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BRAIN PEPTIDES
(Second of Two Parts)

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PEPTIDE FUNCTIONS IN THE CENTRAL NERVOUS SYSTEM

Brain Peptides as Neuronal Markers

Most degenerative neurologic disorders are characterized by premature cell death in discrete neuronal populations. In some cases, the cellular components affected can be characterized partly by their functional roles in neuronal systems. Further delineation of the cellular basis of such neurologic disorders may contribute important new information about their pathogeneses. Immunocytochemical characterization of the cell types that are commonly affected in degenerative diseases, together with measurement of regional peptide concentrations, may provide clues to the neuronal specificity (or lack of it) involved in a given disorder. It is conceivable that one or more of the metabolic processes subserving synthesis, processing, or degradation of specific peptides is the locus of a pathologic process resulting in or contributing to cell death. An example is the recent report by Brandt et al.[92] postulating a hyper-endorphin syndrome in a child with fatal necrotizing encephalomyelopathy (Leigh's disease). Neuronal dysfunction may also result in defects in peptide release leading to loss of transsynaptic or trophic effects that are normally exerted on other neurons.

The idea that a specific neurotransmitter deficiency is important in the pathophysiology and clinical manifestations of a neuronal-system degeneration has been developed most completely in Parkinson's disease and Huntington's chorea. Both disorders have specific clinical and neuropathologic features. Their pathogeneses are different, since Parkinson's disease is usually sporadic, whereas Huntington's disease is an autosomal-dominant disorder with a high degree of penetrance.

The documented loss of dopaminergic cells in the substantia nigra in Parkinson's disease appears to account for most of the clinical manifestations, including slowness of movement, rigidity, and tremor, and also for its successful, though temporary, alleviation with L-dopa. However, the recognition of the loss of nigral dopaminergic cells has not provided any clues to the fundamental nature of the degenerative process. Hypothalamic dopaminergic neurons are largely preserved in this disorder, as is their neuroendocrine function, so that a generalized dopaminergic cellular disorder does not appear to occur.[93] Undefined additional factors must contribute to the selectivity of the degenerative process. Several peptides, including somatostatin, substance P, cholecystokinin (CCK), and the enkephalins, are present in high concentration in the basal ganglia (Table 3, Part 1).[12,13] Immunocytochemical studies and measurement of peptide changes in Parkinson's disease may contribute to a further definition of the disorder and possibly to a clarification of its pathogenesis.

Huntington's disease affects other neuronal populations; cellular loss is most extensive in the putamen and caudate nucleus and less widespread in the lower laminae of the cerebral cortex. Other areas of the basal ganglia are less severely affected. There is no explanation for this pattern of cell death. Neurons in these regions originate from different areas of the brain during development, differ markedly in cytologic features and connectivity, have dissimilar functions, and contain several neurotransmitters. The cellular loss in the putamen and caudate is accompanied by a loss of the neurotransmitter gamma-aminobutyric acid (GABA) and of glutamic acid decarboxylase, its synthesizing enzyme.[94] However, it is clear that the deficiency of this neurotransmitter is not itself the cause of cell death, because GABA-containing neurons elsewhere in the brain survive.

The neuronal loss in Huntington's disease is also accompanied by changes in the regional content of acetylcholine and certain peptides. The concentration of substance P is decreased in the globus pallidus and the putamen.[94] Levels of CCK[95] and met-enkephalin[96] are reported to be decreased in the basal ganglia in Huntington's disease, whereas levels of vasoactive in-

Abbreviations Used:

ACTH	Adrenocorticotropic hormone
β-LPH	β-Lipotropin
CCK	Cholecystokinin
CNS	Central nervous system
CSF	Cerebrospinal fluid
GABA	Gamma-aminobutyric acid
MSH	Melanocyte-stimulating hormone (α, β, and γ types)
PAG	Periaqueductal gray
TRH	Thyrotropin-releasing hormone
VIP	Vasoactive intestinal peptide

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testinal peptide (VIP) are normal.[97] We have recently found that concentrations of somatostatin are considerably increased in the caudate, putamen, and globus pallidus.[98] Spindel et al. have also found an increase in thyrotropin-releasing hormone (TRH) in tissue at autopsy of patients with Huntington's disease.[99] These findings point to a degree of neuronal selectivity in the degenerative process.

Alzheimer's disease, the most common cause of dementia in the United States, is characterized by loss of neurons in specific areas of the cerebral cortex, including the association areas of the orbital frontal, parietal, and temporal lobes. Changes are particularly extensive in the hippocampus. The disorder is usually sporadic but occasionally familial, and it occurs with increasing incidence in the seventh decade and beyond. The nature of the degenerative process is entirely unknown. The earliest cellular lesion, the neurofibrillary tangle, consists of an ultrastructurally identifiable alteration in the neurofilaments and neurotubules. Several studies have documented a decrease in acetylcholine content and choline acetyltransferase activity in the cortical regions affected. A recent report provided evidence for a selective decrease in somatostatin concentration in the hippocampus and other cortical regions in this disease.[100]

It will also be of interest to investigate a group of sensory disorders in which disorders of peptidergic function seem probable. One of these, congenital insensitivity or indifference to pain, is a condition in which the patient seems unresponsive to painful stimuli. Such patients may also have anhidrosis, poor temperature regulation, and orthostatic hypotension — features that point to dysfunction of the autonomic nervous system. The cellular defect in this disorder includes loss of small neurons in the dorsal-root ganglions, degeneration in the tract of Lissauer, and diminishment of the spinal tract of the trigeminal nerve. Interestingly enough, the neuropathologic changes recognized give no explanation for the commonly associated mental subnormality. Another disorder of potential importance for students of peptide function is familial dysautonomia (Riley–Day syndrome). This disorder, which is inherited as an autosomal-recessive trait, is recognizable by failure to thrive early in infancy, episodes of autonomic dysfunction, hyporeflexia, and impaired sensation of pain and temperature. Peripheral-nerve biopsy reveals a loss of small myelinated and unmyelinated fibers. The disorder is thought to be the result of failure in neural-crest cellular migration or differentiation, giving rise to a combination of cell loss in the dorsal-root ganglions and autonomic disturbance. Associated peptide dysfunction remains to be determined.

Perhaps the most intriguing development concerning peptide functions in relation to premature neuronal-cell death will be the evolution of molecular-biologic probes that measure cellular secretory products for tagging of cell dysfunctions. Purification of messenger RNA with preserved translation capabilities has been achieved in brain tissue post mortem.[101] Attempts to determine abnormalities of cell products in single neurons obtained from brain tissue affected by Alzheimer's disease and Huntington's disease may soon be feasible.

Trophic Functions of Peptides in Neural Tissue

The possibility that peptides have trophic effects in the central nervous system (CNS) has been considered.[102] In general terms, substances of small molecular weight, such as acetylcholine, GABA, glycine, and in most cases serotonin and norepinephrine, exert specific effects through receptors that are identifiable on either presynaptic or postsynaptic membranes. Many of these effects, but not all, involve alterations in ionic channels that secondarily influence transmembrane potentials and cellular electrical excitability. Some, such as dopamine, also exert effects by activation of membrane-bound adenylate cyclases. The effects of small peptides on neurons have been much more difficult to elucidate. They almost certainly include effects that are mediated by specific receptors (e.g., opioid peptides)[50] or by adenylate cyclase (e.g., VIP).[103] Other biochemical effects at the cellular level are presumed to occur. Some of these reactions may mediate chemotrophic functions that are important for intercellular connectivity during development and potentially for nervous-system regeneration. The extent to which peptidergic substances of low molecular weight may contribute to developmental structure-function relations and to plasticity within the brain are important areas for future investigation.

Peptides in Cerebrospinal Fluid

Various peptides have been detected by radioimmunoassay in cerebrospinal fluid (CSF)[104] (Table 4). The origin and fate of peptides found in the CSF are entirely unknown. The CSF is generally considered to be an important route for the removal of substances from the brain extracellular space, which is continuous with CSF, but it is also possible that such substances may be transported from the CSF to the brain extracellular space. Secretion of a peptide into the CSF could represent one mechanism for dissemination of the peptide to the brain parenchyma, although such a mechanism has not yet been demonstrated.

It is of interest that peptides' behavioral effects, which are often specific for an individual peptide, occur after administration through either the cerebroventricular or cisternal route. Although the concentrations given generally exceed those normally

Table 4. Peptides Detected in Human Cerebrospinal Fluid.

Thyrotropin-releasing hormone	Enkephalins
Luteinizing hormone-releasing hormone	Neurohypophyseal hormones
Somatostatin	Gastrin
Prolactin	Cholecystokinin
Growth hormone	Vasoactive intestinal peptide
ACTH	Angiotensin II
β-Endorphin	Substance P

found in CSF under physiologic conditions, the specificity of such effects is striking, and it implies that the peptide is capable of reaching specific target receptor sites and evoking selective responses. Immunoreactivity of peptides in CSF appears to be stable even when the fluid is kept at room temperature for several hours, suggesting that degradation is minimal. However, full characterization of the molecules that show peptide immunoreactivity in the CSF has not been accomplished, and further investigations are necessary.

Some fundamental observations must be made before a full understanding of peptides in CSF is achieved. These investigations would include sequential CSF sampling from lumbar cisternal and ventricular sites in human beings and primates in order to establish the dynamic characteristics of peptide secretion into CSF, further studies to document transport (active or passive) from blood to CSF and from CSF to blood, and anatomic studies of peptide penetration into the brain extracellular space after CSF instillation. The methods for these and other studies are now available and should provide important information.

Because CSF is accessible to study, it will be important to pursue analysis of peptide content in a variety of neurologic and psychiatric disorders that are unexplained at present. A few reports have documented changes in CSF concentrations of peptides either in neurologic disorders or after experimental manipulation. Levels of somatostatin are increased in lumbar CSF in various destructive and degenerative disorders of the CNS.[105] CSF levels of substance P are reported to be low in certain peripheral neuropathies and in the Shy–Drager syndrome[106] and to be elevated in spinal arachnoiditis.[107] Concentrations of immunoreactive β-endorphin and ACTH in CSF are reported to be normal in schizophrenia and acromegaly; a marked reduction in levels of both occurs in Cushing's disease.[108] Additional CSF studies in human beings are now feasible and may be pursued in association with efforts to stimulate or inhibit release of peptides selectively through peripheral-nerve stimulation or administration of neuropharmacologically active drugs. It is possible that assessment of peptide concentrations in chronic pain, narcolepsy, dystonia musculorum deformans, schizophrenia, and manic-depressive illness may contribute useful clinical information. A limiting factor, as in measurements of CSF concentrations of the metabolic products of conventional neurotransmitters, is the fact that lumbar CSF samples may principally reflect the release of spinal-cord rather than brain peptides.

Pain

The relay of painful sensations from peripheral tissues to the CNS occurs through unmyelinated or thinly myelinated nerve fibers that terminate in the outer laminae of the dorsal horn of the spinal cord. Fibers from the face end in the medulla oblongata in the spinal nucleus of the fifth cranial nerve. The pain fibers for the body arise from small bipolar neurons of the dorsal-root ganglions; these neurons send processes outward that end in peripheral tissues, primarily as free nerve endings, and centrally through the dorsal root to end in the substantia gelatinosa. The neurotransmitters that relay nociception have been extensively investigated, and recent experiments have implicated several peptides, notably substance P. In addition to the initial processing of nociceptive inputs that occurs at the spinal-cord level, there are also descending inputs from brain-stem centers to the spinal cord that exert effects over local circuits.

Immunocytochemical studies indicate that substance P, somatostatin, CCK, angiotensin II, and VIP are present in spinal-ganglion neurons.[11] It has been estimated that 20 per cent of all ganglion cells in the cat and rat contain substance P. A smaller proportion contain somatostatin. Both cell types have extensive terminations in the substantia gelatinosa. Dense-core granules located in primary afferent terminals in the monkey show a positive reaction product for substance P.[109] These terminations appear to occur largely by axosomatic and axodendritic contacts on spinothalamic relay cells of the dorsal horn. Some of these cells can be identified as enkephalin-containing cells.

The evidence that substance P is a primary sensory neurotransmitter is convincing. The substance is released from the spinal cord after depolarization by potassium or electrical stimulation.[110] Peripheral-nerve stimulation of nociceptive fibers elicits release of the peptide into the CSF.[110] Microiontophoretic application of substance P results in prolonged excitation of dorsal-horn neurons, which can also be shown to be activated by noxious peripheral stimuli.[111]

Analgesia can be induced by agents that cause depletion of substance P. Capsaicin, a substance that is obtained from red pepper and has been shown to be structurally related to homovanillic acid, causes release and nerve-terminal depletion of substance P from the spinal cord, accompanied by elevated peripheral thresholds to painful stimuli.[112] Long-term administration of capsaicin leads to degeneration of small-diameter sensory neurons that contain substance P, and the concentration of the peptide in the spinal cord is reduced by 50 per cent. These observations provide evidence for a function of the peptide in pain transmission at the spinal-cord level. An interaction of substance P with enkephalins at the spinal-cord level is suggested by evidence that enkephalins inhibit release of substance P from sensory neurons in culture.[113]

Peptides also function in pain pathways at other sites in the CNS. In the early 1970s it was shown that electrical stimulation of discrete areas of the brain stem, especially the ventrolateral periaqueductal gray (PAG) matter of the midbrain, produces analgesia in animals[114] and human beings.[115] The presence of opioid receptors has been documented in similar brain regions. Considerable overlap is found between the

sites of stimulation-produced analgesia and of analgesia induced by intracerebral opiate injection; the PAG is the most effective site for both. These data suggest that endogenous opioids may be active in this system. In addition to high receptor concentration in the PAG, immunohistochemical studies show a rich field of enkephalin terminations. Further evidence that opioid peptides are involved in the pain relay at this level is the finding that analgesia produced by PAG stimulation in human beings is partially blocked by naloxone[115] and is associated with a rise in β-endorphin immunoreactivity in the CSF.[116] Intraventricular administration of β-endorphin is effective in causing analgesia in laboratory animals, whereas the intravenous route is not, presumably because of failure to cross the blood-brain barrier.[83] Intrathecal injection of β-endorphin in human beings is effective in causing profound analgesia.[117]

The question of whether acupuncture is effective in altering nociceptive inputs and whether it acts by means of endogenous opioids is still unresolved. Electroacupuncture is reported to stimulate release of met-enkephalin into the CSF in human beings.[118] As recently reviewed by Wall and Woolf,[119] there are few controlled clinical trials of the efficacy of acupuncture in the treatment of chronic pain, and the results are inconclusive. There is no doubt, however, that acupuncture can induce powerful, though transient, analgesic effects in selected persons. The effectiveness of transcutaneous stimulation in alleviation of certain kinds of pain in the segmental distribution of the stimulation provides support for a role of sensory convergence and interdependence at the spinal-cord level. The role of peptides in mediation of these responses requires further study. Naloxone, an opiate antagonist, completely blocks the analgesic effects of exogenously administered narcotics. However, naloxone has little effect on pain thresholds in human beings, although it is postulated to be effective when given in high doses to block placebo-induced analgesia in some subjects.[120] In some but not all studies, naloxone has been reported to block acupuncture-induced analgesia in animals and human beings.[119]

Peptides and Cerebral Circulation

Autoregulation of the cerebral circulation is only partly understood. Blood flow to the brain parenchyma is regulated within a narrow range despite large fluctuations in systemic blood pressure. Neuronal activity is known to increase local blood flow. Peptides with known vasoactive properties are found within the CNS in axonal processes that terminate on or near blood vessels.

VIP, a 28-amino acid peptide, is found in highest concentrations in the cerebral cortex rather than the hypothalamus, unlike most other peptides. A well-developed plexus of VIP-immunoreactive nerve fibers is present around the anterior cerebral, proximal middle cerebral, and posterior communicating arteries.[121] Terminals of these fibers penetrate the adventitia-media border and terminate in a morphologic arrangement that closely resembles the pattern of noradrenergic and cholinergic fibers.

In vitro studies support a function of VIP in vasomotor regulation. Larsson et al.[121] found that VIP applied to a segment of cat middle-cerebral artery in an organ bath had no effect on resting tone; however, in the presence of tonic contraction induced by 5-hydroxytryptamine, VIP produced a dose-dependent dilatation. This observation suggests that the effects of VIP on cerebral blood-vessel tone are modulatory rather than direct.

There is no definitive evidence to define the physiologic role of peptides in the regulation of cerebral blood flow or oxygen metabolism. A recent report indicates that intracarotid injection of VIP increases cerebral blood flow in anesthetized animals.[122] The fact that peptides with known vasoactive properties, such as VIP, substance P, neurotensin, bradykinin, oxytocin, and angiotensin, are found within the CNS in nerve terminals, some of which end on or near blood vessels, suggests that these peptides may contribute to regulation of cerebral vascular tone.

Opioid Peptides and Epilepsy

Parenteral administration of high doses of morphine or withdrawal of morphine in habituated persons is associated with changes in seizure threshold or the appearance of epileptiform discharges on the electroencephalogram.[123-125] Opioid peptides applied iontophoretically usually inhibit neuronal firing,[126-129] although an excitatory action is seen in the hippocampus.[129] Cortical epileptic seizures can be induced in rats by the cerebroventricular administration of met-enkephalin or leu-enkephalin.[84,130] Chronic motor seizures in rats resulted in elevated levels of met-enkephalin in the hippocampus.[131] Interestingly enough, enkephalin induces seizures in doses that are devoid of analgesic activity, and the seizures are attenuated or prevented by naloxone.[84] Conversely, morphine produces analgesia at low doses, and much higher doses are required to produce seizures.[125] A recent report indicates that anticonvulsants that are most effective in petit mal epilepsy, such as ethosuximide, trimethadione, and valproate sodium, are effective in blocking leu-enkephalin seizures, whereas major anticonvulsants such as phenytoin and phenobarbital, are ineffective.[132]

The epileptogenic and analgesic properties of the enkephalins appear to be both dose-specific and site-specific. The same dose of enkephalin that causes analgesia without seizures when injected near the PAG causes seizures without analgesia when administered near the dorsomedial nucleus of the thalamus.[84,132] Moreover, β-endorphin induces epileptiform activity in the limbic cortex when administered into the CSF of rats.[83] This activity is induced by doses that are devoid of analgesic activity, and the epileptiform activity is not associated with discernible behavioral effects.

In the baboon, *Papio papio*, which is photosensitive for seizures, the opioid peptides are without epileptogenic effect.[133] Cerebroventricular injection of met-enkephalin and leu-enkephalin, β-endorphin, FK 33.824 (a long-acting met-enkephalin analogue), and morphine all failed to produce epileptic effects. Although the susceptibility of met-enkephalin and leu-enkephalin to rapid biologic degradation could explain their lack of activity in the baboon, if diffusion through periventricular tissue were required to reach epileptogenic sites, this argument does not apply to the other compounds, which are stable.

In the rat, the epileptogenic effects of opiates and opioid peptides may depend on a selective inhibition of inhibitory neurons in the hippocampus.[134] Since the hippocampus does not participate in the genesis of photically induced seizures in the baboon,[135] these data are consistent with the failure of morphinomimetic peptides to facilitate such seizures. The absence of any signs of hippocampal seizures after administration of morphine or opioid peptides suggests that the baboon may be less sensitive than the rat to the indirect excitant effect of enkephalins on the hippocampus. The importance of these substances in human epilepsy remains to be determined.

Effects of Peptides on Behavior

Evidence has accumulated over the past two decades to indicate that impairment of conditioned avoidance behavior, which is present in hypophysectomized animals, is corrected by systemic or cerebroventricular administration of ACTH, α-melanotropin (α-MSH), and vasopressin. This effect can also be induced by fragments or analogues of these hormones that are devoid of any endocrine effects.[136] ACTH fragments 4-7 and 4-10, which are sequences common to ACTH, α-MSH, and the "β-MSH-like" part of β-lipotropin (β-LPH) and of γ-MSH, are effective in this regard. Similar behavioral effects of these peptides can also be observed in intact animals. The data suggest that these peptides can enhance the rate of acquisition of avoidance behavior — an effect interpreted as memory formation — and can inhibit the extinction of such avoidance behavior on stimulus withdrawal — an effect interpreted as persistence of a learned response. Further studies suggest that ACTH fragments are involved in short-term memory processes, whereas vasopressin is involved in long-term memory. It has subsequently been shown that vasopressin and oxytocin have opposite effects on avoidance behavior. Some of the effects of vasopressin in correcting deficient passive-avoidance behavior in Brattleboro rats with hereditary vasopressin deficiency may be due to enhanced central availability of oxytocin, since oxytocin levels in the CSF of these rats are elevated.[137]

More recently, endorphins have also been reported to affect avoidance behavior.[136] Subcutaneously administered α-endorphin is more effective than γ-endorphin in facilitating acquisition of avoidance behavior and delaying extinction, whereas γ-endorphin facilitates extinction, and des-tyrosine γ-endorphin is even more active.[76] In view of the inability of the latter derivative to bind to opiate receptors, such observations suggest a dissociation of behavioral effects from opiate binding.

The effects of vasopressin on learning may be mediated by modulation of neurotransmission in distinct catecholamine systems distributed through the dorsal noradrenergic bundle.[138] Evidence from electrophysiologic studies suggests that the mechanism responsible for the effects of ACTH on behavior involves facilitation of a selective arousal state of limbic-midbrain structures, resulting in increased attention and perception and enhancement of stimulus-specific behavioral responses.[139] The biochemical basis for these effects, whether through alterations in cellular second-messenger systems such as cyclic AMP, protein synthesis, membrane phosphorylation, or neurotransmitter turnover, remains to be established.

When behavioral effects of exogenously administered peptides were initially reported, it was concluded that they might be derived from endogenous pituitary hormones secreted into plasma, with degradation fragments entering the brain. However, to date there has been no evidence of generation of such fragments in plasma; it is also doubtful, in view of the short half-life of such fragments in the blood after exogenous administration, that such a mechanism could be important. The demonstration of the synthesis of the ACTH precursor molecule in the brain suggests the possibility that these fragments are derived locally; anatomic pathways from the site of synthesis in the hypothalamic arcuate nucleus to the limbic system have been reported.[140] The postulated existence of vascular pathways providing for retrograde flow from the pituitary to the brain has also been suggested as the route whereby such peptides may reach the CNS.[3,4] The latter explanation implies that conditions that affect pituitary secretion, such as stress, are involved in learning. The more attractive postulation of a CNS source for these peptides provides a means for integration of diverse types of neural mechanisms.

Initially, the physiologic relevance of these animal studies was questioned, since the major conditioned avoidance response studied was that motivated by fear. Subsequent studies have indicated the effectiveness of these peptides in operant-conditioning situations in which animals were motivated by hunger or sex.[141] To date, few studies have been performed in a double-blind manner; there is still limited information on dose-response characteristics, the relation of the dose administered to physiologic concentrations of peptides present in the animal, sex differences in response, and circadian variability of response. Questions also arise as to whether the active ACTH 4-7 fragment (Met-Glu-His-Phe) is derived from the ACTH/MSH molecule or whether this sequence occurs in another uncharacterized peptide. Since the *dextro*-7 isomer of ACTH 4-7 has effects similar to

those of the *levo-* isomer in avoidance acquisition but opposite effects on extinction, this observation raises questions about the nature of the receptor involved. There are also reports indicating an affinity of ACTH and its fragments for opiate receptors.[142] It is apparent that although a role for these peptides in cognitive function appears to have been shown, the specificity of these responses and their biochemical and physiologic basis require extended investigation.

The appearance of these studies has occasioned questions on their applicability to human learning and memory. There are reports that systemic administration of ACTH 4-10 improved the attention of mentally retarded subjects[143] and increased visual discrimination in normal men, whereas it augmented verbal skills in women.[144] Negative findings have also been reported,[145] and the number of clinical observations thus far is insufficient to yield any definite conclusions. Most of the studies to date have been performed in young, healthy volunteers; studies in persons in whom cognitive functions are disturbed, such as the elderly, may provide more consequential information.

Studies with vasopressin or its long-acting analogue 1-desamino-8-D-arginine vasopressin have reported improvements of ability to learn new information,[146] and beneficial effects in patients with long-term amnesia resulting from car accidents.[147] Beneficial effects of vasopressin have also been noted in several tests of attention and memory in elderly persons.[148]

Feeding Behavior

The relation of food intake to caloric needs represents one of the body's major homeostatic mechanisms. Previous studies have described satiety centers located in the ventromedial nucleus, which receives stimulatory serotonergic inputs from the raphe nuclei and inhibitory inputs from the ventral adrenergic bundles, and feeding centers in the lateral hypothalamus, which receives a prominent dopaminergic input.[149] There is controversy over whether dopamine has a stimulatory or inhibitory role.[150] There appears to be a reciprocal interaction between the ventromedial hypothalamus and the lateral hypothalamus, characterized by mutual inhibition — that is, activation of one area results in inhibition of the other, whereas suppression of one results in activation of the other.

Recent studies in animals have implicated several peptides in the regulation of feeding behavior.[151] CCK,[152] TRH,[153] and insulin[154] are reported to be satiety factors, decreasing food intake, whereas β-endorphin has been implicated in states of increased food ingestion.[155] The site of action of these peptides in affecting feeding behavior has been presumed to be within the CNS, with controversy over whether this effect is mediated through the ventromedial hypothalamus[156]; interaction with the noradrenergic system has been proposed.[157] Suppression of feeding by CCK has also been reported to be mediated through a parenteral abdominal site.[158]

Peptidergic effects on glucoregulation have also been described. Systemic administration of neurotensin and bombesin and intraventricular administration of CCK have been shown to produce hyperglycemia.[159,160] Studies in human subjects, however, using physiologically relevant doses of neurotensin, which were fivefold lower than those employed in animal studies, have failed to reveal a hyperglycemic effect.[161]

It has been suggested that the low levels of CCK reported to be present in the brains of genetically obese (ob/ob) mice may be causally related to the hyperphagia present in these animals.[162] Other studies,[163-165] however, have failed to show a notable alteration in brain CCK in obese animals. It has also been suggested that the elevated pituitary β-endorphin concentrations present in genetically obese animals[155] are causally related to such obesity. This hypothesis has been questioned,[166] since such elevations follow but do not precede the development of obesity. In addition, there are reports of reversal of hyperphagia by naloxone in several experimental models of obesity, not all of which were characterized by increased pituitary β-endorphin concentrations.[167] It would be expected, however, that central rather than pituitary β-endorphin concentrations would provide a more meaningful insight into the role of β-endorphin in obese states, and there are recent reports that brain β-endorphin concentrations are increased in genetically obese rats[168] and that starvation decreases such concentrations.[169] In view of the known interaction of β-endorphin with hypothalamic serotonin and dopamine turnover, it is indeed possible that interactions between the peptidergic and monoaminergic systems are involved in feeding regulation. There is an intriguing report that the body weight of the genetically obese rat is greatly reduced after long-term ingestion of L-dopa.[170]

Temperature Regulation

Temperature regulation represents a complex interplay between peripheral and central receptors.[149,171] There have been numerous studies of the effects of changes of temperature on neurotransmitter release (centrally and peripherally), as well as on hormone release and, conversely, on the effect of neurotransmitters (usually administered intracisternally) on temperature regulation.[149] With regard to the central mechanisms involved in temperature regulation, those studies have emphasized the role of noradrenergic and serotonergic involvement, although controversy exists over the specific effects of these substances on body temperature among various species. The effects of central cooling on peripheral release of norepinephrine and thyroid hormone also appear to be well substantiated.

Recent studies have implicated several brain peptides in the regulation of body temperature. These ef-

fects have yet to be fully integrated into any of the above schemes. Intracisternal injection of TRH causes hyperthermia, whereas small amounts (10^{-10} to 10^{-15}M) of β-endorphin, neurotensin, and bombesin result in hypothermia.[172-174] There is some evidence of an interaction of neurotensin with dopaminergic systems and with the hypothalamic-pituitary-thyroid axis.[175] Bombesin has different effects in different species, and it is still uncertain whether the hypothermic effect occurs at ambient temperatures[172] or only in animals exposed to cold.[176] The effects of bombesin are reversed by administration of either TRH, prostaglandins E_1 and E_2, or naloxone.[174] TRH also reverses the hypothermic effect of endorphin, but not the antinociceptive effect of morphine.[177] The effect of TRH is observed in hypophysectomized animals, implying a central rather than a peripheral effect. A recent report has described a function of vasopressin in suppression of the febrile response in newborn sheep.[178]

A possible common mechanism responsible for all the above effects is suggested by findings that a decrease in hypothalamic calcium concentration or an increase in sodium concentration elevates the core temperature,[179] whereas an increase in hypothalamic calcium concentration leads to a drop in core temperature.[180] Prostaglandins, which are reported to be thermogenic, facilitate mitochondrial uptake of calcium, thereby decreasing local concentrations.

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