation Blood pressure modulation Modulation of parturition Emotional attachment Lactation and milk let-down reflex	Vasopressin, oxytocin
	Paraventricular (parvocellular)		CRH, TRH, GlucR, somatostatin
	Anterior hypothalamic	Thermoregulation, sweating, panting, parasympathetic control TRH inhibition	
	Suprachiasmatic	Circadian rhythms Salt and water balance	Vasopressin, VIP

(continued)

Table 5.1 (continued)

Region/zone	Nucleus	Functional role	Chemical mediators
Anterolateral	Lateral hypothalamic	Appetite and feeding modulation	Orexins
Middle	Periventricular	GH secretion inhibition, ovulation modulation	Somatostatin, kisspeptin ER beta, ER alpha
	Dorsomedial	Blood pressure control	NPY, GhR
	Hypothalamic	Heart rate control Gastrointestinal motility Behavioral rhythms	
	Ventromedial	Satiety modulation female sexual behavior	GhRH, ER beta, ER alpha
	Arcuate	Feeding behavior, energy expenditure modulation neurosecretory control of prolactin and GH secretion	POMC, NPY, AgRP, GhRH dopamine, kisspeptin, ER beta, ER alpha, ProgR, GhR, lepR
Posterior	Mamillary	Memory modulation	Vasopressin
	Posterior	Blood pressure control	
	Hypothalamic	Pupillary dilation Thermoregulation Sympathetic modulation Shivering Salt and water balance	
	Tuberomamillary	Arousal Wakefulness + attention Feeding + energy balance Learning Memory modulation Sleep modulation	

Abbreviations: *GnRH* gonadotrophin-releasing hormone, *TRH* thyrotropin-releasing hormone, *ER alpha* and *beta* (estrogen receptor subtypes), *ProgR* progesterone receptor, *AR* androgen receptor, *CRH* corticotropin-releasing hormone, *GlucR* glucocorticoid receptor, *NPY* neuropeptide Y, *GhR* growth hormone receptor, *GhRH* growth hormone-releasing hormone, *POMC* pro-opiomelanocortin, *AgRP* agouti-related peptide, *lepR* leptin receptor

Hypothalamic Neuronal Connections

As Fig. 5.6 attests, the hypothalamus is a relay station that connects to every level of the central and peripheral nervous system. In particular, it has rich neuronal connections to the brainstem and reticular formation. It forms an integral part of the limbic system (the brain central way station for memory and emotional integration) that includes the limbic lobe, nuclei, and connections including the hippocampus, amygdala, mamillary bodies, mamillothalamic tracts, striae terminalis, median forebrain bundles, the anterior thalamus, etc. as depicted in Fig. 5.7. The hypothalamus has extensive neuronal connections to these other components of the limbic system as well as other areas of the autonomic nervous system.

In addition, the hypothalamus has extensive afferent and efferent neuronal connections with

the brainstem chief among which are those with the solitary tract, the nucleus tractus solitarius, the locus coeruleus, and the ventrolateral medulla. It is important to appreciate that most of the neuronal connections within the hypothalamus are bidirectional, thus optimizing fine balance tuning of signal tone to the unique needs of the organism at spatial points in time. Most commonly neuronal projections to loci below the hypothalamus are mediated via the medial forebrain bundle, the mamillo-tegmental tract, and the dorsal longitudinal fasciculus. Neuronal projections to loci above the hypothalamus are typically mediated via the mamillothalamic tract, the fornix, and the terminal striae. Connections between the hypothalamus and the sympathetic motor system are mediated via the hypothalamo-spinal tract.

It is important to be aware that several of the hypothalamic nuclei are sexually dimorphic (i.e., they have distinctively different structural and

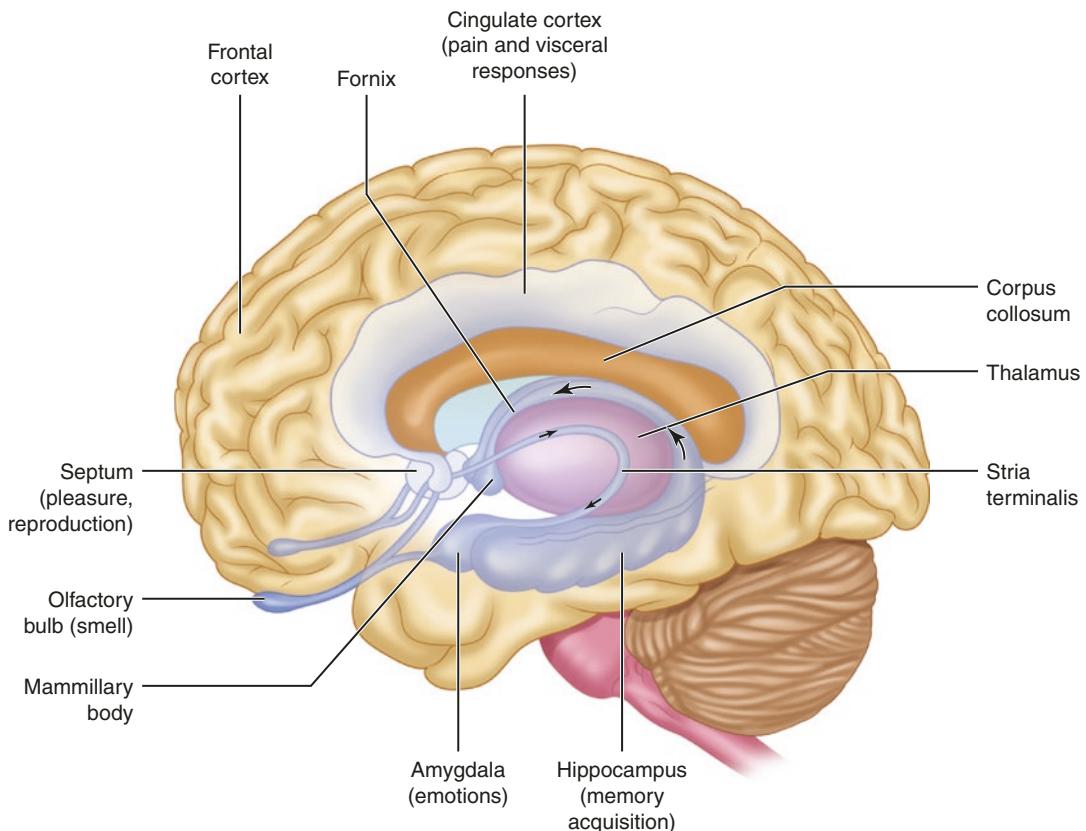


Fig. 5.7 Components of the limbic system

functional features dichotomized based on male and female gender) [33]. The PON particularly illustrates this and forms an important basis for gender-specific behavioral patterns. Growth hormone secretion and its hypothalamic-based modulation is another example of this phenomenon [34]. The variable effects of ovarian steroids based on gender is another example and is due to the differential expression of estrogen-sensitive neurons in the hypothalamus (due to differential expression of estrogen receptors) based on gender.

This difference in expression and location of estrogen-responsive neurons based on gender has been shown to be largely established early in neonatal development and is due to variable neonatal sex steroid milieu and exposure based on gender. Estrogen and progesterone receptors are located mainly in neurons in the anterior and medio-basal hypothalamus. These include but are not

restricted to the PON where luteinizing hormone-releasing hormone (LHRH) neurons are found and which modulate dopamine (and thus prolactin release as well as maternal behavior [35]. Other hypothalamic nuclei with demonstrated sexual dimorphism include the periventricular nucleus (PeVN) which expresses somatostatin and is involved in stress response as well as the ventromedial nucleus (VMN) which is integrally involved in hunger and sexual arousal modulation [36].

Appropriate gonadal steroid exposure during neonatal development is now known to be central to normal gender-appropriate development of the neuroendocrine hypothalamus including establishment of normal reproductive cycles and menstruation in women as well as development of gender-appropriate sexual and reproductive behavior among men and women. Animal studies and clinical scenarios in human patients have

demonstrated how potent exposure of the female neonatal hypothalamus to testosterone during the so-called critical period of sexual steroid influence can be on subsequent sexual behavior and orientation with the concept of permanent masculinization presumed as occurring in such scenarios. Opposite phenotypic behavior has been demonstrated when the male neonatal hypothalamus is artificially feminized by gonadal androgen deprivation during the same “critical period” of sexual steroid influence [37].

The Role and Place of the Circumventricular Organs

As earlier indicated the relationship of the hypothalamus with the rest of the brain and the rest of the organ systems of the organism is a bidirectional one. This includes as a critical part of this relationship the capacity of systemically produced and circulatory humoral factors to exert functional and modulatory effects on hypothalamic nuclei. This is not however a straightforward situation as most of the brain is importantly “walled” off from the systemic circulation via a robust vascular-mediated “blood-brain” barrier. The important exceptions to these are the circumventricular organs (CVO). The main components of the CVO are depicted in Fig. 5.8 and include

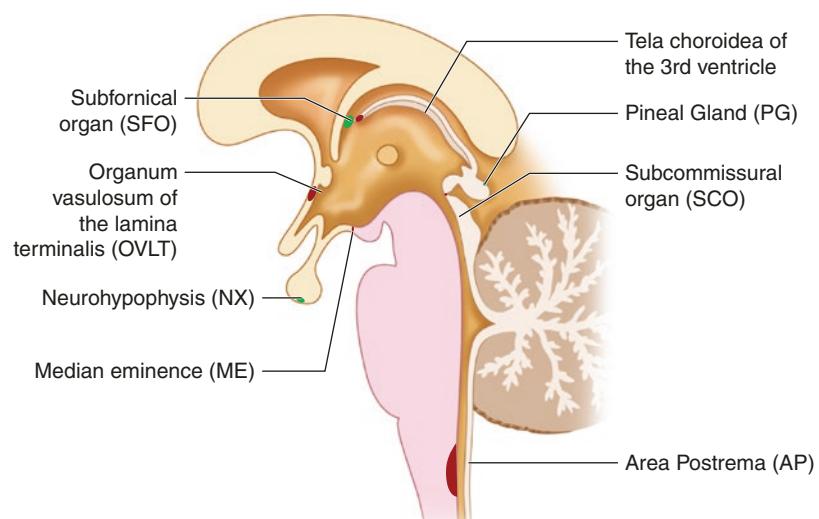
the neurohypophysis, the organum vasculosum of the lamina terminalis (OVLT), the median eminence, the area postrema, the subcommisural organ (SCO), the tela choroidea of the third ventricle, and the pineal (aka epiphysis cerebri) and the subfornical organ (SFO) [38, 39]. Common to this motley crew is that they are all circumventricular (around the lateral, third and fourth ventricles) and that the endothelial cells of the brain capillaries that permeate all of these structures lack the typical “tight junctions” present in other brain capillaries and instead are typically fenestrated forming a histologic basis for the known physiologic capacity for considerable diffusion of various chemical mediators from the systemic circulation to the central nervous system as well as the diffusion of various neurosecretory products from nearby neurons to the systemic circulation [40].

The circumventricular organs can be conceptualized as either (a) sensory organs, which include the area postrema (APr) and the SFO, or (b) secretory organs including the SCO, neurohypophysis, median eminence, and pineal gland.

The Median Eminence (ME)

This midline structure is found beside the AC and ventral to the third ventricle. This is the central

Fig. 5.8 The circumventricular organs



convergence station of the various hypophysiotropic hormones produced by the superiorly located hypothalamic nuclei prior to their conveyance to the pituitary gland. The proximity of the ME to the AN allows various blood-borne chemical mediators including glucose, amino acids, fatty acids, steroid hormones, etc. to access the AN and thus play a modulating role in the homeostatic regulation of appetite, satiety, and energy balance mediated via the AN. The ME includes a distinct internal (zona interna) and external (zona externa) layers. There is also an ependymal layer which forms the floor of the third ventricle. The ME is rich in portal capillary blood cells and specialized cells called tanycytes. They have multiple functions and have extensions (microvilli) into the ventricular space as well as serving as scaffolding cells for the neurons in the ME and a perivascular sheath of the capillary blood vessels. Notably they are very rich in type 2 deiodinase as well as the degrading and reactivating enzymes (WSB-1 and VUD-1) of this deiodinase which is the major enzymatic mediator of levothyroxine to liothyronine conversion. These cells of the ME are thus presumed to play a central modulatory role in the hypothalamic-pituitary-thyroid (HPT) axis and in regulating tissue levels of various thyroid hormone moieties in the hypothalamus [41–43]. Tanycytes have also been shown to express embryonic genes suggesting their potential capacity to also serve as stem cells. Their regenerative capacity in response to damage is well demonstrated and thus distinct and different from typical neurons [44].

The zona interna mainly consists of unmyelinated axonal processes en route to the neurohypophysis. These axons contain distinctive neurosecretory granules visible on electron photomicrographs called *Herring bodies*.

The OVLT

This is located in the midline of the lamina terminalis and forms a portion of the anterior wall of the third ventricle. The cells of the OVLT are thus consistently exposed to the cerebrospinal fluid

from the third ventricle. It has been shown to serve as an osmoreceptor integrally involved in vasopressin secretion and the consequent regulation of volume status, water balance, and thirst. It has also been implicated in mediating the thermic effects of systemically circulating chemokines and cytokines. The OVLT has been shown to include myriad cells including specialized neurons, tanycytes, ciliated ependymal cells, and supportive glial cells. Among the neurotransmitters, neurohormones, and chemical mediators produced by the cells of the OVLT are atrial natriuretic peptide (ANP), vasopressin, somatostatin, and GnRH [39, 45]. Unlike the ME however, the major capillary drainage from the OVLT is to the medial POA rather than to the portal plexus. The major neuronal projections of the OVLT are to the PON, SFO, AN, SON, medial thalamus, and parts of the limbic system. The OVLT has also been demonstrated to be responsive to systemically circulating angiotensin 2 (AG-2) and relaxin [46, 47]. There are some rodent-based findings that also suggest a potential role for the OVLT in regulation of pituitary gonadotrophin production [48].

The SFO

This “organ” is located in the midline beneath the fornix hence its name. It is located at the junction of the lamina terminalis and the tela choroidea. Its embryologic origin is similar to that of the OVLT and thus shares commonalities in cellular structure, microarchitecture, and functionality [49, 50]. The SFO has important roles in fluid, electrolyte, and volume balance. It also modulates drinking behavior especially in the setting of hypovolemic and hemorrhagic states. Neuronal projections from the SFO extend to many other hypothalamic nuclei including the PON, OVLT, SON, PVN, and lateral hypothalamus [51, 52]. The surrounding blood supply and fenestrated capillaries enable the SFO cells to be modulated by circulating angiotensin 2 via relevant receptors. The SFO neurons via their aforementioned neuronal connections stimulate the release of vasopressin from the neurohypophysis as well as

potentially also vasoactive intestinal peptide (VIP) release from the adenohypophysis [53–55]. There is some evidence to suggest some in situ production of both angiotensin 2 and the inhibitory neuropeptide galanin also from the SFO [56, 57]. There is other data that suggests the presence of several other peptides and/or their receptors in the SFO, and these include somatostatin, obestatin, leptin receptors, and TRH. These are suggested to influence fluid ingestion with meals as well as sleep-wake cyclicity and regulation [58–64].

The Tela Choroidea

This is the double-layered portion of the meningeal pia matter and ependyma that upon extension forms the choroid plexuses in the fourth ventricles from which the cerebrospinal fluid is produced. It is “c” shaped and forms the choroidal fissure that runs between the fornix and thalamus in the wall of the body of the third ventricle. It is a thin weblike membrane with prodigious vasculature that includes the typical fenestrated capillary of the circumventricular organs and based on its anatomic proximity to both the systemic circulation and the CSF in the ventricles can be viewed as the “gateway” of the systemic circulation to the brain. The choroidal plexuses receive the majority of their blood supply via the anterior and posterior choroidal arteries. Medial posterior branches from these supply the majority of the blood supply to the tela choroidea in the third ventricle.

The SCO

The SCO is a small secretory organ found in the anteroinferior portion of the posterior commissure near the anterior ostium of the cerebral aqueduct [65]. It is distinctive from the other circumventricular organs in not having a high concentration of fenestrated capillaries, and consequently the blood-brain barrier permeability is

demonstrably less in its location. It does include some ependymal cells which are ciliated and contain secretory granules. The dominant secretory product of these cells is glycoprotein SCO-spondin [65, 66]. The glycoprotein SCO-spondin is secreted into the third ventricles and there aggregates to form *Reissner's fiber*. This is a fibrous projection that extends from the SCO via the sylvian aqueduct to the spinal cord [67]. The fiber is presumed to play a role in maintenance of the patency and fidelity of the sylvian aqueduct and thus in the normal flow and pressure maintenance of cerebrospinal fluid (CSF). The exact functional role of the SCO is still the subject of intense investigation though some hypothesize that it may also be involved in aldosterone secretory regulation, fluid and water homeostasis, as well as CSF detoxification.

The APr

The APr is the most caudally placed of the circumventricular organs and is located at the junction of the medulla and spinal cord. They are typically small prominences on either side of the fourth ventricle. It is a vascular area of the brain with the typical fenestrated capillaries seen in most of the circumventricular organs. It appears to be primarily a sensory organ that acts as the chemoreceptor trigger zone for emesis which results from noxious stimuli in the blood [68–70]. There is also some evidence to suggest that the APr is a location that is responsive to angiotensin 2 with a hyperglycemic stimulatory response [71–74]. This may explain the observations first made by Claude Bernard in 1849 with needle-based lesioning of floor of the fourth ventricle resulting in marked transitory hyperglycemia that he termed *pique diabetes* [75, 76]. There is also some evidence suggesting the potential role of the APr in blood pressure and thirst modulation. Furthermore it has neuronal projections to brainstem nuclei associated with the autonomic integrative regulation of cardiovascular and respiratory activities [70–74].

The Pineal Gland

The pineal is the “other” endocrine gland of the brain. Also known as the conarium and epiphysis cerebri, it is a tiny organ (~0.8 cm length and 0.1 g weight in human adults) about the size of an average rice grain that has critically important physiologic functions related to circadian rhythmicity and sleep-wake cycle modulation. Figure 5.9 depicts the established neurocircuitry of the pineal gland. It is the last of the circumventricular organs, and as typical

of them, it is richly vascularized and endowed with fenestrated capillary that ensure its permeability from the typical blood-brain barrier.

As Fig. 5.10 illustrates, it is a posterior located, centrally placed organ that sits above the corpora quadrigemina (the inferior and superior colliculi). Internally, its pineal recess forms part of the hinder-most wall of the third ventricle and thus like most of the other circumventricular organs has simultaneous intimate contact with both the systemic circulation and the CSF conduit system

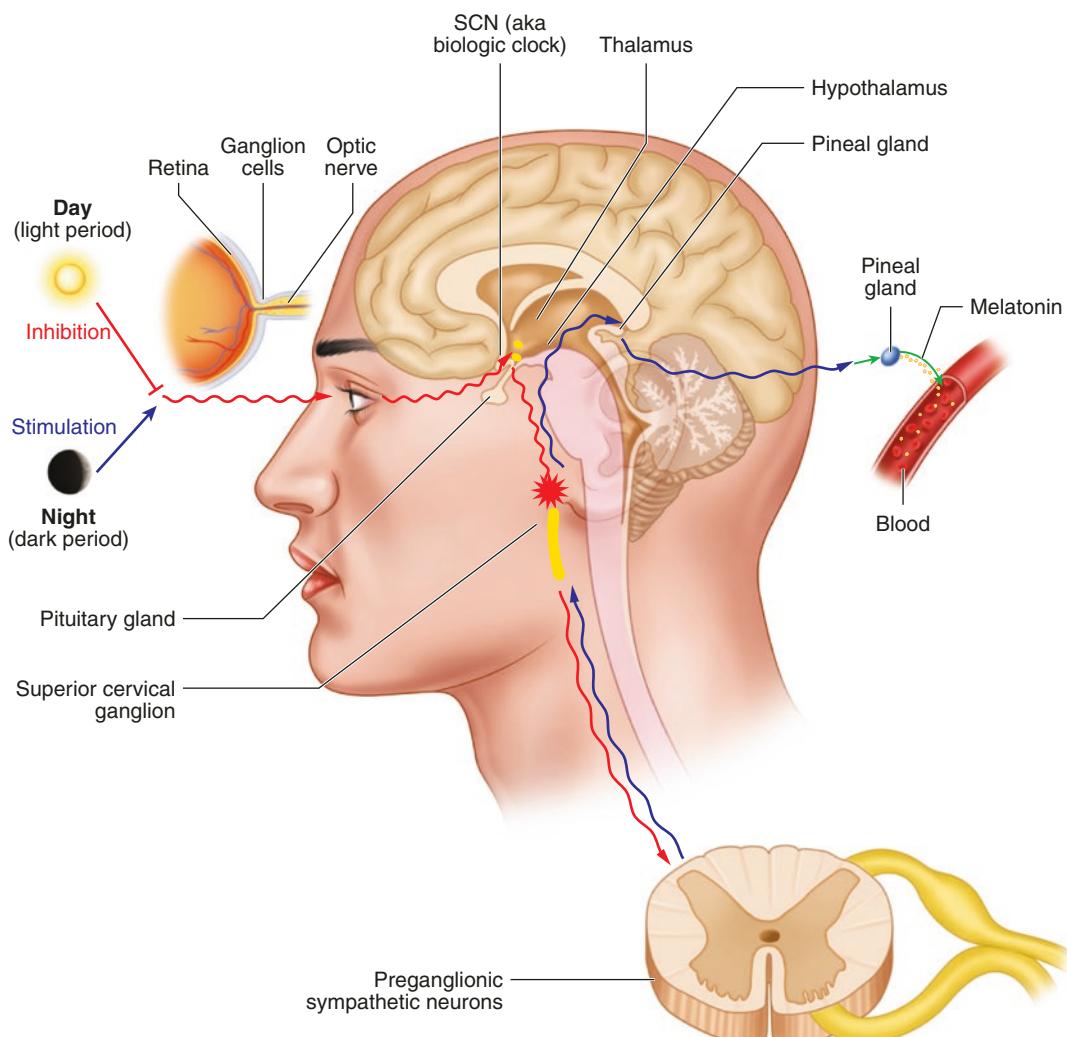
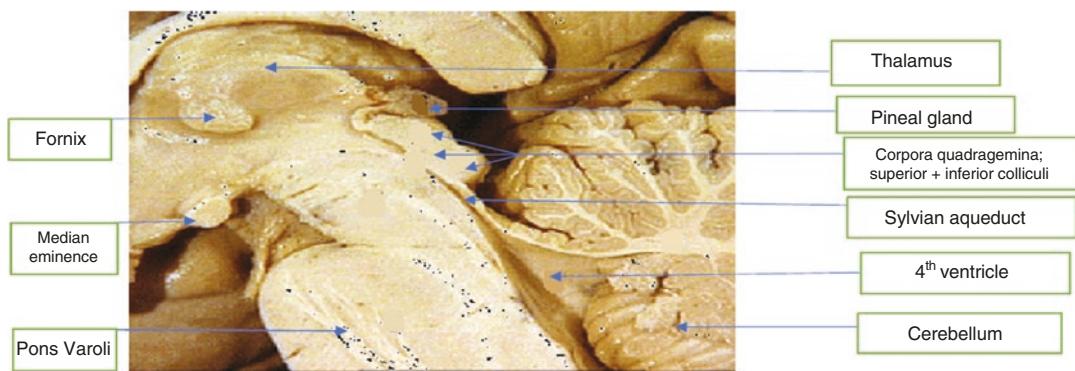
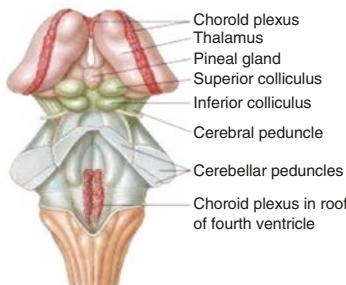


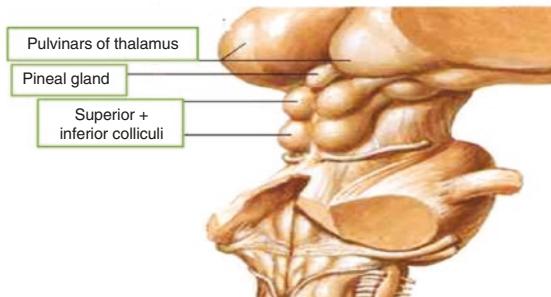
Fig. 5.9 Neurocircuitry of the pineal gland



A; Sagittal view of the Pineal gland and surrounding structures



B; Posterior view of the Pineal gland and surrounding structures



C; Postero-lateral view of the Pineal gland and surrounding structures

Fig. 5.10 Anatomic views of the pineal gland and surrounding structures: (a) sagittal view of the pineal gland and surrounding structure, (b) posterior view of the pineal

gland and surrounding structure, (c) and posterolateral view of the pineal gland and surrounding structure

[77–79]. The gland has a shape akin to a pine cone hence its name, and it is almost universally found in all vertebrates (with the hagfish being the lone exception though this animal does have an identified “pineal equivalent” in its diencephalon), thus underlining its central physiologic importance.

While shrouded in lay press and historical mystery, romanticism, and mysticism, the known

verifiable data regarding the pineal is probably even more fascinating. Comparative neuroanatomy, neurophysiology, and neuroendocrinology across various vertebrate species suggest that it seems to be a phylogenetically atrophied photoreceptor. Its relationship to photosensitivity is more apparent in amphibians and reptiles where its lay press reputation as a “third eye” appears more warranted.

The pineal receives most of its prodigious blood supply from choroidal branches of the posterior cerebral artery [80, 81]. As depicted in Fig. 5.9, the pineal has afferent sympathetic innervation from the superior cervical ganglion. It also receives parasympathetic innervation from the otic and pterygopalatine ganglia. It also has afferent inputs from the trigeminal ganglia [82].

The microarchitecture of the pineal consists of specialty neuronal cells called pinealocytes (which are the cellular source of the neurohormone melatonin) surrounded by connective tissue spaces. The gland is also covered by a thin pia matter-derived capsule. The pineal is significantly more cellular than typical brain cortical gray or white matter. In addition to the dense concentration of pinealocytes, it also has supportive interstitial cells which interdigitate between pinealocytes, perivascular phagocytes, blood vessels with fenestrated capillaries, pineal neurons (typical neurons with no apparent neurosecretory functional capacity), and peptidergic neuron like cells whose exact functional significance is unclear but which are presumed to have some paracrine regulatory functional significance [83, 84].

Typically the human pineal grows predominantly during the first 2 years of life and gradually thereafter at puberty and then remains relatively stable thereafter until old age when it can undergo some degree of involution. Beyond the well-defined role of melatonin in sleep-wake cycle modulation, it also appears to have a role in delay of puberty onset as its levels are particularly high in prepubertal children and reduce with the onset of puberty and childhood pineal tumors that disrupt endogenous melatonin production are associated with precocious puberty [85–88].

The dominant endocrine product of the pineal is melatonin which is a biosynthetic product of the amino acid tryptophan and the bioamine 5-hydroxytryptamine (serotonin) as depicted in Fig. 5.11. This was first isolated from the pineal glands of cows in 1958 by the Yale University dermatologist, Aaron Lerner, and in view of its capacity to lighten the skin tone of frog's skin was initially presumed to have therapeutic poten-

tial for human skin diseases which has not however turned out to be the case [89]. Among its numerous actions is the modulation of sleep-wake cycling as depicted in Fig. 5.9. Melatonin production is enhanced during darkness and inhibited by increased ambient light. The photo-sensitive rod and cone cells of the retina on detection of external light stimuli are stimulated and signal via the optic nerve to the SCN (which is often colloquially referred to as the biologic clock) which then provides day-night and sleep-wake synchrony. The SCN's neuronal projections to the PVN and further neuronal signals from the PVN to the superior cervical ganglion (SCG) form the rest of the neurocircuit. Neuronal projections from the SCG to the pineal gland stimulate melatonin secretion during dark ambient conditions, and the hormone circulates via the systemic circulation to mediate its sleep modulatory and other related effects [90, 91].

Beyond melatonin there is some research that suggests other hormonal and chemical mediators produced by the pineal gland one of which is the beta-carboline, pinoline. Its functional significance if any remains unclear at the moment though it appears to have some antioxidant protective properties [92–102]. There are other experimental and clinical observations suggesting roles of the pineal gland in bone metabolism, pituitary gonadotroph production, and glucose metabolism, but most of this is in rodent and other animal models with no strong evidence of similar physiologic roles in humans [102–108].

The pineal also appears to be a repository for a host of other chemical mediators and peptides which appear to be related to pineal peptidergic innervation networks. It is presumed that these peptides and mediators accumulate and are possibly stored in the pineal but are not de novo produced there. These include vasopressin, oxytocin, vasoactive intestinal peptide (VIP), peptide histidine isoleucine, calcitonin gene-related peptide (CGRP), substance P, and somatostatin. Their physiologic significance and role in this location is at present unclear but remains the subject of intense investigation [78].

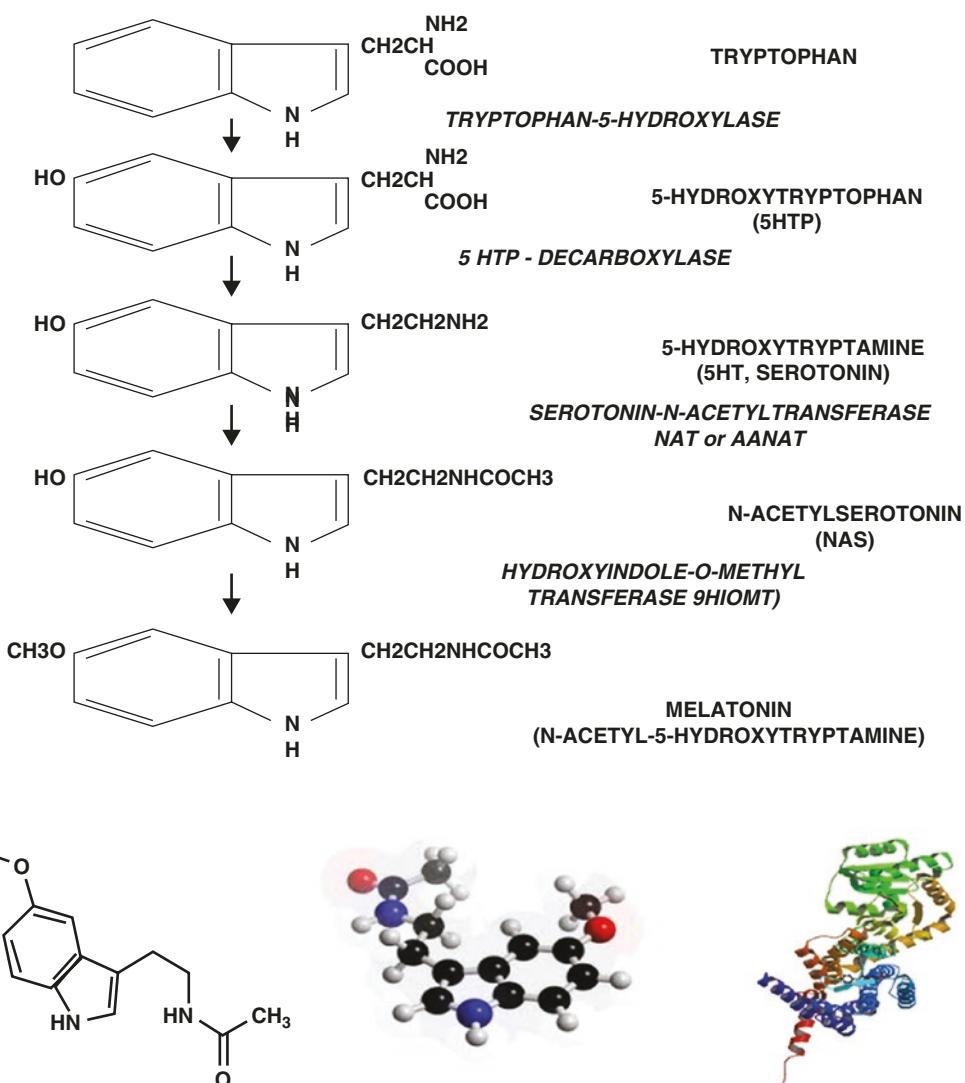


Fig. 5.11 Biosynthesis and structure of melatonin

The exact functional significance and determinants of pineal calcification are unclear. It appears to be a form of dystrophic calcification that is associated histologically with so-called corpora arenacea (aka “brain sand”). While overall pineal calcification increases in prevalence and degree with age, it has been described in young children and found in ~40% of North American teenagers [109–113]. In-depth discussion of pathologic lesions and correlates of the pineal is beyond the scope of this chapter and will be addressed in other chapters.

Hypothalamic Functional Connections

As previously indicated the hypothalamus mainly mediates its functional and modulatory activities by two distinct but interrelated functional systems: neuronal connections with the rest of the central nervous system and peripheral nervous system as well as by production and release of hormones (so-called neurosecretory mechanisms).

Neuronal connections: Considering the multiplicity and complexity of the neuronal connections between the hypothalamus and the rest of the nervous system for the purpose of this review, a detailed description of the neuronal connections is beyond our scope and won't be done. More detailed descriptions in this regard are included in the relevant neuroanatomical chapters of this book volume.

Of relevance though is awareness of the major afferent and efferent neuronal connections central to human hypothalamic function, and these are described below.

Major Afferent Hypothalamic Neuronal Connections

These are mainly from the limbic system, reticular brain system formation, thalamus, basal ganglia, subthalamus, retina, and neocortex [16, 114–119].

The limbic system afferents include the medial forebrain bundle, the stria terminalis, and the fornix. Those from the brainstem reticular formation include the dorsal longitudinal fasciculus (aka the Schutz fasciculus), the periventricular fiber system, and the medial forebrain bundle. The dorso-longitudinal fasciculus is the major afferent connection between the hypothalamus and the major autonomic centers of the midbrain including the limbic midbrain area (mesencephalic tegmentum), reticular raphe nuclei of the pons Varoli, and the nucleus tractus solitarius of the medulla oblongata.

The hypothalamus also receives important afferent input from the thalamus chief of which are from the median and medial thalamic areas. There are also afferent inputs from the periventricular system and the inferior thalamic peduncle of the ansa peduncularis which is an extension of the medial forebrain bundle. Afferents from the subthalamus mainly originating from the subthalamic nucleus and zona incerta project to the lateral hypothalamic walls.

The basal ganglia-originating afferents mainly arise from the nucleus accumbens which is located in the anteroinferior portion of the cau-

date nucleus as well as the substantia innominata from which they also project to lateral parts of the hypothalamic walls.

The retinal afferents which have already been alluded to in the discussion above regarding the pineal gland reach the hypothalamus via the retino-hypothalamic tract which projects from the posterior aspect of the retina via the optic nerves and chiasm to end at the SCN.

The neocortical (cerebral cortex) afferents originate mainly from the frontal cortex and travel via the medial forebrain bundle again projecting to the lateral portions of the hypothalamus abutting the third ventricle.

Major Efferent Hypothalamic Neuronal Connections

The major outputs of the hypothalamus to the adeno- and neurohypophysis are discussed below in some detail and form a major part of the neuroendocrine hypothalamic system, but the hypothalamus also has neuronal projections to other brain and nervous system targets including the limbic system, reticular formation of the brainstem, thalamus, subthalamus, basal ganglia, superior colliculi, substantia nigra, cerebellum, and cerebral cortex [16, 114–119].

As is evident from prior discussion, many of these projections are reciprocal in nature from brain locations from which it receives afferents, thus enabling an intricate system of cross talk, feedback, and thus close modulation and regulation of the associated bio-systems that these connections mediate and control.

The efferents to the limbic system include the medial forebrain bundle from the lateral hypothalamic areas to the septal and the amygdalopiriform cortex complex. Also included is the stria terminalis which projects from the inner hypothalamic areas abutting the third ventricle to the amygdala.

The efferents to the reticular formation of the brainstem include the dorsal longitudinal fasciculus and projecting from the PVN down to the brainstem where it innervates various motor, sensory, and somatic nuclei (including the nuclei of

cranial nerves 3, 5, 7, 9, 10, and 11). The same fasciculus also projects to autonomic sympathetic and parasympathetic preganglionic neurons in the spinal cord. Another major hypothalamic efferent channel to the brainstem is the medial forebrain bundle which projects from the hypothalamus to the medial nuclei of the mesencephalic reticular formation (the limbic midbrain area). It does this via the mammillo-tegmental tract and the mamillary peduncle.

The main hypothalamic efferents to the thalamus include the mammillothalamic tract which connects posterior hypothalamus to the cingulate gyrus of the limbic cortex (a part of the so-called Papez circuit), the periventricular fiber system which connects to the medial and lateral thalamic areas as well as the epithalamic habenulae via the stria medullaris, and finally the medial forebrain bundle which travels via the inferior thalamic peduncle of the ansa peduncularis to terminate in the medial thalamic nuclei.

The hypothalamic efferents to the subthalamus and basal ganglia extend from the lateral walls of the hypothalamus through the mammillo-subthalamic tract to the substantia innominata of the subthalamus.

The hypothalamic efferents to the superior colliculi, substantia nigra, and cerebellum all travel via the stria terminalis, periventricular fiber system, and the medial forebrain bundle. The medial forebrain bundle is also the primary efferent carrier of projections from the hypothalamus to the cerebral cortex.

Neurosecretory Connections of the Hypothalamus

These include two major groups of specialized neurosecretory neurons: those of the neurohypophyseal system connecting to the neurohypophysis and those of the tuberoinfundibular system connecting to the adenohypophysis. While most of these specialty secretory neurons have peptidergic hormonal products, there are others that produce non-peptide products including monoamines, steroid, specialty fatty acids, endocannabinoids, and other chemical mediators.

While the neurosecretory cells of the hypothalamus on face value resemble regular neurons on having dendrites, perikaryal, axons, and typical neuronal junctions with typical neurotransmitters, their distinctiveness lies in their capacity to produce large amounts of myriad hormonal products and other chemical mediators with auto-crine, local paracrine, and distant endocrine effects. While the various nuclei have dominant products, there is generally not absolute exclusivity, and so many of these specialty neurosecretory cells have pluri-hormonal secretory capacity. As is typical of other peptide-producing cells elsewhere in the body, these neurosecretory cells consequently in addition to the typical features of neurons typically have abundant rough endoplasmic reticuli, Golgi apparatus, and membrane-bound secretory granules belying their specialty functional capacity.

The hypothalamic tuberoinfundibular system refers to the dominant hypothalamic connection to the adenohypophysis and as a basic model consists of various hypothalamic neurosecretory cells having the neuronal signals transformed into end-organ hormonal signals (either stimulatory/releasing hormones or inhibitory hormones), and this is called neuroendocrine transduction. Figure 5.12 illustrates schematically the five major hormonal control systems that are well described using this model.

Among the source nuclei for these hypothalamic stimulatory and inhibitory hormones are the parvicellular nuclei of the AN and PeVN. Also involved are the parvicellular nuclei of the PVN and the medial preoptic septal hypothalamic region. Among the identified effector neurotransmitters for these neurosecretory cells are dopamine, GHRH, galanin, galanin-like peptide, and neuropeptides [120–126]. Other neurohormones and neurotransmitters expressed from the neurosecretory cells of these nuclei include enkephalin, TRH, CRH, somatostatin, and VIP [127–135].

The hypothalamic neurohypophyseal system is the dominant system subserving the neurohypophyseal hormonal secretory system and consists of the magnocellular neurons of PVN and SON and the neurohypophyseal tract that termi-

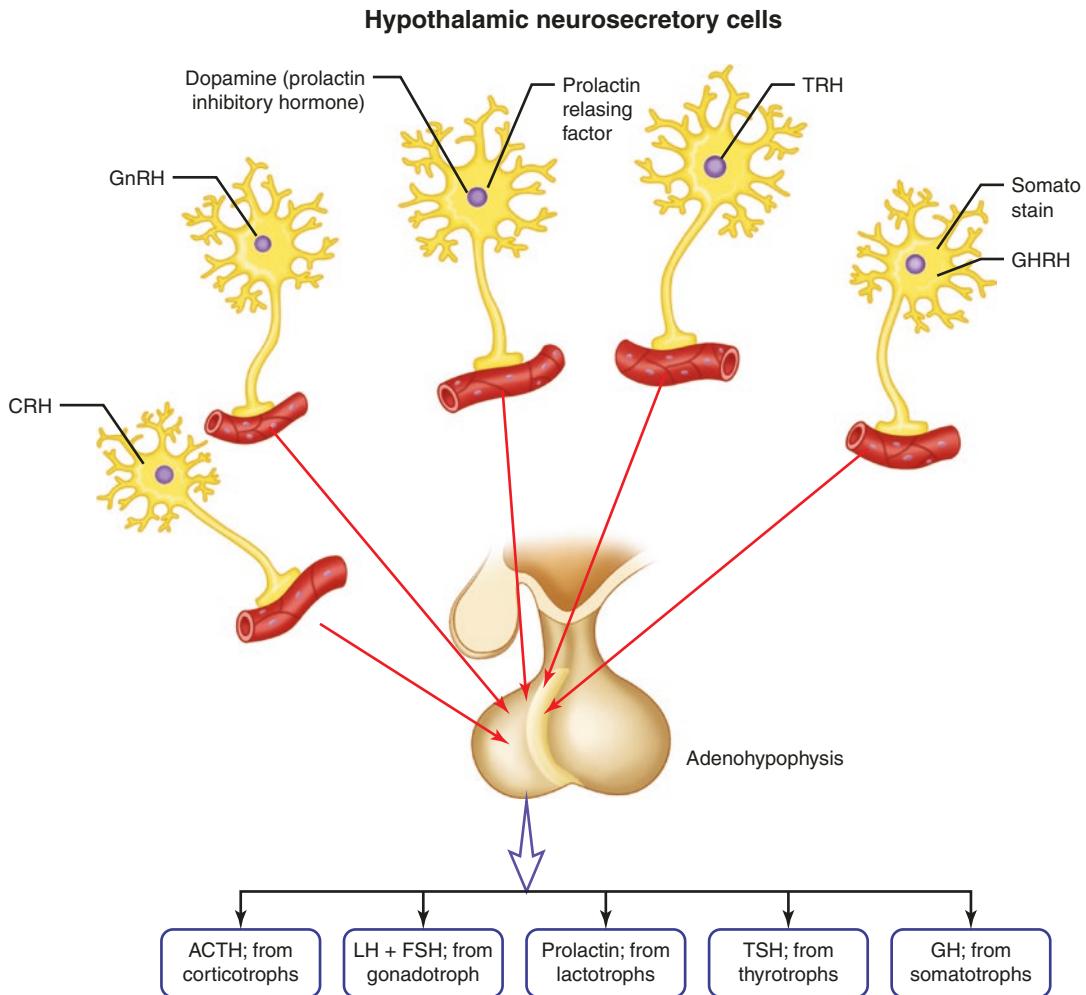


Fig. 5.12 Schema of adenohypophyseal controlling hypothalamic neurosecretory systems

nates in the neurohypophysis producing predominantly vasopressin and oxytocin which are then secreted into the systemic circulation to mediate a host of physiologic functions including antidiuresis, milk let-down and lactation, uterine contraction, and modulation of behavioral patterns related to parenting, affection, etc. [136–141]. Vasopressin has been identified as a weak corticotropin-releasing factor that enhances ACTH secretion in the presence of CRH, and this forms the basis for the vasopressin stimulation test sometimes used as an alternative to the CRH stimulation test in the clinical evaluation of clinical hypercortisolism states. Vasopressin also plays a major mediatory role in the physiologic stimulation of

ACTH production in response to hypoglycemia [142–145].

As with the adenohypophyseal controlling hypothalamic neurosecretory neurons, the neurohypophyseal controlling ones are also plurihormonal, and beyond oxytocin and vasopressin have been demonstrated to produce various other peptides and other chemical mediators that are also deposited in the neurohypophysis including dynorphin, enkephalin, galanin, cholecystokinin (CCK), dopamine, TRH, VIP, neuropeptide Y, substance P, CRH, and endothelin [146–150]. There is also some evidence suggesting that some of the parvocellular hypothalamic neurosecretory cells that dominantly subserve the adenohypoph-

ysis also have minor projections to the neurohypophysis delivery neuropeptides and hormones including GnRH, TRH, somatostatin, enkephalin, neuropeptideneurotensin, CRH, and dopamine [151]. The exact physiologic functional significance of all these other chemical mediators is at present unclear but the subject of intense ongoing study with the propensity of evidence, thus far (largely derived from animal models) suggesting that they mediate mostly autocrine and paracrine effects including modulation of adenohypophyseal hormonal release in stress situations rather than having independent systemic effects.

Beyond these two major neurosecretory systems, it is also important to be familiar with the sympathetic innervation of the adrenal medullary chromaffin cells with the origin of these neural secretory cells being from central sympathetic neurons and their target neurotransmitter being acetylcholine (ACH). The stimulated chromaffin cells in response produce adrenaline and noradrenaline which are then released systemically to mediate myriad endocrine effects related to the traditional “fight and flight” response to physiologic stress and mediate the well-known “sympathoadrenal” clinical symptoms and signs seen in such clinical states as the typical clinical response to hypoglycemia.

In addition, the final distinct neuroendocrine secretory system is the unique system for melatonin secretion and modulation which are been previously discussed and involves postganglionic sympathetic neurons as the originator neurons from the superior cervical ganglion. These terminate in the pineal with adrenaline as their target neuronal neurotransmitter which then stimulates melatonin release from the pinealocytes. Figure 5.13 illustrates in schema form these other neurosecretory cell systems.

The communicatory system between the hypothalamus and the rest of the brain as well as the rest of the body is multifaceted and complex. The traditional local autocrine and paracrine interactions are still being elucidated, while the traditional neuronal connections and systemic circulation-mediated traditional hormonal-mediated systems are largely fairly well elucidated. It is however important to be aware of the

role also played by CSF flow as much of the hypothalamus abuts directly into the ventricular flow system via the third ventricle. There are in addition central nervous system lymphatics and another distinct conduit system called the glymphatic system which are other alternate systems of chemical-mediated communication and functional modulation by which the hypothalamus mediates its homeostatic and system defensive functions. The glymphatic system which is well described in animal models but also well documented in the human brain is a perivascular network of channels that contains CSF, water, lymph, nutritional metabolites, peptides, and tissue water metabolites including alpha amyloid [152, 153].

Regulation of the hypothalamic releasing and inhibitory hormones from the axons of the neurosecretory cells is carried out in a multilayer fashion. They can be affected in negative feedback fashion by the end-organ hormones that they stimulate production of both at the level of the adenohypophysis and specific target peripheral endocrine organs. These effects are either mediated via systemic circulation with entry to the brain via the circumventricular organs or direct diffusion for smaller chemical mediators and fat-soluble steroids or via flow through the CSF.

Figure 5.14 provides a schematic of the various feedback systems by which peripherally derived hormones modulate the hypothalamic- and pituitary-derived stimulatory (and in some cases inhibitory) hormones. The basic underlying system of neuroendocrine modulation of homeostasis has some basic recurring themes characterized by the intent of maintaining a specific physiologic variable (be it appetite, weight, sleep-wake, etc.) around a predetermined range established to be optimal for function under current environmental circumstances. These systems all have a so-called set point of norm, a sensor detector system, a controlling element, a control element effector, a feedback signal, and a feedback effector. The feedback systems are mostly negative but in some unique circumstances can be positive. There are short-loop feedbacks that involve adenohypophyseal hormone effects on

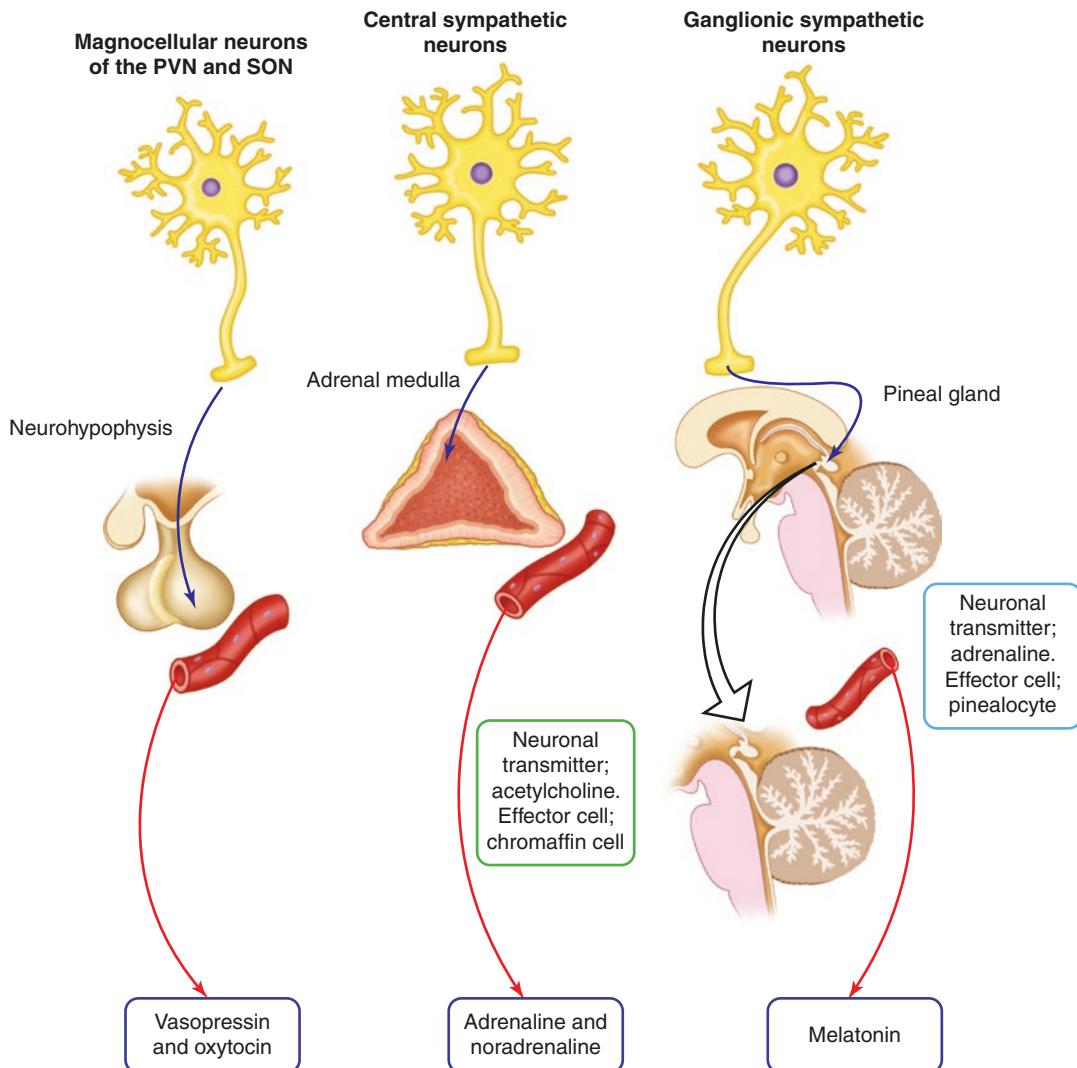


Fig. 5.13 Schema of neurohypophyseal controlling and other neurosecretory cell systems

their controlling hypothalamic neurons, while long-loop feedback systems involve peripheral end-organ hormones having effects at the central level of both the pituitary and hypothalamic controlling neurons and neurosecretory cells. The hypothalamic-pituitary-thyroid (HPT), hypothalamic-pituitary-gonadal (HPG), and hypothalamic-pituitary-adrenocortical (HPA) axes are all three-tiered neuroendocrine control systems, while hypothalamic-pituitary growth hormone and IGF-1 (HPGhI) and the hypothalamic-pituitary-prolactin (HPP) systems are two-tiered control systems.

The HPGhI Axis and Modulation of Growth and Development

Normal growth hormone secretion is pulsatile with an established regular periodic cadence of a pulse typically every 2–4 h with intervening very low to undetectable levels in between pulses [154, 155]. This periodicity is carefully modulated by the balance between the stimulatory GHRH-secreting neurons from the basolateral portion of the AN and the inhibitory somatostatin-secreting neurons from PeVN both of which secrete into the systemic circulation via the portal capillary plexus. Each of these neurosecretory

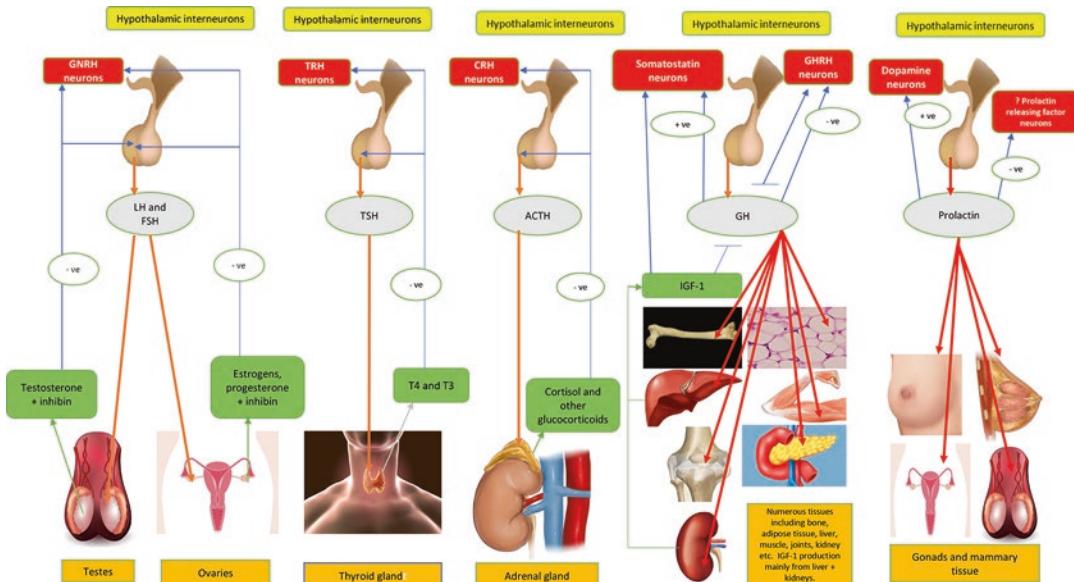


Fig. 5.14 Schema of feedback control mechanisms of hypothalamic neurosecretory systems

cells receives input signals from the other to also exert modulatory control on their secretory functions. In addition, both these sets of neurons also have modulatory effects exerted on them by the peripheral signaling from systemic GH and IGF-1 (aka somatomedin-C) as illustrated in Fig. 5.14. GH production is in addition further modulated by other systemically transported factors and mediators including serum glucose, free fatty acids, other neurotransmitters, and peptides. The well-established GH surge associated with sleep appears to be mediated by cholinergic pathways that suppress somatostatin secretion. Stress and sepsis are other well-known stimulatory secretagogues of GH. Glutamate and N-methyl-D-aspartate (NMDA) are additional known GH stimulatory secretagogues. Another important and relatively recently recognized component of the GH modulatory system is the role of ghrelin (Ghre). Ghre on a molar basis is the most potent GH stimulatory secretagogue in humans [156]. Its primary source is from the stomach but is also produced by neurons from the AN and circulates systemically. With single intravenous injections, it induces acute GH secretory surge, while continuous intravenous infusion induces increase in 24-h pulsatile secretion of GH. Ghre mediates its

GH secretagogue effects by stimulating both GH secretion for the adenohypophysis and GHRH secretion from the relevant hypothalamic neurons. There is also evidence that Ghre secretion and levels reduce with increasing GH levels indicating the presence of a gastro-hypophyseal feedback loop system. There may also be a hypothalamic modulatory feedback component to Ghre production, but this has not yet been exhaustively established thus far [157–162]. The further role that Ghre plays in acute modulation of dietary ingestive behaviors will be discussed later in this chapter.

The HPA Axis and Modulation of Stress Response

The parvcellular neurosecretory cells of the PVN are the main sources of the hypothalamic-derived CRH that is the top tier of the three-tier HPA axis. It receives numerous local and systemic inputs that modulate its secretory function and thus enable it to be a central and important modulator for systemic stress responses. Among its major afferents are inputs from various autonomic centers in the lower brainstem including the nucleus tractus solitarius (NTS), dorsal motor neuron of the vagus nerve, and various inputs

from the dorsal and ventrolateral medulla via the vagus and glossopharyngeal nerves. Other inputs are from catecholamine-secreting neurons (especially noradrenaline) but also neuropeptide Y (NPY), activin, and GLP-1-producing neurons [163–167]. Other noradrenergic releasing neurons that pass via the medial forebrain bundle to the parvicellular PVN provide a means to control CRH release in response to peripheral signals related to volume status, blood pressure, and pulse rate which are all important surrogates of potentially life-threatening stress situations such as hemorrhage, shock, or sepsis. These inputs thus provide noradrenaline (norepinephrine) as the major neuronal transmitter effector for CRH release which then by the HPA cascade system result in increased ACTH and then glucocorticoid (and to a lesser degree mineralocorticoid and adrenal medullary-derived catecholamine) release for the typical “flight or fight” physiologic response. Increased glucocorticoid release is also mediated by systemic surrogates of inflammation and infection including endotoxin and various proinflammatory cytokines like interleukin-1 (IL-1). In these unique potentially life-threatening circumstances, the typical glucocorticoid-associated long-loop inhibitory feedback on CRH and ACTH secretion is abrogated to allow sustained glucocorticoid secretion and its capacity to positively impact and limit the severity of the inflammatory response [168, 169]. The CRH-producing neurons of the PVN receive afferent inputs from other parts of the brain including the forebrain limbic system and the AN. The NPY-producing neuronal inputs from the AN appear to play a central role in increased CRH production from the PVN that occurs as a consequent stress response to hypoglycemia [170, 171]. Other neuronal inputs to the parvicellular PVN modulating CRH release include neurons with gamma-aminobutyric acid (GABA), glutamate, and endocannabinoid neurotransmitters. These also appear to play a role in the stress-induced CRH activation cascade [172]. Consequently while CRH activation and subsequently increased systemic glucocorticoid levels are a common final pathway response to various forms of systemic stress, the initiating sources and mediators are

variable depending on the unique form of stress and provide means to customize the degree and duration of the CRH response. There is also a degree of synaptic plasticity of the neural circuitry that regulates the HPA axis especially in the setting of chronic stress states.

The HPT Axis and Modulation of General Metabolism

The HPT is another three-tiered hypothalamic-centered neurosecretory regulatory system as illustrated in Fig. 5.14. It has the typical long- and short-loop negative feedback loop control systems. Circulating T4 and T3 are the major systemic peripheral signals that influence the synthesis, secretion, and release of TRH which is the main hypothalamic neurosecretory product at the head of the system cascade. Like the HPA system, the parvicellular neurons of the PVN are the main source of the TRH-producing neurons. T4 and T3 also have inhibitory feedback effects on adenohypophyseal production of TSH. There also appears to be a role of T3 and T4 in upregulating the expression of the TRH-degrading enzyme pyroglutamyl peptidase 2 which seems to be mainly expressed and produced from surrounding tanycytes [173]. Thyroid hormone has extensive functional roles in various aspects of human metabolism which won’t be elucidated here; however it is noteworthy to be aware that in the setting of prolonged fasting and/or systemic infections (two distinct physiologic/pathologic stress states), the typical HPT homeostatic system is altered presumably for survival benefit of the organism. This tends to be associated with reduction in TRH production and consequently systemic thyroid hormone production and TSH. The response is somewhat paradoxical and forms the basis for the well-known “non-thyroidal illness” changes in thyroid function test profile (previously known as the “sick-euthyroid state”). The overall systemic hormonal profile is akin to one of transient central hypothyroidism rather than typical serum profile typical of either primary hypo- or hyperthyroidism [43, 174–178]. It is presumed that the reduced thyroid hormone levels in such states by reducing thyroid hormone associate thermogenesis and catabolism results in

preservation of energy and nitrogen stores which is an appropriate adaptive response that reduces energy expenditure while preserving caloric resources and stores till the noxious stimulus or environmental situation is resolved or overcome. The importance of this adaptive response is demonstrated by the fact that the prior attempts at thyroid hormone repletion in such states have been shown to be potentially deleterious and the place of thyroid hormone repletion in this state remains very contentious [179–185]. The HPT-related hypothalamic nuclei also receive important afferent inputs from other parts of the hypothalamus including the AN which have negative/inhibitory modulating effects. These neurons have a myriad host of effector neurotransmitters including proopiomelanocortin (POMC), NPY, agouti-related peptide (AGRP), and cocaine amphetamine-related transcript (CART) [186–191]. Both the AN- and HPT-related PVN have leptin receptors and are thus leptin responsive. While alpha-melanocyte-stimulating hormone (α -MSH) (a POMC translation product) and CART stimulate TRH gene production and TRH release, NPY and AGRP have inhibitory effects. NPY mediates its effects by direct Y1 and 5 receptor-mediated effects, while AGRP mediates its effects indirectly by inhibiting α -MSH action on melanocortin receptors. The inhibitory and stimulatory neurons thus establish a steady-state homeostatic balance of TRH production based on the environmental dictated needs of the organism [128, 186–190, 192]. Thus in the setting of prolonged fasts when serum leptin production declines, the POMC and CART expressions from these central nuclei simultaneously decline, while NPY and AGRP expressions increase and consequently enhance the aforementioned TRH secretory decline seen in this state [193, 194].

The HPG Axis and Modulation of Gonadal Function and Pregnancy

The HPG control system is another example of a three-tiered system. Pulsatile GnRH production comes from the preoptic nucleus to the external layers of the median eminence among other sources for the central modulatory control of LH

and FSH adenohypophyseal production and release [195–197]. The intermittent gonadotrophin pulses of LH and FSH are central to normal human pubertal onset and progression as well as for normal reproductive and sexual function including but not restricted to ovulatory cycling, pregnancy, and other reproductive behaviors. Abolition of GnRH pulsatile secretion which can result from GnRH absence or continuous exogenous GnRH (or agonist analog) administration results in marked suppression of gonadotrophin production and secretion consequent upon desensitization of the GnRH receptors [198]. This forms the basis for the therapeutic use of GnRH analogs to achieve “medical castration” in such scenarios as the management of androgen-sensitive prostate cancer. While the physiologic basis for pulsatile GnRH production is still the subject of active investigation, one of the most important modulators of this process is the kisspeptin/G protein-coupled receptor 54 (GPCR-54) neuroregulatory system [199, 200]. The kisspeptins are a family of small peptides (usually ~10–54 amino acid length) that as a commonality activate and stimulate the GPCR-54s. In humans, kisspeptin 54 in particular is also known as metastin because of its additional capacity to inhibit cancer cell metastasis [199, 201, 202]. There is some evidence to suggest that the GnRH secretory hypothalamic nuclei also have some intrinsic oscillatory pulsatility as well. The fact that the kisspeptin GPCR-54 system however plays a dominant role in GnRH secretory pulsatility is underlined by the fact that both humans and animals with GPCR-54 deficiency demonstrate hypogonadotropic hypogonadism despite having normal GnRH neurons and normal LH and FSH secretion with exogenous GnRH [195, 203]. Furthermore central and peripheral exogenous administration of kisspeptides have been shown to be potential gonadotrophin secretagogues [204–206]. Kisspeptin-producing neurons have been demonstrated in the AN and in some species also from the anteroventral portions of the PVN. These neurons importantly express the alpha estrogen receptor [207–210]. These two sources of kisspeptin production are regulated inversely. The

AN-derived kisspeptin production increases with oophorectomy but decreases with exogenous estrogen administration, while the PVN-derived kisspeptin production does the opposite. It has thus been suggested that the two kisspeptin-producing hypothalamic neurons may mediate the positive and negative feedback effects estrogen has on GnRH neurons and gonadotrophin production [210–212]. It appears that the PVN-derived kisspeptin-producing neurons are central to the known estradiol- and progesterone-induced preovulatory GnRH and LH surge that precedes ovulation [213, 214]. The PVN-derived kisspeptin neurons are also sexually dimorphic, abundant in females but virtually absent in males [215–217]. In contradistinction, the AN-derived kisspeptin neurons co-secrete neurokinin B and dynorphin both of which enhance GnRH pulsatility by having an autocrine stimulatory effect on kisspeptin production but show no evidence of significant sexual dimorphism [218–221]. In addition, the AN-derived kisspeptin neurons also mediate the inhibitory effects of anorexia and tissue wasting on reproductive function utilizing a leptin-mediated mechanism [222].

The major elements of the kisspeptin-GnRH hypothalamic modulatory system are schematically detailed in Fig. 5.15.

The HPP Axis and the Modulation of Mammary Function and Lactation

The HPP axis is a two-tiered neurosecretory system that modulates the production and release of the adenohypophyseal hormone prolactin. This system has some links to the oxytocin neurohypophyseal secretory system whose secretory end product is the nonapeptide (nine-amino acid component small peptide) oxytocin. The secretions of both prolactin and oxytocin are stimulated by suckling of the mammary nipple [223]. These tactile stimuli are relayed to the hypothalamus via the spinal cord and brainstem via intra-hypothalamic pathways that have not yet been fully elucidated. Among the thus far defined brainstem relay stations for this process are ventrolateral medulla, the locus coeruleus, lateral parabrachial nucleus, caudal portions of the paralemniscal nucleus, and ventrolateral portions of

the periaqueductal gray [224]. Prolactin synthesis and release is the net result of a balance between inhibitory and stimulatory signaling set on a background of tonic prolactin release from the adenohypophyseal lactotrophs. Sucking has been demonstrated to inhibit the tuberoinfundibular release of prolactin inhibitory hormone (PIH) which is dopamine and whose main neurosecretory neurons are in the AN. Simultaneously, sucking stimulates increase in the production of prolactin-releasing factors from the PVN and neurohypophysis [225]. The exact details of the prolactin-releasing factor(s) (PRF) is still the subject of intense ongoing investigation, but among the suggested putative candidates are TRH, oxytocin, serotonin (5-hydroxytryptamine, 5HT), opioid peptides, and the tuberoinfundibular peptide of 39 residues (TIP39) [226]. TIP39 is a unique 39-amino acid small peptide that is the peptide product of the PTH2 gene. It is structurally related to PTH and the PTH-related peptide (PTHRP). It is a ligand for the PTH receptor 2. Its exact role and significance in human physiology is yet to be clearly elucidated [227, 228]. As regards its modulation of prolactin release, it appears to do this by increasing dynorphin production from relevant hypothalamic neurosecretory nuclei cells [226]. Prolactin does have a negative feedback effect on dopamine release from the AN which consequent of dopamine action as PIH results in a net positive autofeedback of prolactin on its secretion from the adenohypophysis. This enables sustained prolactin secretion and consequent sustained lactation with sucking. The sustained prolactin secretion also stimulates maternal behavior and “contraceptive” effect of inhibiting menstrual cycling and further reproductive activity and fertility [223, 229, 230]. Beyond prolactin’s effects on mammary tissue, its CNS effects are mediated by upregulation of prolactin receptors in the choroid plexuses especially during lactation as well as in the medial PON, PVN, SON, and AN [231, 232]. Pulsatile GnRH secretion and kisspeptin signaling also have important roles in normal prolactin secretory dynamics [223, 233, 234].

Sucking also increases NPY production from the AN via neuronal afferents from the brainstem

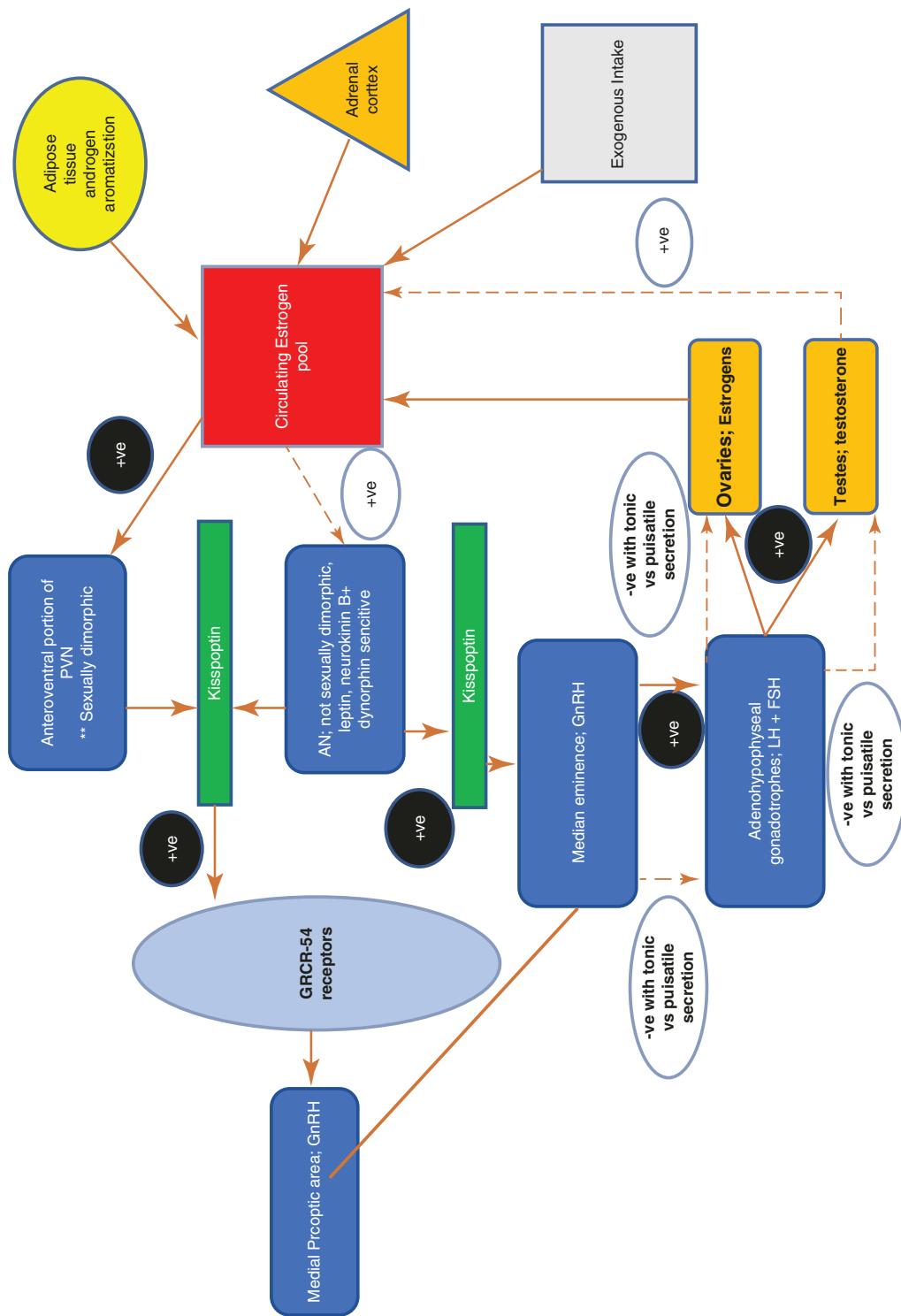


Fig. 5.15 Schema of the kisspeptin-GnRH hypothalamic system

as well as by reduction in serum leptin levels. NPY is a powerful orexigenic mediator, and thus its increased production with suckling and lactation mediates the hyperphagic response associated with lactation and breastfeeding ostensibly to compensate for the increased energy demands consequent upon lactation for feeding the young infant [235–237]. Other potential contributors to this lactation-induced hyperphagic response include increased AGRP production and concomitant reductions in POMC and CART production leading to net increase in orexigenic factors and net reduction in anorexigenic factors [238–242].

It is also important to be aware of the effect of suckling on oxytocin production and release from the neurohypophysis with the consequent milk let-down reflex. Some of the anatomical pathways that mediate this parallel those for prolactin production, but there are others unique to this physiologic response as well. Oxytocin-producing neurons from the PVN and SON produce oxytocin in pulsatile fashion as a response to suckling stimuli. This coordinated response is at least partly mediated by afferent inputs to these nuclei from glutamine-producing neurons from the lateral septum of the stria terminalis [226]. Local release of oxytocin from the neurohypophysis in response to suckling has a positive autoreceptor feedback effect to increase further oxytocin gene expression and oxytocin production. The salient elements of the HPP system and its role in modulating mammary function, lactation, and the milk let-down reflex are summarized in schematic form in Fig. 5.16.

The neurohypophyseal vasopressin system and modulation of osmoregulation and volume status will be discussed in depth in the section discussion of the neurohypophysis as will be the neurohypophyseal oxytocin system and its co-modulation of lactation, milk let-down, and uterine parturition functions.

Other Aspects of Hypothalamic Neuroendocrinology

Beyond the systems already discussed, the hypothalamus is sensitive and responsive to a host of other endogenous and external stimuli including light (which is involved in the regula-

tion of circadian and seasonal rhythms), various olfactory stimuli including pheromones, various steroids including gonadal and corticosteroids, various neuronal afferents (including inputs from the heart, enteric neural network as well as the gonads and reproductive system), autonomic nervous system inputs, stress, infective states associated with pyrexia and hyperthermia, and various blood-borne chemical mediators.

Among the blood-borne mediators known to modulate hypothalamic function include hormones, leptin, ghrelin, angiotensin, insulin, the various pituitary hormones, as well as cytokines, and serum analytes including glucose and osmolarity.

Hypothalamic Modulation of Food Intake

Lesional experiments from rodent models have demonstrated that the lateral portions of the VMN are intricately involved in control of food intake [243]. Electrical stimulation of this area results in increased food intake which if sustained can result in an obese phenotype. Consequently, in rodents this has been colloquially referred to as the “feeding center (aka hunger center).” Bilateral lesions in this area result in complete cessation of food intake which if permanent can then lead to cachetic wasting syndrome and ultimately death of the animal. Medial portions of the VMN contrawise have a modulatory effect on these effects of the lateral portions of the VMN. Bilateral lesions of medial portions of the VMN result in a voracious, hyperphagic clinical phenotype which if permanent results in development of obesity in the animal and is thus colloquially called the “appetite center (aka satiety center).” Electrical stimulation of this portion of the VML results in satiety state characterized by cessation in food intake which if sustained results in a cachetic wasting state akin to the wasting syndrome seen with bilateral lesions of the lateral portions of the VML [243]. Human equivalents of these syndromes have been described secondary to lesions in the VML including the classic descriptions of a woman with a VML-affected hypothalamic hamartoma [244].

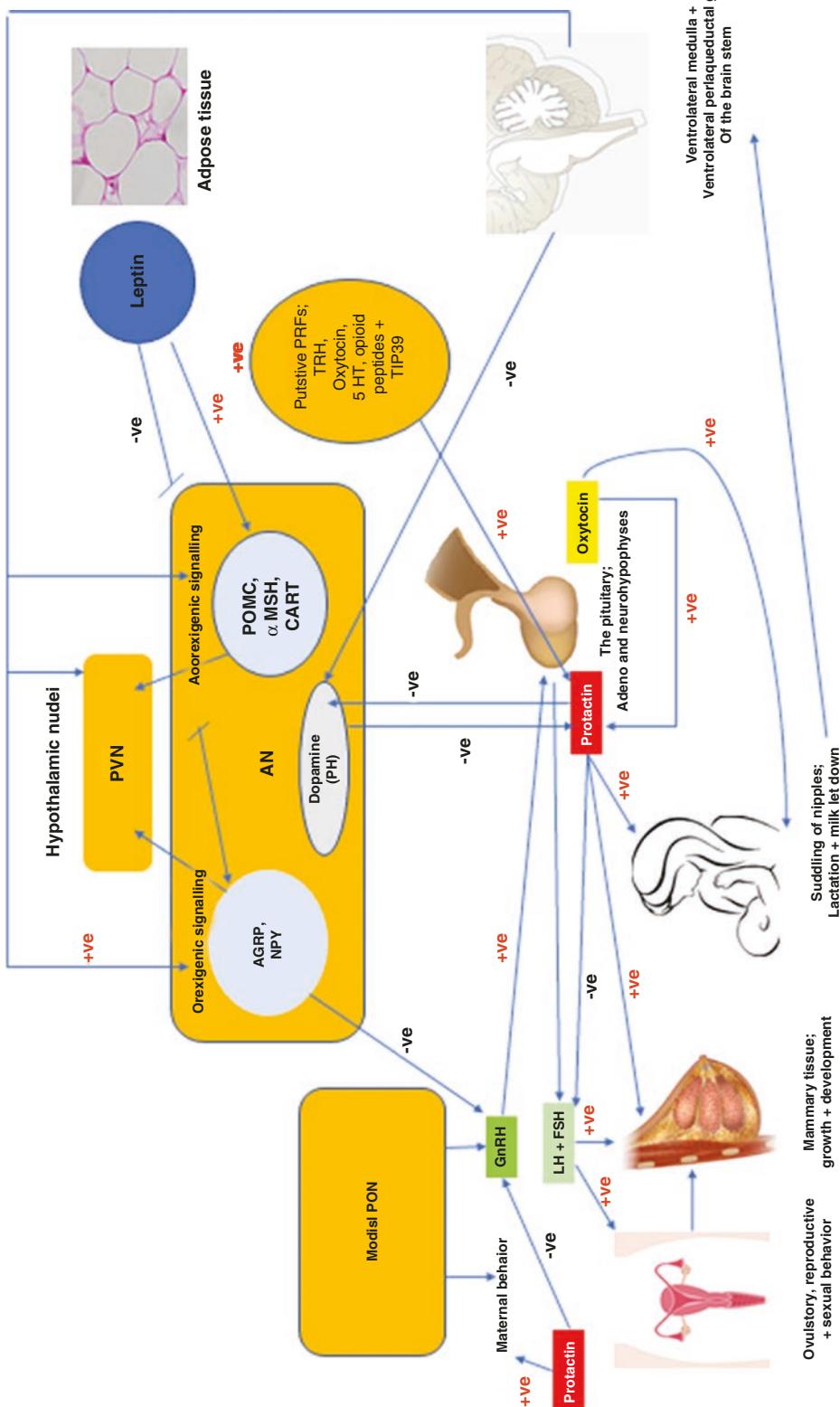


Fig. 5.16 Schema of the HPP axis and its modulation of lactation, mammary function, milk let-down, and related reproductive functions

The hypothalamic processes and mechanisms modulating food intake in humans are significantly more complex and will be discussed in more depth in the chapter on hypothalamic obesity and wasting syndromes. There are multiple suggested hypotheses suggested regarding hypothalamic regulation of food intake. It is likely that elements of each of these are involved in the global control system of food intake [245, 246].

Among the most prominent hypotheses are:

- (a) The lipostatic hypothesis which is adipocentric and indicates that adipose tissue produces a humoral signal(s) proportionate to amount of adipose tissue stores of the organism and that these then act on the hypothalamus to modulate food intake and energy expenditure depending on the current needs of the organism. Leptin and its related hypothalamic neurocircuitry are central to this hypothesis.
- (b) The gut-peptide hypothesis which is enterocentric and suggests that myriad gastrointestinal hormones including glucagon-like intestinal peptide-1 (GLP-1), gastric inhibitory peptide (GIP), glucagon, cholecystokinin (CCK), ghrelin, peptide YY (PYY), motilin, etc. have modulatory effects on food intake (some orexigenic and others anorexigenic). The production of these hormones is controlled by the entry of food into the gastrointestinal tract which then act secondarily on various hypothalamic and other brain nuclei and targets to modulate satiety vs hunger. Receptors for many of these gut-derived hormones have been demonstrated in various nuclei of the hypothalamus and other sections of the brain.
- (c) The glucostatic hypothesis is glucocentric and suggests that the satiety center of the VML is primarily glucose utilization sensing in its neurons. With reduced glucose utilization associated with reduced circulating glucose levels, the stimulation and activity of the neurons in this nuclei is reduced, and thus their satiety-mediating effect is reduced resulting in increased caloric food intake to normalize the circulating glucose levels. The

opposite occurs in settings of increased glucose utilization in these nuclei which then result in increased satiety signaling and thus reduced food intake.

- (d) The thermostatic hypothesis is temperature centric and suggests that reduced central body temperature below a predetermined set point stimulates appetite and food intake, while increase above the set point elicits the opposite response.

Table 5.2 details some of the better established hypothalamic mediators of orexigenic and anorexigenic feeding behavior.

The current understanding of hypothalamic modulation of appetite, satiety, energy balance, and consequently weight in humans apportions a major role to leptin pharmacodynamics [247]. Leptin is a major peripheral humoral signal

Table 5.2 Neuropeptides and other chemical mediators of hypothalamic mediation of satiety, appetite, and energy expenditure

Neuropeptides and other hypothalamic chemical mediators that modulate feeding, satiety, energy expenditure, and related behavior	
Orexigenic factors	Anorexigenic factors
Ghrelin	Leptin
NPY	α -, β -, and γ -MSH
AGRP	POMC
Orexins A and B	CART
Melanocyte-concentrating hormone (MCH)	CCK
Insulin ^a	Insulin ^a
Galanin	GLP-1
Pancreatic polypeptide	Amylin
Thyroid hormone; LT4 and LT3	Oxytomodulin
Adiponectin	PYY
Endocannabinoids (ECBs)	Obestatin
Dopamine	Nesfatin-1
Serum hypoglycemia	Bile acids
	Serotonin (5HT)
	Free fatty acids (FFA)
	L-Leucine

^aInsulins effect on feeding behavior is variable depending on the route and location of exposure with capacity to induce both orexigenic and anorexigenic feeding responses. The orexigenic response invariably occurs in the setting of associated consequent hypoglycemia

reflective body fat stores. Its primary secretory source is the adipocyte, but its major effector sites and receptors are the brain (and especially the hypothalamus) which acts on discrete nuclei and regions to affect behavioral, metabolic, and neuroendocrine behaviors reflective of either satiety or caloric intake depending on current environmental circumstances and needs [192, 193, 248–253]. In settings of caloric and nutrient excess, endogenous leptin secretion is reduced resulting on reduced appetite and increased energy and caloric expenditure. Settings of nutrient lack and starvation/prolonged fasting elicit the opposite leptin secretory response and consequent metabolic effects.

One of the main sites of action of leptin in the hypothalamus is the mediobasal hypothalamus in the AN via the specific leptin receptor (Ob-R or Lep-R). Leptin regulates the secretory response of two major groups of neurons in this nucleus: one set of orexigenic signals and another set of anorexigenic signals. The orexigenic AGRP/NPY neurons and the anorexigenic α -MSH/CART neurons of the AN have a close symbiotic interaction characterized by reciprocal connections between the two sets of neurons and antagonism of each by the other. The α -MSH neurons mediate their downstream effects mainly via the melanocortin 3 and 4 receptors (MCR-3 and MCR-4) [254, 255]. The melanocortin signaling pathway appears to be the dominant regulatory system controlling appetite and satiety in mammals including humans. While precise NPY deficiencies in various animal models have essentially normal phenotypes, various derangements of the melanocortin signaling pathways in animals and humans including but not restricted to MCR-4 loss of function mutations, POMC deficiency, prohormone convertase deficiency states, etc. all result in phenotypes of severe hypothalamic obesity [256–260]. Contrawise, several studies demonstrate the capacity to abrogate cancer cachexia in animal models by administration of MCR antagonists [261, 262].

Leptin-responsive neurons from the AN have projections to the lateral hypothalamus with melanocyte-concentrating hormone (MCH) and orexin as secretory products. From this point there are then neuronal projections to multiple

other locations including the cerebral neocortex, the midbrain, and the pons Varoli including the ventral tegmental area (VTA) and the nucleus accumbens which are both well-established “reward centers” involved in hedonic eating and food-related addictions [263, 264]. Beyond the AN, there are other hypothalamic nuclei of note that express leptin receptors including the hypothalamic dorsomedial nucleus and the dorsomedial portions of the VMN [265].

Beyond leptin as indicated by the gut-peptide hypothesis mentioned prior, a panoply of gut-derived peptides and other chemical mediators also plays important roles in modulating appetite and satiety by their action on brain centers and especially the hypothalamic AN. These include insulin, CCK, peptide YY (PYY), pancreatic polypeptide, GLP-1, amylin, oxyntomodulin, and ghrelin [266]. Unlike its peripheral circulating effects in causing hypoglycemia and hunger with increased caloric intake, the intracerebroventricular injection of insulin has an anorexiant effect and reduces body weight in addition to increasing NPY and AGRP production from the AN [267, 268]. Ghrelin as earlier detailed is a primarily stomach-derived orexigenic factor, but recently two other less well-characterized peptides have been identified: obestatin which is another peptide product of the ghrelin gene transcription and which appears to have an anorexiант effect again mediated via the AN and nesfatin-1 which co-localizes with ghrelin in gastric cells and also has anorexiант effects inducing satiety [61, 269–273]. It again mediates its appetite modulating activities via action on the AN.

New clinical and experimental observations are also detailing the roles of bile acids (which appear to have both a thermogenic and anorexiант effect resulting in increased energy expenditure and reduced food intake) and various gut microbiome profiles in modulating food intake and satiety. These observations are still being actively investigated, and the exact central locations in the hypothalamus and the rest of the brain that mediate their effects are thus unclear [274, 275].

Another peripheral hormonal signal with a role in modulating satiety and appetite via hypothalamic-mediated effects is thyroid hor-

mone (both levothyroxine, LT4, and liothyronine, LT3). The clinical syndrome of thyrotoxicosis and hyperthyroidism have been long known to be associated with hyperphagic response, and some recent work now suggests that this may be at least in part mediated by NPY secretory response from the AN [276–281]. There is also evidence that some of the orexigenic effects of T3 in particular are mediated via signaling at the VMN [282, 283].

There is also accumulating evidence for the presence of other adipose-derived hormonal agents: adipokines beyond leptin that in conjunction with leptin modulate satiety, food intake, and energy expenditure. Chief among these other adipokines is adiponectin (aka GBP-28, ACRP30, AdipoQ, and ApM1) [284, 285]. Adiponectin has a functional role that is opposite that of leptin apparently serving primarily as a starvation signal to preserve adipose stores. Its circulating levels increase in fasting/starvation states and reduce in states of satiety. It mediates an orexigenic response opposite to that of leptin which is again mediated by signaling in the AN. It does this by acting on the adiponectin receptor 1 to increase caloric intake and reduce energy expenditure by reducing uncoupling protein-1 (UCP-1) expression from brown adipose tissue depots [286].

Another group of chemical mediators that are involved on the regulation of satiety, appetite, and energy expenditure are the endocannabinoids (ECBs) and the now better appreciated systemic endocannabinoid system (ECS) [287, 288]. A more detailed discussion of this system and its role in weight, appetite, and satiety regulation will be included in the chapter on hypothalamic obesity and wasting syndromes.

The main endogenous ligands of the ECS are anandamide and 2-arachidonoylglycerol (2-AG). In addition to these endogenous ligands, marijuana and the myriad exogenous natural and bio-engineered cannabinoids modulate this system to varying degrees. The major effector for the ECS in the brain is the cannabinoid receptor type 1: CB1. It is widely distributed in the hypothalamus and the limbic system [289–291]. ECBs induce an orexigenic response when injected into the hypothalamus and may play an enabling role in

ghrelin's central phagic response. The ECBs effects of food intake and satiety appear to be mainly mediated via lateral hypothalamus and the PVN. They also activate the mesolimbic dopamine system that is involved in mediation of hedonistic eating [292, 293].

Dopamine and 5HT are two biogenic amines that also have important roles in regulation of satiety, appetite, and energy expenditure. 5HT appears to mediate its profound effects on caloric intake by acting on a subset of POMC neurons in the AN to reduce food intake and increase energy expenditure. This effect is mediated via action on the serotonin 2C receptors and has already been the subject of significant clinical and pharmacologic manipulation for obesity therapeutics in such medications as bupropion, fenfluramine, and lorcaserin [294, 295]. Dopamine on the other hand is more associated with reward-related hedonistic eating behavior, and this is mediated via leptin-responsive dopamine-producing neurons of the ventral tegmental area (VTA). It clearly plays a central role in the central-mediated “pleasurable reward response” associated with certain drug addiction scenarios as well as the hedonistic response associated with the ingestion of certain carbohydrate- and fat-rich foods [296–299]. Defective dopamine transmission in the mesolimbic system is known to be associated with diet-induced obesity, and the dopamine-mediated activation of hypothalamic “reward” centers has been demonstrated visually via functional PET scan imaging [300–306].

Nutrient sensing is another important modulator of appetite- and satiety-related behavior that is again mediated by action on hypothalamic nuclei. Hypoglycemia stimulates increased food intake by stimulating brainstem-located neurons that project to the hypothalamus with catecholamine neurotransmitter release [307]. Among the amino acids, L-leucine is unique in having anorexigenic effects mediated by inhibiting the AN-located NPY/AGRP neurons secretory output, while circulating free fatty acids (FFA) exert their anorexiant effects by reducing AMP-activated protein kinase (AMPK) and consequently NPY secretory output from the AN [308, 309].