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Serotonin and the Neuroendocrine Regulation of the Hypothalamic–Pituitary–Adrenal Axis in Health and Disease

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Serotonin (5-hydroxytryptamine, 5-HT)-containing neurons in the midbrain directly innervate corticotropin-releasing hormone (CRH)-containing cells located in paraventricular nucleus of the hypothalamus. Serotonergic inputs into the paraventricular nucleus mediate the release of CRH, leading to the release of adrenocorticotropin, which triggers glucocorticoid secretion from the adrenal cortex. 5-HT_{1A} and 5-HT_{2A} receptors are the main receptors mediating the serotonergic stimulation of the hypothalamic–pituitary–adrenal axis. In turn, both CRH and glucocorticoids have multiple and complex effects on the serotonergic neurons. Therefore, these two systems are interwoven and communicate closely. The intimate relationship between serotonin and the hypothalamic–pituitary–adrenal axis is of great importance in normal physiology such as circadian rhythm and stress, as well as pathophysiological disorders such as depression, anxiety, eating disorders, and chronic fatigue.

I. OVERVIEW OF SEROTONIN

The serotonergic neurons are located in discrete midline nuclei in the brainstem, termed the raphé nuclei. Most ascending serotonergic pathways that innervate the forebrain originate in the dorsal raphé nucleus, the median raphé nucleus, and a lateral–ventral group of serotonergic neurons known as the B9 cell group (Dahlstrom and Fuxe, 1964).

A. THE DISCOVERY OF SEROTONIN

The first interest in serotonin (5-hydroxytryptamine, 5-HT) began when Stevens and Lee (1884) recognized that there was a substance, in clotting blood, that caused vasoconstriction. Because of its characterization as a

"tonic" substance in "serum," the name serotonin was coined. However, more than 60 years would pass before Rapport and colleagues at the Cleveland Clinic (Cleveland, OH) would isolate and purify 5-HT from serum in order to investigate it as a possible cause of high blood pressure (Rapport *et al.*, 1948). At this point Rapport was able to give the first proposed structure of 5-HT (Rapport, 1949).

Evidence of the presence of 5-HT in the brain was not available until 1953, during an analysis of various tissues (Twarog and Page, 1953). After this discovery, the role of 5-HT as a chemical messenger in the brain was investigated (Amin *et al.*, 1954; Florey and Florey, 1954; Welsh, 1957), marking the beginning of the neuropharmacological study of 5-HT.

B. ANATOMY OF SEROTONERGIC PATHWAYS

With the development of the Falck–Hillarp histochemical technique (Falck *et al.*, 1962), Carlsson and colleagues (1962) demonstrated that after exposing freeze–dried tissue sections to formaldehyde vapors, indoleamine compounds such as serotonin emit a yellow fluorescence. Using this method, Dahlstrom and Fuxe (1964) demonstrated that the highest concentration of 5-HT was found in the brainstem raphé nuclei. In their work they described the ascending pathways from the raphé as traveling through the medial forebrain bundle to provide the primary serotonergic innervation of the forebrain; they also described descending pathways from the raphé to the intermediolateral cell column and the dorsal and lateral horns of the spinal cord.

The serotonergic cell bodies located in the midline of the brainstem have been designated B1–B9 (Dahlstrom and Fuxe, 1964). Immunofluorescence techniques have gone further to identify 5-HT cell bodies in the locus coeruleus, subcoeruleus, and the substantia nigra (Liposits *et al.*, 1987b). The primary pathway for serotonergic axons to the forebrain travels through the medial forebrain bundle (Azmitia and Segal, 1978; Steinbusch, 1981; Molliver, 1987; Petrov *et al.*, 1992b). B1–B5 cell groups send projections to the spinal cord and brainstem, while B7–B9 cell groups are the two raphé nuclei and ventrolateral mesencephalic cell group that give rise to much of the ascending serotonergic projections to the forebrain (Molliver, 1987). The serotonergic nuclei involved in the regulation of the neuroendocrine system are located in the midbrain and pons. Serotonin fibers extend from the dorsal (B7) and median (B8) raphé to the hypothalamus (Azmitia and Segal, 1978; Van de Kar and Lorens, 1979; Van de Kar *et al.*, 1980; Sawchenko *et al.*, 1983).

C. SEROTONIN RECEPTORS

In 1979, only one serotonin receptor was believed to exist. Over the next 20 years, however, several serotonin receptors were identified and

characterized. The most recent criteria for classification of 5-HT receptors were set forth by the International Union of Pharmacology Committee on Drug Classification and Receptor Nomenclature (Hoyer *et al.*, 1994). This rigorous classification led to the modern nomenclature for 5-HT receptors, which now comprises seven families (5-$HT_{1–7}$) totaling 14 structurally and pharmacologically different receptors (Hoyer *et al.*, 1994; Hoyer and Martin, 1997) (Table I). The criteria are operational, that is, drug-related data such as selective agonists, selective antagonists, and ligand-binding affinities; structural, that is, molecular structure; and transductional, that is, nature of effector system (Humphrey *et al.*, 1993; Hoyer *et al.*, 1994). Much of the interest behind classifying receptors lies in the need to produce more selective drugs.

The large family of serotonin receptors can be divided into two distinct families: seven-transmembrane proteins that are G protein-coupled receptors and ligand-gated ion channels. The G protein-coupled receptor family consists of 5-HT_1, 5-HT_2, 5-HT_4, 5-HT_5, 5-HT_6, and 5-HT_7 receptors whereas the 5-HT_3 receptors are the sole family consisting of serotonin-gated ion channels. The G protein-coupled receptor family can be further divided into three diverse families on the basis of their coupling to different G proteins. These families include those that couple to $G_{i/o/z}$ proteins (5-HT_1), to $G_{q/11}$ proteins (5-HT_2), and to G_s protein (5-$HT_{4,6,7}$). The receptors coupled to $G_{i/o/z}$ proteins (5-HT_1 receptor subtypes) inhibit adenylyl cyclase activity, thus decreasing the formation of cyclic AMP (cAMP). The 5-HT_2 receptor subtypes, which couple to $G_{q/11}$ proteins, activate phospholipase C, leading to the formation of the two second messengers inositol triphosphate (IP_3) and diacylglycerol (DAG). The 5-$HT_{4,6–7}$ receptor subtypes couple to G_s proteins and activate adenylyl cyclase, leading to an increase in cAMP formation. To date, the coupling of 5-HT_5 receptors has not been fully elucidated.

The serotonin receptors can also be divided into two groups on the basis of their neuronal location; the receptors can be located on either a target neuron or on the 5-HT neuron itself. Serotonergic receptors expressed by the 5-HT neurons are considered to be 5-HT autoreceptors. Autoreceptors are defined as receptors that respond to the transmitter substance released by their own nerve endings. The serotonergic system has two classes of autoreceptors: somatodendritic (5-HT_{1A}) and presynaptic (5-$HT_{1B/1D}$). The somatodendritic autoreceptors are defined by their location on the cell bodies and dendrites of serotonergic neurons and are composed of the 5-HT_{1A} receptor subtype. When the somatodendritic 5-HT_{1A} autoreceptors are activated by the release of 5-HT from collaterals of the same neuron or neighboring neurons, there is a decrease in raphé cell firing (Barnes and Sharp, 1999). It should be noted that 5-HT_{1A} receptors are also located on target neurons. Presynaptic serotonin autoreceptors are located on serotonergic axon terminals. The 5-HT_{1B} and 5-HT_{1D} receptors are the two

TABLE I. Characterization of Serotonergic Receptors

Receptor	Location	Coupling	Transduction system	Agonist	Antagonist
5-HT$_1$					
5-HT$_{1A}$	Neuronal: primarily in CNS	$G_i/G_o/G_z$	Adenylyl cyclase (–), K^+ channel (↑), Ca^{2+} channel (↓), MAP kinase (↑)	8-OH-DPAT, buspirone, 5-CT, ipsapirone, flesinoxan, gepirone, tandospirone	WAY 100635, WAY 100135, methiothepin, spiperone, pindolol, NAN-190
5-HT$_{1B}$	CNS	G_i/G_o	Adenylyl cyclase (–)	Sumatriptan, L-694247, RU 24969, 5-CT, CP-93, 129, CP-94, 253	SB-224289, SB-236057, SB-216641, GR 127935, methiothepin
5-HT$_{1D}$	CNS, vascular smooth muscle	G_i/G_o	Adenylyl cyclase (–)	Sumatriptan, PNU 109291 L-694247, RU 24969, 5-CT, naratriptan, zolmitryptan	BRL 15572, GR 127935, methiothepin
5-HT$_{1E}$	CNS	G_i/G_o	Adenylyl cyclase (–)	5-HT	methiothepin (very weak)
5-HT$_{1F}$	CNS	G_i/G_o	Adenylyl cyclase (–)	LY344 864, LY334 370, sumatriptan, 5-HT	methiothepin (very weak)
5-HT$_2$					
5-HT$_{2A}$	CNS, vascular smooth muscle, platelets, gastrointestinal tract, lung	$G_{q/11}$	PI hydrolysis, Ca^{2+} (↑), PLA_2 → arachidonic Acid, JAK-STAT (?), MAP kinase (?)	DOI, DOB, MK-212, quipazine, m-CPP	MDL 100,907, ketanserin, spiperone, mianserin
5-HT$_{2B}$	Stomach, vascular smooth muscle, CNS (?)	$G_{q/11}$	PI hydrolysis, Ca^{2+} (↑)	BW 723C86, α-methyl-5-HT, DOI	SB-200646, SB-204741
5-HT$_{2C}$	CNS	$G_{q/11}$	PI hydrolysis, Ca^{2+} (↑), PLA_2 → arachidonic acid	DOI, DOB, Ro 60-0175, m-CPP	SB-242084, SB-200646A, SB-206553, mesulergine, RS102221, ritanserin, mianserin

Continued

TABLE I. (*Continued*)

Receptor	Location	Coupling	Transduction system	Agonist	Antagonist
5-HT$_3$					
5-HT$_{3(A–B)}$ 5-HT$_{3C}$	CNS, peripheral neurons, gastrointestinal tract	Ligand-gated cation channel		α-Methyl-5-HT, SR 57227, phenylbiguanide	Ondansetron, granisetron, tropisetron, MDL 72222, lerisetron, zacopride
5-HT$_4$					
5-HT$_{4(a–h,hb,n)}$	Gastrointestinal tract, CNS, heart, bladder, adrenal gland	G_s	Adenylyl cyclase (+), Ca^{2+} channel (↑), K^+ channel (↓)	TS-951, metoclopramide, prucalopride, tegaserod, zacopride, cisapride, BIMU 1, BIMU 8	GR 113808, BJP 118655, SB-207226, SB-207710, SB-204070, SDZ205-557, RS 100235
5-HT$_5$ 5-HT$_{6(a–b)}$	CNS	(?)	Adenylyl cyclase (–) (?)	5-HT, 5-CT, LSD	Methiothepin
5-HT$_6$	CNS	G_s	Adenylyl cyclase (+)	2-methyl-5-HT, 5-HT, LSD	SB-271046, SB-258585, SB-357134, Ro 04-6790, Ro 63-0563, olanzapine, clozapine, methiothepin
5 -HT$_7$ 5-HT$_{7(a–e)}$	CNS, cardiovascular, gastrointestinal tract	G_s	Adenylyl cyclase (+), Ca^{2+} (↑)	5-CT, 5-HT, 8-OH-DPAT	SB-269970, SB-258719, DR 4004, clozapine, methiothepin

5-HT presynaptic autoreceptors. On activation of these presynaptic autoreceptors, there is a decrease in 5-HT release. All of the 5-HT receptor subtypes are in all likelihood expressed by target neurons.

II. NEUROANATOMY OF THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS

A. HYPOTHALAMUS

The hypothalamus is a division of the diencephalon, the ventral portion of the forebrain. The location of the hypothalamus is above the pituitary gland and ventral to the thalamus, separated from the thalamus by the hypothalamic sulcus in the wall of the third ventricle. The hypothalamus continues from the optic chiasm to the mammillary bodies. The ventral portion of the hypothalamus, which includes the infundibular stalk and mammillary bodies, is visible on the ventral surface of the brain.

From rostral to caudal, the hypothalamus can be separated into three regions. The anterior region is the area above the optic chiasm; the mammillary bodies and the area dorsal to the mammillary bodies comprise the posterior region; and the tuberal region is the area between the two. Table II lists the major nuclei found within each hypothalamic region.

TABLE II. Major Hypothalamic Nuclei Found in the Anterior, Tuberal, and Posterior Regions of the Hypothalamus[a]

Region	Medial zone	Lateral zone
Anterior	Anterior nucleus	Lateral nucleus
	Medial preoptic nucleus	Lateral preoptic nucleus
	Paraventricular nucleus	Magnocellular preoptic nucleus
	Suprachiasmatic nucleus	
	Nucleus medianus	Supraoptic nucleus
Tuberal	Arcuate nucleus	Lateral nucleus
	Dorsomedial nucleus	Lateral tuberal nucleus
	Posterior periventricular nucleus	Supaoptic nucleus
	Ventromedial nucleus	
Posterior	Mammillary complex	Lateral nucleus
	Posterior nucleus	
	Premammillary nucleus	
	Tuberomammillary nucleus	

[a]The nuclei are further divided into medial or lateral, based on their location relative to the third ventricle

Hypothalamic inputs originating primarily from the forebrain convey information relevant to the autonomic and somatic facets of affective states. Those that originate from the brainstem and spinal cord convey visceral and somatic sensory information. Hypothalamic efferents include the forebrain, brainstem, spinal cord, pituitary portal vessels in the median eminence, and the posterior (neural) lobe of the pituitary gland.

The medial forebrain bundle is a major fiber pathway running longitudinally through the lateral hypothalamus, making several reciprocal connections (Millhouse, 1969; Mizuno *et al*., 1969; Conrad and Pfaff, 1976). Medial forebrain bundle fibers begin in the olfactory portion of the basal forebrain and the limbic septal nuclei. As the axons pass through the hypothalamus, they project numerous fibers before traveling on to the brainstem; much of the information in this pathway relates to visceral and olfactory information. Conversely, neurons in the brainstem send efferents via the medial forebrain bundle to the hypothalamus. The hypothalamus receives input from the amygdala by way of the amygdalo–hypothalamic pathway (Gray *et al*., 1989; Gray, 1993; Prewitt and Herman, 1998). The amygdalo–hypothalamic pathway is believed to be involved in the adrenocortical response to a number of somatosensory stimuli (Davis and Whalen, 2001). The key role of this pathway is to process emotional content. The hippocampal–hypothalamic tract, beginning in the hippocampus and traveling to the hypothalamus via the mammillary bodies, shares information among the hippocampus, thalamus, hypothalamus, and cingulate gyrus. The retino–hypothalamic tract sends information originating in the retina to the suprachiasmatic nucleus; this tract conveys information about light and helps regulate the circadian rhythm (Hannibal, 2002). Information traveling from the neocortex passes to the hypothalamus through the cortico–hypothalamic tract (Canteras and Swanson, 1992). The dorsal longitudinal fasciculus sends efferents from the hypothalamus to the midbrain to convey information to the visceral and sympathetic motor neurons (Ban *et al*., 1975; Bernardis, 1975).

The paraventricular nucleus, which is the hypothalamic nucleus most closely associated with the hypothalamic–pituitary–adrenal (HPA) axis, has several afferents. Sensory information arrives from the telencephalic limbic system through the stria terminalis (Moga and Saper, 1994), as well as from the cardiovascular regulatory centers in the hindbrain (Kannan and Yamashita, 1985). Catecholaminergic inputs into the paraventricular nucleus mediate the effects of stress on adrenocorticotropin (ACTH) and glucocorticoid secretion (Van de Kar and Blair, 1999). The hypothalamus receives many of its catecholaminergic inputs as collaterals stemming from catecholaminergic innervations to the central nucleus of the amygdala (Petrov *et al*., 1993). The arcuate nucleus sends neuropeptide-Y-containing axons (Baker and Herkenham, 1995; Kalra and Kalra, 1996) and β-endorphin-containing axons (Russell *et al*., 1995) directly to the

paraventricular nucleus. The serotonergic system sends nerve terminals into the paraventricular nucleus as well. The dorsal raphé, a brainstem nucleus rich in serotonergic cell bodies, sends collateral innervations to both the amygdala and the paraventricular nucleus (Petrov *et al*., 1992b, 1994). In addition, immunohistochemical studies have shown that serotonergic nerve terminals make direct synaptic contacts with corticotropin-releasing hormone (CRH)-immunoreactive neurons in the paraventricular nucleus (Liposits *et al*., 1987a). Intrahypothalamic γ-aminobutyric acid (GABA)-ergic neurons innervate CRH neurons to inhibit the activity of the hypothalamic–pituitary–adrenal axis (DiMicco *et al*., 1996; Herman and Cullinan, 1997).

The paraventricular hypothalamic nucleus plays a central role in the regulation of hormone secretion from the pituitary gland. The releasing/inhibitory factors released from the parvocellular neurons include thyrotropin (TRH), growth hormone-releasing hormone (GHRH), the growth hormone-inhibiting hormone (GHIH, somatostatin), and CRH. CRH, synthesized and released from the paraventricular nucleus (Makara *et al*., 1981; Olschowka *et al*., 1982; Bruhn *et al*., 1984; Reul and Holsboer, 2002), is the primary stimulus activating the HPA axis, increasing the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland.

Most magnocellular neurons are located in the paraventricular nucleus and supraoptic nucleus. Magnocellular neurons synthesize and directly secrete vasopressin and oxytocin into the systemic circulation via their nerve terminals in the posterior lobe of the pituitary gland.

B. PITUITARY GLAND

The pituitary gland is located in the sella turcica, a cavity at the base of the skull, and is connected to the hypothalamus by the infundibular or pituitary stalk. One of the primary responsibilities of the hypothalamus is to control the pituitary gland, which secretes several trophic hormones. The pituitary is composed primarily of anterior and posterior lobes with a small avascular zone located between the two lobes called the pars intermedia (or intermediate lobe).

The anterior and posterior lobes of the pituitary play different roles regarding hormone release. Hormones released from the posterior pituitary are not actually synthesized in the pituitary but rather in the hypothalamus. The hypothalamic magnocellular neurons, which are located primarily in the supraoptic and paraventricular nuclei, synthesize and package their hormonal peptides, which travel by axonal flow down the hypothalamic–hypophysial tract through the infundibular stalk into the nerve endings located in the posterior lobe of the pituitary. When an action potential travels from the cells in the hypothalamus to the nerve terminals in the

TABLE III. Hormones Synthesized and Released from Specific Anterior Pituitary Cells

Cell type	Hormone released
Corticotophs	Adrenocorticotropinc hormone (ACTH)
Gonadotrophs	Follicle-stimulating hormone (FSH)
	Luteinizing hormone (LH)
Lactotrophs	Prolactin (PRL)
Somatotrophs	Growth hormone (GH)
Thyrotrophs	Thyroid-stimulating hormone (TSH)

posterior pituitary, oxytocin and vasopressin are released into the systemic circulation.

The anterior pituitary however, consists of many different cell types that selectively synthesize and secrete hormones (Table III). The anterior pituitary is the lobe specifically involved in the HPA axis. Corticotrophs located in the anterior lobe of the pituitary synthesize and release ACTH into the circulation. The primary stimulus for ACTH release is CRH, which reaches the pituitary through the pituitary portal vessels.

C. ADRENAL GLAND

The adrenal gland comprises the third component of the HPA axis. One adrenal gland is located directly above each kidney. Each adrenal gland is composed of the adrenal medulla surrounded by the adrenal cortex. Located in the core of the adrenal gland, the cells of the adrenal medulla synthesize and release norepinephrine and epinephrine in response to sympathetic nervous system stimulation.

The adrenal cortex consists of three layers, listed from most superficial to deepest: zona glomerulosa, zona fasciculata, and zona reticularis. Table IV lists the hormones released by each layer. In regard to the HPA axis, we discuss the actions of ACTH on the zona fasciculata leading to the release of glucocorticoids.

D. NEURAL CIRCUITRY THAT REGULATES THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS

The regulation of the HPA axis is highly integrated. The hypothalamus exerts control of the anterior pituitary, which governs the release of steroid hormones from the adrenal cortex. At each step of the HPA axis there is an amplification of hormone release, and the products of the HPA axis are also able to regulate their own secretion through negative feedback loops (see Fig. 1).

TABLE IV. Hormones Synthesized and Released from the Different Layers of the Adrenal Cortex

Adrenal cortex layer	Hormones released
Zona glomerulosa	Aldosterone
Zona fasciculata	Corticosterone, cortisol androgens
Zona reticularis	Corticosterone, cortisol androgens

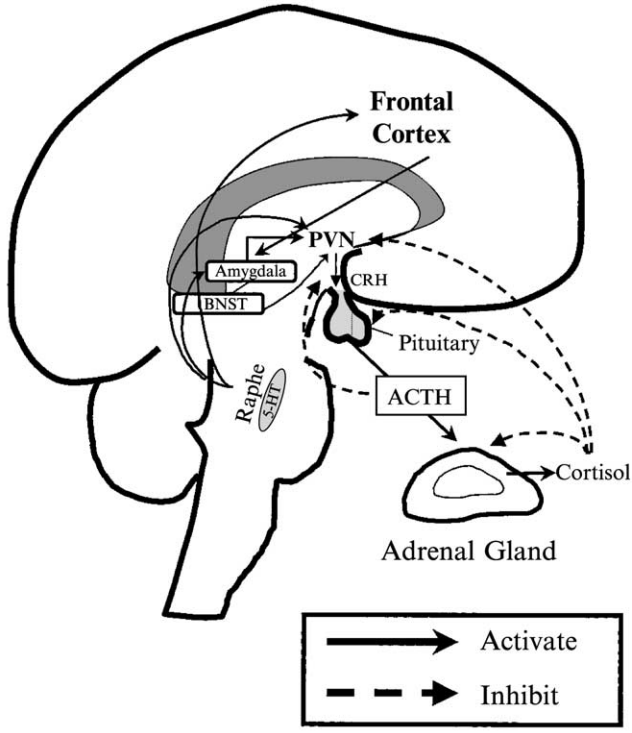

FIGURE 1. Summary of the neural circuits involved in regulation of the HPA axis. ACTH, Adrenocorticotropic hormone; BNST, bed nucleus of the stria terminalis; CRH, corticotropin-releasing hormone; 5-HT, serotonin; PVN, paraventricular nucleus.

On stimulation of the parvocellular neurons in the paraventricular nucleus, they release CRH into the portal system. CRH then travels to the anterior pituitary, where it binds to CRH (CRH-R1, type 1) receptors located on corticotrophs. Binding of CRH to the CRH-R1

receptors activates adenylyl cyclase, to regulate gene expression of pro-opiomelanocortin (POMC), a prohormone that gives rise to three families of peptide hormones: ACTH, α-melanocyte-stimulating hormone (α-MSH), and β-endorphin. The nature of pro-opiomelanocortin processing varies in different cell locations in the pituitary (Levin and Roberts, 1991). α-Melanocyte-stimulating hormone and ACTH are primarily synthesized and secreted from the pars intermedia and anterior lobe, respectively, whereas β-endorphin is synthesized and secreted from both lobes. CRH binding specifically results in the cleavage and release of ACTH into the systemic circulation (see Levin and Roberts, 1991).

ACTH is the anterior pituitary hormone that controls the size of the adrenal gland and synthesis of glucocorticoids in the adrenal gland (Holsboer and Barden, 1996). ACTH binds with high affinity to specific ACTH receptors located on cells in the adrenal cortex. The ACTH receptor, a member of the melanocortin receptor subfamily, is a seven-transmembrane receptor coupled to G_s proteins leading to the activation of adenylyl cyclase (Cone *et al.*, 1993). Exposure to ACTH results in a paradoxical upregulation of ACTH-binding sites *in vivo* (Durand and Locatelli, 1980) and *in vitro* (Penhoat *et al.*, 1989; Lebrethon *et al.*, 1994) as well as an increase in ACTH receptor mRNA *in vitro* (Lebrethon *et al.*, 1994).

Two types of receptors have been identified for corticosterone on the basis of their affinity for corticosterone. The type I receptor is similar to the classic mineralocorticoid receptor and it exhibits a higher affinity for corticosterone (K_d = 0.5–1 nM) than the type II receptor. The type II receptor is closer to the classic glucocorticoid receptors and possesses a lower affinity for corticosterone (K_d = 2.5–5 nM) (Veldhuis *et al.*, 1982; Reul and De Kloet, 1985). Both of these receptors also differ in location. The type II receptors are found throughout the brain including the limbic system, frontal cortex, brainstem, pituitary, paraventricular nucleus, and other hypothalamic nuclei (Reul and De Kloet, 1985; Jacobson and Sapolsky, 1991; Deak *et al.*, 1999). The type I receptors, on the other hand, are expressed in fewer brain regions and are limited principally to the limbic system (primarily the hippocampus), pituitary, and a few nuclei in the brainstem (Reul and De Kloet, 1985; Jacobson and Sapolsky, 1991; Deak *et al.*, 1999). Interestingly, type I receptor expression in the paraventricular nuclei is found either in low concentrations or not at all (Reul and De Kloet, 1985; Arriza *et al.*, 1988; Meyer *et al.*, 1998).

The HPA axis can also be regulated by its own products in a negative feedback manner. ACTH may act as a negative neuromodulator of the synthesis and secretion of CRH (Suda *et al.*, 1987; Sawchenko *et al.*, 1992). Glucocorticoids not only act to influence the metabolism of proteins, glucose, and fats as well as immune function; they also exert a negative feedback inhibition at almost all levels of the HPA axis

(Feldman and Weidenfeld, 1995). Glucocorticoids exert their negative feedback inhibition through both the type I and type II receptors. Each receptor may mediate different aspects of the feedback regulation, which is discussed further later with regard to circadian rhythmicity. The actions of glucocorticoids on ACTH secretion can be direct or indirect, by swift (within minutes) or delayed (>2 h) mechanisms (Keller-Wood and Dallman, 1984).

Several of the parvocellular neurons in the paraventricular nucleus express not only CRH but also mRNA encoding additional peptide hormones such as vasopressin in rats (Sawchenko *et al*., 1984a,b; Whitnall, 1988). Vasopressin immunoreactivity was also observed in the parvocellular hypothalamic neurons in humans (Mouri *et al*., 1993; Raadsheer *et al*., 1993). Colocalization of CRH and vasopressin within parvocellular neurons may be due to low glucocorticoid levels given that adrenalectomized rats show an increase in coexpression (Sawchenko *et al*., 1984a).

Vasopressin has been identified in the portal blood and is believed to be involved in ACTH secretion (Plotsky, 1991). Vasopressin alone has a weak stimulatory effect on ACTH release, but it may act to potentiate the ability of CRH to stimulate ACTH secretion *in vitro* (Giguere and Labrie, 1982; Turkelson *et al*., 1982; Aguilera *et al*., 1983; Rivier and Vale, 1983) and *in vivo* (Yates *et al*., 1971; Graf *et al*., 1985; von Bardeleben and Holsboer, 1989). In cell culture, the action by which vasopressin can potentiate ACTH release induced by CRH is by way of increasing cAMP levels (Giguere and Labrie, 1982). In the rat, the potentiation of the ACTH-releasing effect of CRH appeared to be greater if it was injected before vasopressin (Graf *et al*., 1985). In addition, the combination of CRH and vasopressin may be less sensitive to glucocorticoid negative feedback than CRH alone (Holsboer and Barden, 1996).

E. EXTRAHYPOTHALAMIC EFFECTS ON THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS

The amygdala plays a prominent role in the activation and regulation of the HPA axis, especially during stressful situations (see Gray, 1993). Destruction of the amygdala results in a reduction of fear in rats (Campeau and Davis, 1995a,b), and direct stimulation of the amygdala in conscious human subjects elicits strong emotional fear (Chapman *et al*., 1954). More specifically, the central nucleus of the amygdala appears to be involved in the hypothalamic–pituitary–adrenal stress response. Lesions in the central nucleus of the amygdala inhibit the HPA axis response to conditioned fear stress (Van de Kar *et al*., 1991a; Campeau and Davis, 1995b; Van de Kar and Blair, 1999). Direct stimulation of the central nucleus of the amygdala in conscious animals results in physiological responses, such as pupillary dilation and increased arterial pressure and heart rate, which are classically

associated with fear (Kaada, 1951; Iwata *et al*., 1987). Interestingly, 5-HT in the hypothalamus as well as the amygdala is important for amygdala-mediated activation of the HPA axis. The need for 5-HT is demonstrated by a lack of HPA axis response to stressful neural stimulation following 5-HT depletion in either the amygdala or the hypothalamus (Feldman *et al*., 1998; Feldman and Weidenfeld, 1998).

Immunohistochemical studies have located CRH cell bodies within the central amygdala (Swanson *et al*., 1983; Sakanaka *et al*., 1987; Gray, 1993). One of the possible targets of the CRH neurons located in the central nucleus of the amygdala includes the paraventricular nucleus (Gray *et al*., 1989). In turn, a heterogeneous assortment of neurons innervate the CRH cell bodies in the central nucleus of the amygdala, including CRH neurons from the lateral hypothalamus and dorsal raphé that project back to the amygdala as well as intrinsic CRH cells in the central nucleus of the amygdala (Gray, 1993). The CRH neurons in the central amygdala also innervate serotonergic neurons in the caudal portion of the dorsal raphé nucleus (Price *et al*., 1998; Kirby *et al*., 2000). Thus, the amygdala appears to serve as a hub of CRH information in response to stressful situations.

The hippocampus is seen mainly as a feedback regulator of the HPA axis. Removing the ability of the hippocampus to interact with the hypothalamus by way of hippocampectomy or lesions in the hippocampus or fornix increases the basal activity of the HPA axis (Herman *et al*., 1989; Fischette *et al*., 1980; Sapolsky *et al*., 1991; see Jacobson and Sapolsky, 1991). Correspondingly, electrical stimulation of the hippocampus results in a decrease in plasma glucocorticoids in cats (Slusher and Hyde, 1961) as well as in humans (Sapolsky *et al*., 1991; Rubin *et al*., 1966). Furthermore, microinfusion of glucocorticoid receptor antagonists directly into the hippocampus of rats results in hypersecretion of ACTH (Bradbury and Dallman, 1989). In a stressful situation, it has been postulated that the hippocampus is able to regulate both the peak of stress-induced ACTH release following the activation of the hypothalamic–pituitary–adrenal axis as well as the recovery (Jacobson and Sapolsky, 1991). Rats with a fiber-sparing kainic acid-induced lesion of cells in the hippocampus responded to restraint stress with an increase in corticosterone concentration twice that of sham animals. However, 1 h poststress, the rats with hippocampal lesions maintained the elevated corticosterone levels, whereas the corticosterone levels of the sham-control animals had returned to basal concentrations (Sapolsky *et al*., 1984).

On the other hand, several investigators report that interrupting hippocampal input by lesions results in an inhibition of glucocorticoid secretion in stressful (Conforti and Feldman, 1976) and unstressful situations (Herman *et al*., 1989). Similarly, there are reports that electrical stimulation of the dorsal or ventral hippocampus leads to an increase in

plasma corticosterone concentrations (Smith and Root, 1971; Feldman *et al.*, 1982,1987b). The differences between the view that the hippocampus is inhibitory or stimulatory may result in part from differences in the way the experiments were carried out. In the lesion experiments, there may be variability in recovery time following the production of the lesion prior to the experiment; a longer duration may result in functional recovery of the animal (Fischette *et al.*, 1980; Sapolsky *et al.*, 1991). The extent of the lesion or type of stress may also affect corticosterone levels. For example, Regestein and colleagues (1986) demonstrated that lesions in the posterior hippocampus did not alter the cortisol levels of rhesus monkeys in response to shock avoidance or restraint, as compared with controls; however, near-complete destruction of the hippocampus resulted in an increase in cortisol levels in response to shock avoidance and a decrease in cortisol levels in response to restraint (Regestein *et al.*, 1986). In the experiments involving electrical stimulation, the resulting change in corticosterone levels could result from electrical stimulations in distinctly different areas of the hippocampus. See Jacobson and Sapolsky (1991) for a complete discussion.

Neuronal efferents from the hippocampus could influence the HPA axis. However, these connections may not be direct. Although a direct connection from the hippocampus to the paraventricular nucleus has been detected by retrograde transport (Silverman *et al.*, 1981; Sawchenko and Swanson, 1983a,b), this direct connection has not been corroborated by anterograde transport (Sawchenko and Swanson, 1983a,b). If the projections are not direct, it is possible that the hippocampus sends neuronal projections to other brain regions that in turn project to the paraventricular nucleus. Such areas would include the bed nucleus of the stria terminalis, the lateral septum, and the ventromedial hypothalamus (Jacobson and Sapolsky, 1991). The hippocampus expresses both type I and type II glucocorticoid receptors; in fact, the hippocampus has the highest level of glucocorticoid type I receptors within the brain (De Kloet *et al.*, 1975; Reul and De Kloet, 1985; Jacobson and Sapolsky, 1991), making the hippocampus a target for glucocorticoid action. The cells in the hippocampus also express 11β-hydroxysteroid dehydrogenase, which has been proposed to control the ability of glucocorticoids to regulate their own expression level (Moisan *et al.*, 1990).

III. SEROTONIN AND THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS

The serotonergic system and the HPA axis are able to exert profound effects on one another. In this section, we discuss the changes expressed in one system in response to alterations in the other. The physiological and

pathophysiological interactions between the two systems are discussed more extensively in Section IV and Section V.

A. SEROTONERGIC EFFECTS ON THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS

Serotonin is a known stimulator of the HPA axis (Dinan, 1996; Fuller, 1996). As mentioned in the previous section, serotonergic nerve terminals make direct synaptic connections with CRH-immunoreactive neurons in the paraventricular nucleus (Liposits *et al.*, 1987a), thus giving anatomical context for the involvement of serotonin in the activation of the HPA axis. The increase in synaptic levels of 5-HT potently stimulates the release of CRH, ACTH, and glucocorticoids (Feldman *et al.*, 1987a; Calogero *et al.*, 1989). Furthermore, electrophysiological recordings coupled with lesion studies have established that the hypothalamic paraventricular nucleus is vital for serotonergic stimulation of ACTH and corticosterone as well as the other pituitary hormones (Kawano *et al.*, 1992; Rittenhouse *et al.*, 1992b,1993,1994; Bagdy and Makara, 1994; Van de Kar *et al.*, 1995).

1. Antidepressant Treatment

There are three main classes of antidepressant drugs involving the serotonergic system: monoamine oxidase (MAO) inhibitors that block the metabolism of 5-HT; tricyclic antidepressants that block the reuptake of monoamines; and selective serotonin reuptake inhibitors (SSRIs) that specifically block the reuptake of 5-HT. Each of these drugs acts to increase the amount of 5-HT within the synapse and as a consequence activate presynaptic receptors to control the release of 5-HT and postsynaptic receptors in the hypothalamus to stimulate the release of hormones.

Acute treatment with antidepressant drugs may have a different effect on the hypothalamic–pituitary–adrenal axis than chronic antidepressant treatment. For example, acute treatment with clomipramine, which specifically blocks the reuptake of 5-HT, leads to a stimulation of the HPA axis in humans (Laakmann *et al.*, 1984) and rats (Armario and Garcia-Marquez, 1987). When clomipramine was given to rats chronically, a tolerance to the drug developed (Armario and Garcia-Marquez, 1987). This dual effect was also observed with SSRI treatment. Several studies in rats have demonstrated that a single injection of the SSRI fluoxetine is able to increase the levels of corticosterone (Fuller *et al.*, 1976; Bianchi *et al.*, 1994). Likewise, acute administration of the SSRI fluoxetine or paroxetine leads to an increase in cortisol levels in humans (von Bardeleben *et al.*, 1989; Reist *et al.*, 1996). Chronic treatment with SSRIs has not led to a consistent change in the basal levels of ACTH or glucocorticoids (Raap and Van de Kar, 1999). These studies indicate that acute effects of these antidepressants may be due to the initial rise in synaptic 5-HT concentrations. After chronic

treatment with antidepressant drugs, the rise in synaptic 5-HT results in adaptive changes of the serotonergic system as well as other brain systems, leading to a change in receptor signaling.

2. 5-HT Precursors

L-Tryptophan and 5-hydroxytryptophan (5-HTP), are the two precursors for 5-HT. The essential amino acid L-tryptophan is converted into 5-HTP, which is then converted to 5-HT by 5-hydroxytryptophan decarboxylase. Infusion of L-tryptophan results in an increase in plasma cortisol levels in humans (Bancroft *et al.*, 1991). Intravenous administration of 5-HTP increases cortisol levels in humans (Power and Cowen, 1992). Likewise, oral administration of 5-HTP to humans also leads to an increase in plasma ACTH levels (Maes *et al.*, 1989) and cortisol levels (Meltzer *et al.*, 1984, 1986, 1997; Jacobsen *et al.*, 1987; Maes *et al.*, 1987, 1989, 1990). Westenberg *et al.* (1982), however, did not observe a change in cortisol levels following oral administration of 5-HTP or L-tryptophan.

3. 5-HT-Releasing Drugs

5-HT-releasing drugs activate the release of both ACTH and corticosterone. For example, 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") administration in humans significantly increases plasma ACTH (Grob *et al.*, 1996) and cortisol (Mas *et al.*, 1999) levels. On administration of fenfluramine, there is an associated increase in ACTH (Coccaro *et al.*, 1996) and glucocorticoids (O'Keane *et al.*, 1992; Coccaro *et al.*, 1996; Cleare *et al.*, 1998; Steiner *et al.*, 1999). Other 5-HT-releasing drugs that stimulate ACTH release include *p*-chloroamphetamine (Fuller, 1992a), 1-(1,3-benzodioxol-5-yl)-2-(methylamino)butane (MBDB), 5-methoxy-6-methyl-2-aminoindan (MMAI), and *p*-methylthioamphetamine (MTA) (Li *et al.*, 1996b).

4. 5-HT_{1A} Receptor Agonists

In situ hybridization (Wright *et al.*, 1995; Gundlah *et al.*, 1999; Li *et al.*, 2000) and autoradiograhic (Li *et al.*, 1997a,b; Lu and Bethea, 2002) studies indicate that the 5-HT_{1A} receptors are expressed in the paraventricular nucleus of the hypothalamus.

The ability of 5-HT_{1A} receptor agonists to stimulate the release of corticosterone has been well documented. 5-HT_{1A} agonists such as 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), buspirone, gepirone, ipsapirone, and LY 165163 increase plasma corticosterone levels in rats (Urban *et al.*, 1986; Koenig *et al.*, 1987,1988; Lorens and Van de Kar, 1987; Raap *et al.*, 2000), and buspirone, gepirone, and ipsapirone also increase plasma cortisol levels in humans (Lesch *et al.*, 1990a,b; Sargent *et al.*, 1997; Schwartz *et al.*, 1999). The increase in corticosterone elicited by 5-HT_{1A} agonists such as 8-OH-DPAT involved CRH neurons within the

paraventricular nucleus of the hypothalamus (Calogero *et al*., 1989; Bagdy *et al*., 1990; Pan and Gilbert, 1992). The effects of 8-OH-DPAT in rats can be blocked by pretreatment with 5-HT_{1A} receptor antagonists such as WAY 100635 and spiperone and the 5-HT_{1A}/β-adrenergic receptor antagonists pindolol and propranolol (Koenig *et al*., 1987; Przegalinski *et al*., 1989; Vicentic *et al*., 1998), but not by the 5-HT_2 receptor antagonists altanserin, ketanserin, pirenperone, and ritanserin (Koenig *et al*., 1987; Przegalinski *et al*., 1989). In humans, the effects of ipsapirone can be blocked by the 5-HT_{1A}/β-adrenergic receptor antagonist pindolol (Lesch *et al*., 1990b).

As mentioned in Section I, 5-HT_{1A} receptors are known to couple to the $G_{i/o}$ protein family. Within the hypothalamus the 5-HT_{1A} receptor specifically couple to G_z, a member of the $G_{i/o}$ protein family (Serres *et al*., 2000a). Serres *et al*. (2000a) demonstrated coupling of hypothalamic 5-HT_{1A} receptors to G_z proteins by injecting G_z antisense oligodeoxynucleotides into rat third ventricles and showing that reduced expression of G_z protein resulted in an inhibition of 8-OH-DPAT-mediated ACTH and oxytocin responses. G_z is the only member of the $G_{i/o}$ protein family that is pertussis toxin insensitive. When rats were pretreated with pertussis toxin prior to 8-OH-DPAT challenges, ACTH release was not inhibited, oxytocin release was potentiated, and prolactin release was blocked. This suggests that 8-OH-DPAT-induced release of ACTH involves G_z protein and not the other members of the $G_{i/o}$ protein family (Serres *et al*., 2000a). Interestingly, 5-HT_{1A} receptor-induced ACTH release is able to undergo heterologous desensitization through 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI)-induced activation of the 5-HT_{2A} receptor; however, the desensitization appears to be distal to G_z protein because there is a lack of GTPγS-induced inhibition of 5-HT_{1A} agonist binding (Zhang *et al*., 2001).

5. 5-$HT_{1B/D}$ Receptor Agonists

The 5-HT_{1B} and the 5-HT_{1D} receptors are expressed presynaptically as autoreceptors or postsynaptically to convey serotonergic information to target tissue. Initial studies on the neuroendocrine interaction of the 5-$HT_{1B/1D}$ receptor utilized the moderately specific 5-$HT_{1B/1D}$ receptor agonist sumatriptan, used for the treatment of migraine headaches. Sumatriptan administration gave varying results, which may be because it does not readily penetrate the blood–brain barrier (Proietti-Cecchini *et al*., 1997). For example, Eckland *et al*. (1992) found that oral administration of sumatriptan led to a reduction of plasma cortisol levels during the first 4 h but to no significant change by 24 h. A transient reduction in ACTH and cortisol levels was confirmed in a following study from the same group (Entwisle *et al*., 1995). On the other hand, Facchinetti *et al*. (1994) found an increase in cortisol levels along with no change in prolactin levels following a subcutaneous injection of sumatriptan. Then again, Herdman and

colleagues (1994) found no change in cortisol levels following a subcutaneous injection of sumatriptan; however, they did observe an increase in growth hormone and a decrease in prolactin levels. Other studies have found that sumatriptan produces an increase in growth hormone levels with no effect on the other anterior pituitary hormones (Franceschini *et al.*, 1994; Coiro *et al.*, 1995; Boeles *et al.*, 1997).

With the advent of the newer, more selective 5-$HT_{1B/1D}$ antimigraine drug zolmitriptan, which has greater central nervous system penetration, it became possible to reevaluate the involvement of 5-$HT_{1B/1D}$ receptors within the central nervous system. The first neuroendocrine challenge study involving zolmitriptan found an increase in growth hormone with no change in prolactin levels; there was no report on cortisol concentrations (Whale *et al.*, 1999). Using a lower dose of zolmitriptan, Moeller *et al.* (2000) also found an increase in growth hormone and no change in prolactin levels; in addition, they report no change in plasma cortisol levels. Given that zolmitriptan has a greater ability to penetrate into the central nervous system (Proietti-Cecchini *et al.*, 1997), it would appear that 5-$HT_{1B/1D}$ receptors do not initiate stimulation of the HPA axis.

6. 5-$HT_{2A/2C}$ Receptor Agonists

Autoradiographic (Appel *et al.*, 1990), immunocytochemical (Zhang *et al.*, 2002), and *in situ* hybridization (Wright *et al.*, 1995; Gundlah *et al.*, 1999) studies indicate that 5-HT_{2A} and 5-HT_{2C} receptors are expressed in the paraventricular nucleus of the hypothalamus.

The 5-HT_{2A} and 5-HT_{2C} receptors are well documented as activators of the HPA axis (Koenig *et al.*, 1987; King *et al.*, 1989; Fuller and Snoddy, 1990; Owens *et al.*, 1991; Rittenhouse *et al.*, 1994; Van de Kar *et al.*, 2001). Because there is a lack of sufficiently selective agonists for the 5-HT_2 receptors, the determination of specific 5-HT_{2A} or 5-HT_{2C} receptor involvement in hypothalamic–pituitary–adrenal activation has relied on 5-HT_2 receptor antagonists. For example, the 5-$HT_{2A/2C}$ receptor agonists quipazine and MK-212 are believed to act through the 5-HT_{2A} receptor on the basis of antagonism by the 5-HT_{2A}-selective antagonist MDL 100,907 (Hemrick-Luecke and Fuller, 1996). In rats, the 5-HT_2 agonist DOI stimulates the secretion of ACTH as well as corticosterone (Rittenhouse *et al.*, 1994; Van de Kar *et al.*, 2001). The DOI response can be blocked by spiperone (Rittenhouse *et al.*, 1994), suggesting that DOI is acting through 5-HT_{2A} receptors given that spiperone has a higher affinity for 5-HT_{2A} receptors than for the 5-HT_{2C} receptor (Canton *et al.*, 1990). The fact that the selective 5-HT_{2A} receptor antagonist MDL 100,907 completely blocked DOI-induced ACTH and corticosterone secretion gave further evidence that DOI is acting through the 5-HT_{2A} receptor to mediate its neuroendocrine response (Van de Kar *et al.*, 2001). Furthermore, MDL 100,907 was able to block increases in corticosterone secretion brought about by other 5-HT_2

receptor agonists such as quipazine, DOI, and *m*-chlorophenylpiperazine (*m*-CPP) (Hemrick-Luecke and Evans, 2002). Selective 5-HT_{2C} antagonists had little effect on the corticosterone response to these 5-HT_2 agonists (Hemrick-Luecke and Evans, 2002).

As demonstrated by dual immunohistochemical labeling of CRH and *c-fos*, DOI-induced activation of the HPA axis, through the 5-HT_{2A} receptor, is most likely due to the activation of CRH-containing neurons in the paraventricular nucleus of the hypothalamus (Van de Kar *et al.*, 2001). c-*fos* is a proto-oncogene (immediate early-action gene) activated on synaptic stimulation (Harbuz *et al.*, 1993). There is also evidence that 5-HT_2 receptor agonists may act through peripheral receptors to further stimulate corticosterone release (Alper, 1990; Rittenhouse *et al.*, 1994; Welch and Saphier, 1994).

Given the 10-fold selectivity of *m*-CPP for the 5-HT_{2C} receptor (Hoyer, 1988), some researchers assume that the role of the 5-HT_{2C} receptor in the activation of the HPA axis can be determined by administration of *m*-CPP. Several studies have demonstrated that *m*-CPP is able to stimulate the release of ACTH and glucocorticoids in humans and rats (Bagdy *et al.*, 1989; Murphy *et al.*, 1989; Kahn *et al.*, 1990b; Seibyl *et al.*, 1991; Meltzer and Maes, 1995b; George *et al.*, 1997; Scheepers *et al.*, 2001). Nevertheless, *m*-CPP-induced corticosterone secretion could not be blocked by the 5-HT_{2C} selective antagonist SB-242084, whereas, as mentioned previously, the 5-HT_{2A}-selective antagonist MDL 100,907 was able to block the *m*-CPP-induced response (Hemrick-Luecke and Evans, 2002). To date, most evidence supports a role for the 5-HT_{2A} but not 5-HT_{2C} receptors in regulating the HPA axis.

7. 5-HT_3 Receptor Agonists

A few studies have examined the involvement of 5-HT_3 receptors in activation of the HPA axis. Pretreatment of rat primary anterior pituitary cells with the 5-$HT_{3/4}$ antagonist ICS 205-930 or the more selective 5-HT_3 antagonist MDL 72222 blocked 5-HT-induced ACTH release, and the 5-HT_3 agonist 1-(*m*-chlorophenyl)-biguanide (*m*-CPBG) elicited the release of ACTH from the primary cell culture (Calogero *et al.*, 1995). Likewise, intracerebroventricular injection of the 5-HT_3 antagonist LY-278584 blocked a 5-HT-induced increase in plasma ACTH levels in rats (Kageyama *et al.*, 1998). In contrast, pretreatment of rats with the 5-HT_3 antagonist ondansetron was unable to block 5-HT releaser *p*-chloroamphetamine (PCA)-induced ACTH and corticosterone release (Levy *et al.*, 1993). Ondansetron was also found to have no effect on ACTH release stimulated by either 5-HT or the combination of 5-hydroxytryptophan and the selective serotonin reuptake inhibitor fluoxetine (Jorgensen *et al.*, 1999). Furthermore, the 5-HT_3 receptor agonist 2-methyl-5-HT was found to have either an effect that could not be blocked by ondansetron or no effect on ACTH

release (Levy *et al.*, 1993; Jorgensen *et al.*, 1999). The lack of effect of central 5-HT_3 receptors is not especially unexpected given that there is a relatively low level of expression of 5-HT_3 receptors in the hypothalamus (Laporte *et al.*, 1992).

8. 5-HT_4 Receptor Agonists

The 5-HT_4 receptor has been implicated in the release of glucocorticoids; however, 5-HT_4 receptor-associated release may not involve the brain or pituitary. Initial studies of frog and human adrenal–cortical slices have demonstrated that the stimulatory effects of 5-HT on adrenal steroidogenesis can be reproduced by the 5-HT_4 receptor agonist zacopride, and the effects observed after the combination of zacopride and 5-HT are not additive; together these data suggest that the serotonergic actions are mediated through the 5-HT_4 receptor expressed by adrenal cortical cells (Idres *et al.*, 1991; Lefebvre *et al.*, 1992). Yet *in vivo*, the 5-HT_4 receptor agonist zacopride induces the secretion of aldosterone with no effect on cortisol levels (Lefebvre *et al.*, 1993). Furthermore, when the HPA axis is blocked by dexamethasone treatment, aldosterone levels still increase in response to the 5-HT_4 agonist zacopride or cisapride, suggesting that the stimulation of aldosterone release is not due to the HPA axis (Lefebvre *et al.*, 1993,1995). One study conducted in conscious male rats has demonstrated that the action of either 5-HT or the combination of 5-hydroxytryptophan with the SSRI fluoxetine produces a dose-dependent increase in ACTH levels (Jorgensen *et al.*, 1999). This effect was attenuated by the 5-$HT_{3/4}$ antagonists tropisterone but not the selective 5-HT_3 antagonist ondansetron, implying that the stimulation of ACTH release could be due to the 5-HT_4 receptor (Jorgensen *et al.*, 1999). On the other hand, oral administration of the 5-HT_4 agonist zacopride to humans did not elicit an ACTH or cortisol response (Lefebvre *et al.*, 1997). So far, the most convincing evidence suggests that 5-HT_4 receptors directly stimulate the release of aldosterone from the adrenal cortex.

9.5-HT_7 Receptor Agonists

Northern blot analysis, *in situ* hybridization (Lovenberg *et al.*, 1993; Ruat *et al.*, 1993; Shen *et al.*, 1993), and homogenate binding assays (Sleight *et al.*, 1995; Clemett *et al.*, 1999) indicate that 5-HT_7 receptors are expressed in the hypothalamus.

Little definitive work has been conducted on the involvement of 5-HT_7 receptors in the activation of the HPA axis. This is partly due to the lack of selective 5-HT_7 agonists and antagonists. Clemett *et al.* (1998) probed 5-HT_7 receptor involvement by administering 5-HT_7 receptor antisense oligodeoxynucleotides directly into rat brain cerebral ventricles. In their study, they demonstrate that there is a reduction in 5-HT_7 receptor binding with no associated change in the 5-HT_{2A} receptor. The antisense treatment,

however, had no effect on basal plasma corticosterone levels or corticosterone levels following a 5-min exposure to the elevated plus maze (stress), suggesting that the 5-HT_7 receptor is not involved in the hypothalamic–pituitary–adrenal response to this mild stressor. Koenig *et al.* (1987) have found similar results showing that the 5-HT_7 receptor was not involved in the hypothalamic–pituitary–adrenal response to 8-OH-DPAT by blocking the corticosterone response with the nonselective 5-HT_1 antagonist pindolol but not blocking the 8-OH-DPAT response with ritanserin, a 5-HT_2 antagonist with moderate affinity for the 5-HT_7 receptor (Boess and Martin, 1994). Together, these data suggest that the 5-HT_7 receptor is not involved in serotonergic stimulation of the HPA axis.

B. HYPOTHALAMIC–PITUITARY–ADRENAL AXIS EFFECTS ON THE SEROTONERGIC SYSTEM

CRH-containing neurons innervate the dorsal and median raphé (Austin *et al.*, 1997; Valentino *et al.*, 2001), which in turn serve as the source of serotonergic innervation throughout the forebrain (Dahlstrom and Fuxe, 1964; Azmitia and Segal, 1978). Given this close association, it would seem likely that CRH release will have an effect on the serotonergic system. However, there is much debate on the effects of CRH on the serotonergic system (McAllister-Williams *et al.*, 1998).

1. Effects of CRH on 5-HT

CRH administration directly into the amygdala leads to an increase in the accumulation of 5-hydroxytryptophan levels in the amygdala following the inhibition of the aromatic amino acid decarboxylase (Boadle-Biber *et al.*, 1993). An *in vivo* microdialysis study in the medial hypothalamus and the medial prefrontal cortex demonstrated an increase in extracellular 5-hydroxyindoleacetic acid (5-HIAA) levels following intracerebroventricular CRH administration (Lavicky and Dunn, 1993). *In vivo* microdialysis provides a direct measure of 5-HT release by measuring the amount of 5-HT released into the extracellular space.

There appears to be a different effect on the serotonergic system following chronic versus acute CRH treatment. Within the hippocampus, a dual response to CRH occurs in which acute injection of CRH but not chronic intracerebroventricular injection of CRH increases extracellular 5-HT levels in freely moving rats (Linthorst *et al.*, 1997). Price and colleagues (1998) demonstrated by *in vivo* microdialysis that intracerebroventricular CRH administration has a biphasic effect on extracellular 5-HT within the striatum of freely moving rats; lower doses of CRH (0.1–0.3 μg) decrease 5-HT levels and higher doses of CRH (3 μg) increase 5-HT levels. However, the increase in 5-HT levels in the striatum following the higher dose of CRH was not confirmed in a later study (Price and Lucki, 2001). Interestingly, in

roughskin newts, intracerebroventricular injections of corticosterone, but not CRH, led to an increase in the levels of 5-HT and 5-HIAA in the dorsomedial hypothalamus, a hypothalamic center involved in neuroendocrine responses to stress (Bailey and DiMicco, 2001; Lowry *et al*., 2001; DiMicco *et al*., 2002).

Studies examining directly the activation of dorsal raphé firing have been divided. Investigators have shown that intracerebroventricular and intraraphé administration of CRH leads to an inhibition of 5-HT release (Price *et al*., 1998; Kirby *et al*., 2000; Price and Lucki, 2001). However, Lowry and associates (2000) have demonstrated that CRH is able to induce serotonergic firing in rat dorsal raphé slices. The stimulatory effect of CRH on serotonergic neurons within the midline raphé has been confirmed *in vivo* with roughskin newts (Lowry *et al*., 1996).

2. Effects of Glucocorticoids on 5-HT

Glucocorticoids are also able to affect the serotonergic system. Glucocorticoids can affect tryptophan catabolism, increase precursor availability, as well as increase the synthesis of 5-HT (see McAllister-Williams *et al*., 1998). Glucocorticoids also have an effect on some serotonin receptors as determined after either adrenalectomy or treatment with glucocorticoid agonists.

In the majority of cases, 1 day to 3 weeks following an adrenalectomy there was an increase in postsynaptic 5-HT_{1A} receptor number or mRNA expression in the hippocampus (Mendelson and McEwen, 1992; Chalmers *et al*., 1993; Kuroda *et al*., 1994; Le Corre *et al*., 1997; Neumaier *et al*., 2000). In one study, however 2 weeks after adrenalectomy, there was a decrease in 5-HT_{1A} receptor mRNA expression in the dentate gyrus that was reversed by dexamethasone treatment (Liao *et al*., 1993). In the majority of studies, treatment with either aldosterone or a low dose of corticosterone was able to reverse adrenalectomy-induced increase in expression of 5-HT_{1A} receptors or mRNA in the hippocampus (Mendelson and McEwen, 1992; Chalmers *et al*., 1993; Kuroda *et al*., 1994; Neumaier *et al*., 2000). Acute and chronic corticosterone treatment resulted in a decrease in 5-HT_{1A} receptors in the hippocampus (Fernandes *et al*., 1997; Takao *et al*., 1997). Nearly all studies reviewed found that somatodendritic 5-HT_{1A} receptor density or mRNA expression does not change following adrenalectomy or corticosterone treatment (Tejani-Butt and Labow, 1994; Holmes *et al*., 1995a,b; Le Corre *et al*., 1997; Neumaier *et al*., 2000). One study, however, found a decrease in dorsal raphé 5-HT_{1A} receptor expression within 2 weeks of adrenalectomy (Tejani-Butt and Labow, 1994). In the CA_1 and CA_3 region of the hippocampus, high doses of corticosterone led to a decrease in 5-HT_{1A} receptor-mediated response (Mueller and Beck, 2000; Okuhara and Beck, 1998). Neumaier *et al*. (2000) found no change in pre- or postsynaptic 5-HT_{1B} receptor mRNA following adrenalectomy or glucocorticoid

treatment whereas Mendelson and McEwen (1992) found an increase in 5-HT_{1B} receptor expression following adrenalectomy, which could be reversed by corticosterone treatment.

High glucocorticoid levels affect the 5-HT_{2A} receptor. Adrenalectomy does not change the density of 5-HT_{2A} receptors in the cortex or hypothalamus (Kuroda *et al.*, 1992, 1994; Holmes *et al.*, 1995b; Chaouloff *et al.*, 1993). In contrast, chronic corticosterone treatment of rats leads to an upregulation of 5-HT_{2A} receptor expression in the cortex (Kuroda *et al.*, 1992; Fernandes *et al.*, 1997; Takao *et al.*, 1997). Adrenalectomy produces an increase in 5-HT_{2C} receptor mRNA in the hippocampus (Holmes *et al.*, 1995b).

Hippocampal 5-HT_6 and 5-HT_7 receptors are also affected by a lack of glucocorticoids. For example, in rats 5-HT_6 receptor mRNA is upregulated in the CA_1 region of the hippocampus following chemical adrenalectomy, which can be reversed with corticosterone replacement (Yau *et al.*, 1997). Le Corre and colleagues (1997) found an increase in 5-HT_7 mRNA in the CA_1 and CA_3 regions of the hippocampus following adrenalectomy, whereas Yau *et al.* (1997) found only an increase in the CA_3 region.

IV. PHYSIOLOGICAL INTERACTIONS

This section describes the physiological importance of serotonin in the HPA axis.

A. CIRCADIAN RHYTHM

The circadian rhythm is the biological activity pattern of an organism during 24 h. A number of neuronal areas inside the brain behave as circadian clocks entrained by the light/dark cycle. However, the driving force, which organizes the various internal clocks that are engineered to oscillate in a circadian manner, is located in the suprachiasmatic nucleus within the basal hypothalamus. The suprachiasmatic nucleus receives important information about changes in light and dark from the retina via the retino–hypothalamic tract. Furthermore, the autonomic nervous system, via the superior cervical ganglion and other neural structures, regulates the pineal gland and its secretion of melatonin. In turn, melatonin regulates the suprachiasmatic nucleus. The suprachiasmatic nucleus also receives neuroendocrine information from other hypothalamic nuclei by way of intrahypothalamic connections. The suprachiasmatic nucleus sends outputs to hypothalamic nuclei to synchronize the activity of the hypothalamus with the light/dark cycle (Raisman and Brown-Grant, 1977; Moore, 1980; and see Angeli *et al.*, 1992).

1. Circadian Rhythm of the Hypothalamic–Pituitary–Adrenal Axis

The concentration of hormones in the blood changes with the time of the day. Glucocorticoids are released in a rhythmic fashion (Bradbury *et al.*, 1991; Angeli *et al.*, 1992). In humans, plasma cortisol levels rise in sporadic bursts with periods of quiescence (Llorente *et al.*, 1996; Van Cauter and Buxton, 2001; Mormon *et al.*, 2002). In diurnal mammals, such as humans, cortisol levels are at their highest point in the early morning hours and their lowest levels occur in late evening (Krieger *et al.*, 1971; Van Cauter and Buxton, 2001). Some studies have pinpointed the peak of ACTH and glucocorticoids between the first and the second rapid eye movement (REM) stages (Kupfer *et al.*, 1983), whereas others generalize the cortisol peak to occur during non-REM sleep (Born *et al.*, 1986).

The suprachiasmatic nucleus sends out multiple efferents to other nuclei in the hypothalamus with clear termination in the paraventricular nucleus (Swanson and Cowan, 1975). In the rat, destruction of the suprachiasmatic nucleus results in a loss of corticosterone level circadian peak in the adrenal gland (Moore and Eichler, 1972) and in plasma (Abe *et al.*, 1979; Buijs *et al.*, 1999). Others found only a change in plasma ACTH levels without a change in corticosterone levels (Szafarczyk *et al.*, 1979). Following the dissection of fiber connections in the anterior and lateral hypothalamus or lesions in the medial basal hypothalamus, the ACTH or corticosterone peak is no longer observed (see Bradbury *et al.*, 1991).

The suprachiasmatic nucleus contains vasopressinergic neurons (Swaab and Pool, 1975; Van Leeuwen *et al.*, 1978), and the levels of vasopressin fluctuate along with the circadian rhythm in the rat (George and Jacobowitz, 1975; Noto *et al.*, 1983). Vasopressin was postulated to act as a neurotransmitter in the suprachiasmatic nucleus communicating with the HPA axis (Angeli *et al.*, 1992).

As mentioned previously, glucocorticoids exert negative feedback on the HPA axis by binding to either the type I or type II receptors. On the basis of an observed shift to the right for steroid-induced inhibition of ACTH secretion, researchers have proposed that the inhibition of ACTH release during the nadir, or lower trough, of glucocorticoids during the circadian rhythm is due to the occupancy of the high-affinity type I receptor and that the negative feedback during the glucocorticoid peak is due to occupancy of the lower affinity type II receptor (Reul and De Kloet, 1985; Levin *et al.*, 1987; De Kloet *et al.*, 1993). Some researchers have proposed that the type I receptor is involved in the negative feedback at all times of the circadian rhythm (Dallman *et al.*, 1989; Young *et al.*, 1998). The type I receptor participates in the regulation of the HPA axis during the circadian peak and nadir in humans (Young *et al.*, 1998). Blocking the type I receptor with the aldosterone receptor (i.e., type I) antagonist spironolactone prevents cortisol feedback inhibition, resulting in elevated cortisol levels (Young *et al.*, 1998).

Other investigators demonstrated that the type I receptors act to potentiate type II receptor-induced regulation of cortisol during the circadian peak (Bradbury *et al*., 1994; Spencer *et al*., 1998).

2. The Effect of Serotonin on the Circadian Rhythm of the Hypothalamic–Pituitary–Adrenal Axis

A role for 5-HT in circadian rhythm has been postulated because the suprachiasmatic nucleus receives input from the midbrain raphé (Dudley *et al*., 1999). Serotonin levels in the brain rise and fall with a circadian rhythm (Albrecht *et al*., 1956; Scheving *et al*., 1968). However, the role that 5-HT plays in circadian ACTH and glucocorticoid surges has been controversial. The daily rise and fall of glucocorticoids is paralleled by a change in 5-HT levels in the brain (Dixit and Buckley, 1967; Scapagnini *et al*., 1971). Scapagnini and co-workers (1971) found that the brain regions in which the rise and fall in 5-HT content mirrored the diurnal corticosterone levels in rats were in the hippocampus and amygdala. These observations suggest that the biological clock responsible for 5-HT-induced ACTH secretion may be located outside of the hypothalamus. Indeed, lesions in the hippocampus, by medial fornix ablation, disrupt circadian-induced changes in plasma corticosterone (Fischette *et al*., 1980).

Depletion of 5-HT levels with systemic injections of the 5-HT synthesis inhibitor *p*-chlorophenyl alanine (PCPA) abolished the daily corticosterone rhythm (Scapagnini *et al*., 1971). In support of the positive role of 5-HT in the activation of the HPA axis, lesions aimed at the destruction of 5-HT cells located in the dorsal raphé abolished the circadian rhythm of corticosterone release (see Scapagnini and Preziosi, 1972). Microinjections of the serotonergic neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) into rat suprachiasmatic nucleus blocked the diurnal rhythm of corticosterone as compared with vehicle-treated rats (Williams *et al*., 1983) and prevented the beginning of a corticosterone diurnal rhythm in 16-day-old male rats (Banky *et al*., 1986).

Other investigators have demonstrated that 5-HT has no effect on the diurnal rhythm of the hypothalamic–pituitary–adrenal axis (Dixit and Buckley, 1969; Bhattacharya and Marks, 1970; Rotsztejn *et al*., 1977). For example, Rotsztejn *et al*. (1977) demonstrated that lesions in the dorsal and median raphé nuclei and treatment with PCPA, which both resulted in a significant reduction in whole brain 5-HT levels, did not affect the rhythmic changes in corticosterone in rats. The disparity of these results with those of Scapagnini *et al*. (1971) may be due to incomplete lesions or to the length of time elapsed between creation of the lesion and obtaining of the corticosterone results.

A circadian rhythm of 5-HT receptor density has been described for 5-HT_1 and 5-HT_2 receptors in the frontal cortex (Akiyoshi *et al*., 1989; Weiner *et al*., 1992) and for 5-HT_1 and 5-HT_{2C} receptors in the

hippocampus (Weiner *et al.*, 1992; Holmes *et al.*, 1995a). Others have not found a circadian change in the density of 5-HT receptors in the brainstem, frontal cortex, or hypothalamus as measured by 0.8 n*M* [^{3}H] spiperone, which binds with high affinity to 5-HT_1, 5-HT_2, and dopamine D_2 receptor sites (Di Lauro *et al.*, 1986). Throughout the ventral hippocampus, the 5-HT_{2C} receptor mRNA level has been shown to be higher when 5-HT and plasma corticosterone levels are low (Holmes *et al.*, 1995a,b, 1997). The rhythmic expression of 5-HT_{2C} receptor mRNA in the hippocampus is not sensitive to adrenalectomy, suggesting that circadian changes in 5-HT_{2C} mRNA expression in the hippocampus are not a result of glucocorticoid circadian changes (Holmes *et al.*, 1995b). However, 5-HT_{2C} receptor mRNA expression is sensitive to elevated glucocorticoids and stress, possibly an adaptive response to desensitize the 5-HT_{2C} receptor in response to chronic stress (Holmes *et al.*, 1995a, 1997). 5-HT_{2C} receptor mRNA expression is highest in the CA_1 and subiculum (Holmes *et al.*, 1995a,b, 1997). Both send projections to the paraventricular nucleus, some of which travel thorough the bed nucleus of the stria terminalis (Kiss *et al.*, 1983; Herman *et al.*, 1994). Given that the pathway from the bed nucleus of the stria terminalis is inhibitory (Herman *et al.*, 1994), it is possible that changes in the expression of 5-HT_{2C} receptors may have an effect on the HPA axis via this pathway. As mentioned in Section III.A.6, 5-HT_2 receptor agonist-induced regulation of the HPA axis is mediated through 5-HT_{2A} receptors, rather than 5-HT_{2C} receptors. Because the 5-HT_{2A} receptor, unlike the 5-HT_{2C} receptor, does not appear to have a circadian rhythm of expression in the hippocampus or hypothalamus (Di Lauro *et al.*, 1986; Weiner *et al.*, 1992; Holmes *et al.*, 1995a, 1997), perhaps the 5-HT_{2A} receptor-mediated response is more apparent when the experiments are conducted.

B. STRESS

Stress can be described as the response to a condition that is capable of disrupting homeostasis. Stressors, conditions that jeopardize or are perceived to jeopardize survival, fall into three broad categories: stressors involving a cardiovascular challenge such as hemorrhage, stressors involving a physical stimulus with a strong psychological element such as pain, and stressors involving a psychological response to an aversive condition such as anxiety.

All three stressors lead an organism to respond in a broad manner, which Selye (1936) refers to as the "general adaptation syndrome." The HPA axis serves as a messenger from the brain to the rest of the body, and plasma glucocorticoid levels are a revealing sign that an organism is undergoing stress. The involvement of 5-HT in the response of an organism may be stressor dependent (Fuller, 1992b).

1. Neuroanatomy of Stress

Cardiovascular stressors primarily rely on information regarding blood volume and pressure originating in baroreceptors, found in the wall of the carotid sinus, and the aortic arch and the atrial stretch receptors in the walls of both atria. A decrease in firing frequency signals a drop in arterial blood pressure or atrial pressure, which signals the release of ACTH and glucocorticoids (Baertschi *et al.*, 1976; Anderson *et al.*, 1994, 1995). The nucleus tractus solitarius sends reciprocal projections to areas such as the caudal raphé nuclei (raphé obscurus, raphé pallidus, raphé magnus), periaqueductal gray matter, and the paraventricular and lateral hypothalamus (Loewy and Burton, 1978; Thor and Helke, 1987; Loewy, 1990).

Many brain structures are involved in the response to psychologically stressful stimuli. In this review, we focus on the hypothalamic–pituitary–adrenal aspect of the response to stress; however, more thorough reviews of neuroendocrine response to stress have been published elsewhere (Van de Kar *et al.*, 1991b; Van de Kar and Blair, 1999; Sapolsky *et al.*, 2000; Pacak and Palkovits, 2001). Stimuli from conditioned and unconditioned stressors pass through either the reticular activating system or the thalamus before the sensory input is then relayed to the amygdala and sensory cortex (Pezzone *et al.*, 1992; LeDoux, 1995; Bhatnagar and Dallman, 1998; Van de Kar and Blair, 1999). The information from the neocortex is then sent to the basolateral nucleus of the amygdala (Davis *et al.*, 1994; LeDoux, 1995; Van de Kar and Blair, 1999). In the case of learned psychological stressors such as conditioned fear, the information from the basolateral and lateral nuclei of the amygdala is communicated to the central amygdaloid nucleus and transmitted to the CRH neurons in the paraventricular nucleus either directly or via the bed nucleus of the stria terminalis (Weller and Smith, 1982; Moga *et al.*, 1989; Cullinan *et al.*, 1993; Gray *et al.*, 1993; Herman *et al.*, 1994; Van de Kar and Blair, 1999). In addition to the relay from the amygdala, the ACTH response also requires neural inputs from the serotonergic neurons in the dorsal raphé nucleus as well as A_1, A_2, C_1, and C_2 (nor)adrenergic cell groups located in the brainstem. These brain regions have reciprocal projections with the amygdala (Uryu *et al.*, 1992; Wallace *et al.*, 1992; Petrov *et al.*, 1992a, 1993, 1994).

2. Hemorrhage

Stressors that influence cardiovascular function include exercise, heat exposure, and hemorrhage. These cardiovascular stressors can elicit a neuroendocrine response such as an increase in vasopressin release, which results in vasoconstriction and water retention. These stressors also increase plasma renin levels and formation of angiotensin II and III that lead to the constriction of arterioles in order to raise vascular resistance in the face of decreasing blood volume. Cardiovascular stressors can also bring about the

release of oxytocin, prolactin, and ACTH. For the sake of this discussion, the HPA axis is the focus whereas the other neuroendocrine responses are reviewed extensively elsewhere (Matzen, 1995; Van de Kar and Blair, 1999; Pacak and Palkovits, 2001).

Hemorrhage is a potent cardiovascular stressor. As an organism undergoes hemorrhage, the body begins to initiate compensatory actions to maintain blood flow to the brain and to counteract the ensuing blood loss. The overall response to the decrease in blood volume can be characterized in two distinct stages (Schadt and Ludbrook, 1991). In the first stage, the sympathetic nervous system is activated and leads to increased heart rate and contractility to maintain mean arterial pressure. This is termed the normotensive stage. If blood loss continues, the normotensive stage is then followed by a hypotensive stage resulting from the protracted hemorrhage. In the hypotensive stage, there is a decrease in heart rate and mean arterial pressure due to vasodilatation.

ACTH is released in response to hypotensive hemorrhage (Matzen, 1995). The hypothalamic–pituitary response is believed to be stimulated by cardiopulmonary and arterial baroreceptors. Lesion studies indicate that the nucleus tractus solitarius, dorsal rostral pons, caudal ventrolateral medulla, and paraventricular nucleus of the hypothalamus play an important role in ACTH release in response to hemorrhage (see Matzen, 1995).

In rats, intravenous infusion of 5-HT results in three phases of cardiovascular activity (Fozard, 1982; Kalkman *et al.*, 1984; De Vries *et al.*, 1997). The first phase is a depressor phase and bradycardia, mediated by 5-HT_3 receptors. The second phase is a pressor response, initiated by 5-HT_2 receptors. The last phase is a hypotensive phase related to 5-HT_1-like or 5-HT_7 receptor activation (Kalkman *et al.*, 1984; De Vries *et al.*, 1997).

The involvement of 5-HT in hemorrhage has been studied with the head-up tilt model. Head-up tilt is an experimental model used to study hemorrhage in human volunteers in a relatively noninvasive manner (Matzen *et al.*, 1993; Matzen, 1995). In this model, subjects are slowly tilted 50 degrees to mimic blood loss, thus causing the subjects to undergo both cardiovascular stages of hemorrhage. Likewise, the neuroendocrine responses of the head-up tilt mimic hemorrhage (Matzen *et al.*, 1993; Matzen, 1995); therefore, neuroendocrine responses to various drugs can be measured. Administration of methysergide, the 5-HT_2 receptor antagonist ketanserin (which is also an α_1-adrenergic antagonist), and the 5-HT_3 receptor antagonist ondansetron had no effect on head-up tilt-induced plasma ACTH or cortisol levels (Matzen *et al.*, 1993). Although animal studies have demonstrated an interaction between 5-HT and cardiovascular reflexes during hypovolemia (Matzen *et al.*, 1993), it appears that the actions of 5-HT are not mediated by these particular 5-HT receptors. However, the lack of effect of these 5-HT receptor antagonists may be due in part to a heterogeneous expression of 5-HT receptors as well as a lack of

receptor-specific antagonists available for human investigation. Alternatively, the cardiovascular responses to hemorrhage may be mediated by a different family of 5-HT receptors.

3. Hypoglycemia

The brain requires glucose for the production of energy. Hypoglycemia brings about a rapid neurophysiological change, the most severe being loss of consciousness and seizures. The HPA axis and other effector systems respond to glucoprivation by increasing peripheral plasma glucose levels, thereby delivering glucose to the brain. Hypoglycemia can be induced in normal human subjects by a challenge infusion with insulin, which causes cells to take in glucose, leading to a decrease in plasma glucose levels. Insulin-induced hypoglycemia also leads to increased secretion of epinephrine, glucagon, growth hormone, prolactin, vasopressin, CRH, ACTH, and cortisol in humans (Kletzky *et al*., 1980; Watabe *et al*., 1987). An increase in 5-HT content in the hypothalamus is also evident following insulin-induced hypoglycemia (Gordon and Meldrum, 1970). However, evidence of 5-HT involvement in ACTH and glucocorticoid release in conjunction with hypoglycemia has been contradictory. For example, when Kletsky *et al*. (1980) gave the serotonin antagonist cyproheptadine (also a histamine antagonist) to normal human volunteers prior to insulin-induced hypoglycemia, there was no inhibition of the secretion of prolactin, growth hormone, or cortisol. In contrast, when Plonk *et al*. (1974) administered cyproheptadine, they observed a partial blockade of cortisol release in response to hypoglycemia, and when they used the 5-HT antagonist methysergide, there was no significant blockade of the cortisol response. Much of the controversy stems from inadequate pharmacological tools to examine the involvement of 5-HT in humans. For instance, cyproheptadine possesses anticholinergic, antidopaminergic, and antihistaminic properties (Gilbert and Goldberg, 1975; Stone *et al*., 1961). Methysergide is a 5-HT_2 antagonist but also a dopamine D_2 and 5-HT_{1A} receptor agonist (Hoyer *et al*., 1994).

Treatment with the selective serotonin reuptake inhibitor (SSRI) fluoxetine had no effect on the ACTH response to hypoglycemia (Fuller and Snoddy, 1977). In contrast, Prescott *et al*. (1984) found that the 5-HT_2 antagonist (and α-antagonist) ketanserin inhibited the ACTH response to hypoglycemia by 30%. More recently, Weidenfeld and colleagues (1994) utilized 2-deoxyglucose to decrease intracellular glucose in order to probe the interaction of 5-HT and the hypothalamic–pituitary–adrenal axis. In this experiment, intracerebroventricular injections of ketanserin completely inhibited the 2-deoxyglucose-induced increase in ACTH and cortisol, suggesting that 5-HT_2 receptors are involved in the hypoglycemia-induced hypothalamic–pituitary–adrenal axis response.

4. Foot Shock and Conditioned Stress

Several animal models have been employed to imitate human psychological stress. Conditioned fear and immobilization are two paradigms used to study HPA axis responses to "psychological" stress. Foot shock alone leads to an increase in ACTH and corticosterone (Kant *et al.*, 1983; Paris *et al.*, 1987; Saphier and Welch, 1995). The conditioned fear model trains the animal to associate a noxious stimulus with a neutral stimulus. For example, a foot shock (noxious stimulus) can be paired with a light or simply the placement of a rat in a chamber (neutral stimulus) and eventually the foot shock becomes paired with the light or the chamber (neutral stimulus) in which the shock occurs. Once the two stimuli are associated by the experimental animals, the neutral stimulus will trigger the release of stress hormones. This protocol is known as conditioned fear or conditioned stress response (Fendt and Fanselow, 1999). The conditioned fear response leads to the release of ACTH and corticosterone (Paris *et al.*, 1987) (Rittenhouse *et al.*, 1992a; Gray *et al.*, 1993; Saphier and Welch, 1995; Zhang *et al.*, 2000). Chronic treatment of rats with fluoxetine decreased stress-induced behavior but did not inhibit the neuroendocrine responses to conditioned fear (Zhang *et al.*, 2000). The effects of foot shock on 5-HT levels in the brain have been controversial; the results range from no change in 5-HT content (Paris *et al.*, 1987) to an increase in 5-HT metabolism (Driscoll *et al.*, 1983; Dunn, 1988, 2000; Saphier and Welch, 1995).

Photic stimulation is another physiological stressor involving exposure to frequent flashes of light. Feldman *et al.* (1998) demonstrated that the serotonergic system within the amygdala is necessary for activation of the hypothalamic–pituitary–adrenal axis following photic stimulation. They also demonstrated that 5-HT_2 receptors within the amygdala are involved in the stress-induced response when they observed that direct injections of the 5-HT_2 receptor antagonist ketanserin into the amygdala inhibited the corticosterone response to photic stimuli.

5. Immobilization Stress

Immobilization stress is a "psychological" stressor that, like conditioned fear, leads to the secretion of ACTH and corticosterone (Beaulieu *et al.*, 1986; Rittenhouse *et al.*, 1992a; Gaillet *et al.*, 1993; Gray *et al.*, 1993); however, immobilization stress lacks a learned component. The role of central 5-HT in immobilization stress has been debated. Many investigators found an increase in 5-HT metabolism (Shimizu *et al.*, 1989; Dunn, 1999) as well as 5-HT content in the limbic system (Shimizu *et al.*, 1989; Vahabzadeh and Fillenz, 1994), which accompanies immobilization stress. Others have found no change in 5-HT metabolism in the hypothalamus or amygdala (Morgan *et al.*, 1975; Beaulieu *et al.*, 1986). When rats are given the amino acid valine, which competes with the uptake of the 5-HT precursor

tryptophan, immobilization-induced increase in plasma corticosterone is prevented; the authors conclude that the response of 5-HT to stress is at least partially dependent on the rise of brain tryptophan (Kennett and Joseph, 1981). Likewise, the ACTH response to immobilization stress can be potentiated by blocking the reuptake of 5-HT with fluoxetine and blocked by the nonselective 5-HT receptor antagonist metergoline as well as the 5-$HT_{2C/2A}$ receptor antagonist cinanserin (Bruni *et al.*, 1982). Yet, a reduction in 5-HT content with the serotonin synthesis inhibitor PCPA did not alter immobilization-induced ACTH secretion, nor did it prevent immobilization-induced expression of c-*fos* mRNA in the hypothalamic paraventricular parvocellular neurons (Harbuz *et al.*, 1993). c-*fos* is a proto-oncogene (immediate early-action gene) activated on synaptic stimulation.

To summarize, serotonergic neurons play more of a modulatory than a principal role in stress-induced activation of the HPA axis. This is not entirely surprising considering the importance of glucocorticoids for survival. It is more than likely that multiple neurotransmitter circuits act in a redundant manner to guarantee appropriate secretion of glucocorticoids during life-threatening conditions.

V. PATHOPHYSIOLOGICAL INTERACTIONS

Chronic activation or dysregulation of the HPA axis can lead to pathophysiological stress-related conditions such as depression, anxiety, and chronic fatigue syndrome.

A. DEPRESSION

Depression should be viewed as a collection of symptoms rather than a disease. Depressive symptoms are precursors of other diseases such as coronary artery disease or sleep apnea (Yantis, 1999; Appels *et al.*, 2000). In addition, stress and depression are closely linked (Kessler, 1997; Gold and Chrousos, 2002). The onset of depressive episodes frequently occurs following psychologically as well as physically stressful events, and depression can bring about or aggravate stressful life events (Post, 1992; Kessler, 1997).

1. The Serotonergic System and Depression

The etiology of depression is not fully understood. Research over the past few decades has implicated monoamine dysfunction as a possible cause for depressive symptoms (Delgado, 2000). The fact that not all depressed patients respond to the same antidepressant treatment suggests that dysfunction of many mechanisms or neuronal pathways may be responsible for the precipitation of depressive symptoms.

Evidence implicating a serotonergic deficiency in depression includes the fact that SSRIs, such as fluoxetine and paroxetine, are as effective as the tricyclic antidepressants for the treatment of depressive symptoms (Hirschfeld, 1999). Furthermore, patients responding to imipramine or the MAO inhibitor tranylcypromine relapsed on treatment following the administration of the serotonergic synthesis inhibitor *p*-chlorophenyl alanine (PCPA) (Shopsin *et al*., 1975, 1976), demonstrating that serotonin is necessary to maintain the antidepressant effects in these patients. Likewise, diets deficient in the 5-HT precursor tryptophan can transiently reverse antidepressant therapeutic effects (Delgado *et al*., 1990; Heninger *et al*., 1992; Bremner *et al*., 1997a; Fadda, 2000). In clinical trials in nonmedicated depressed patients, a low-tryptophan diet generally does not exacerbate symptoms (Delgado *et al*., 1994; Heninger *et al*., 1996).

2. The Hypothalamic–Pituitary–Adrenal Axis and Depression

Hyperactivity of the HPA axis is a consistent observation among many depressive patients. Given this observation, several groups associating the dysregulation of the hypothalamic–pituitary–adrenal axis to the causality of depression believe antidepressants may act to normalize the function of the HPA axis (see Holsboer and Barden, 1996; Holsboer, 2001; Pariante and Miller, 2001). The clinical observations leading to this correlation include an increase in CRH-secreting neurons within the limbic region (Raadsheer *et al*., 1994), an increase in CRH levels in the cerebrospinal fluid (Traskman *et al*., 1980; Nemeroff *et al*., 1984), a decrease in CRH-binding sites within in the frontal cortex in response to increased CRH levels (Nemeroff *et al*., 1988), and an increase in cortisol levels in plasma (Gibbons, 1964; Fang *et al*., 1981) and urine (Kathol *et al*., 1989).

An apparent lack of glucocorticoid-induced negative feedback inhibition of the HPA axis in depression has implicated glucocorticoid receptor impairment as a possible cause for HPA axis hyperactivity as well as depression. Much of the research regarding depression and glucocorticoid receptors has focused on the type II receptor, given that type II receptor activation is necessary for HPA axis feedback regulation when glucocorticoid levels are high (De Kloet *et al*., 1998). This is the case for patients with major depression.

Some studies have pointed to genetic alteration of the type II receptor as a possible cause of depression. People who have a high familial risk for depression might inherit a mutated type II receptor (Modell *et al*., 1998). However, to date five novel polymorphisms of the type II receptor gene have been identified, but no specific variant of type II receptor has been found to be associated with depression (Koper *et al*., 1997).

The type I receptor should not be neglected in depression research because it is now apparent that even at the higher levels of glucocorticoids at the circadian peak, type I receptors may play an important role (Dallman

et al., 1989; Bradbury *et al*., 1994; Spencer *et al*., 1998; Young *et al*., 1998). With regard to the delayed therapeutic effects of antidepressants, the change in type I receptor function correlates more closely than do changes in type II receptors (Reul *et al*., 1994). Furthermore, in a double-blind experiment, the behavioral effects of the tricyclic antidepressant amitriptyline in humans were blocked by the type I receptor antagonist spironolactone (see Holsboer, 2001).

The best illustration of CRH and glucocorticoid receptor impairment in depression involves the dexamethasone suppression test and the dexamethasone–CRH test. The dexamethasone suppression test entails the administration of a low dose of dexamethasone (1–2 mg) late in the evening and the measurement of cortisol levels at various time points during the subsequent day. Nondepressed subjects respond to dexamethasone treatment by decreasing cortisol levels. Many but not all depressed subjects fail to exhibit dexamethasone suppression of cortisol levels. This inappropriate dexamethasone response in depressed subjects is likely a result of impaired type II glucocorticoid receptors (Holsboer, 2001).

The dexamethasone suppression test was supplemented by the administration of CRH to create the dexamethasone–CRH test, which is a more sensitive test for the detection of abnormal functions of the HPA axis (Heuser *et al*., 1994). The dexamethasone–CRH test takes into account the regulatory role of CRH by demonstrating the impairment of CRH receptors. In this test, CRH is administered intravenously after pretreatment with vehicle or a low dose of dexamethasone. Without dexamethasone, normal subjects respond to CRH administration by increasing plasma ACTH levels, whereas depressed subjects exhibit a blunted ACTH response. When the subjects are pretreated with dexamethasone to activate the negative feedback response of the type II glucocorticoid receptors, the responses of depressed and nondepressed subjects are reversed: in normal subjects, dexamethasone-induced suppression overrides the CRH-induced increase in ACTH levels; depressed subjects, however, undergo a paradoxical increase in ACTH response.

3. Serotonin and Hypothalamic–Pituitary–Adrenal Axis Interactions in Depression

Neuroendocrine challenge tests with 5-HT releasers (*d*-fenfluramine), SSRIs, precursors, or 5-HT receptor agonists illustrate the altered interactions between the serotonergic system and the HPA axis in depression. In depressed patients, a *d*-fenfluramine-induced increase in cortisol levels is attenuated as compared with healthy control subjects (O'Keane and Dinan, 1991; Lucey *et al*., 1992; Cleare *et al*., 1996, 1998). Likewise, depressed patients experience a blunted ACTH and cortisol response to an acute challenge with clomipramine, a tricyclic drug with high affinity for the serotonin transporter (Golden *et al*., 1992). ACTH and

cortisol responses to the 5-HT_{1A} agonists buspirone, flesinoxan, and ipsapirone are blunted in depression (Lesch *et al.*, 1990a; Meltzer and Maes, 1994, 1995a; Pitchot *et al.*, 1995). With depression, there is no difference in cortisol response to the 5-HT_2 agonists *m*-CPP or MK-212 (Kahn *et al.*, 1988,1990a; Anand *et al.*, 1994).

Antidepressant drugs, which act to increase the amount of 5-HT in the synaptic cleft, have a delayed therapeutic action. Changes in the synapse must occur prior to the therapeutic action of these drugs. One of the proposed changes is that the elevated amount of 5-HT in the synapse, particularly by SSRIs, leads to a desensitization of somatodendritic 5-HT_{1A} autoreceptors (Kreiss and Lucki, 1995; Blier and de Montigny, 1996; Casanovas *et al.*, 1999b; Czachura and Rasmussen, 2000; Le Poul *et al.*, 2000; Hervas *et al.*, 2001; Hensler, 2002) and the desensitization of 5-$HT_{IB/ID}$ synaptic autoreceptors within 2–3 weeks (de Montigny *et al.*, 1990; Blier and Bouchard, 1994; Blier and de Montigny, 1994; Blier, 2001). Combined, the desensitization of autoreceptors releases the serotonergic system from the negative feedback regulation brought about by these receptors.

In addition to the autoreceptor-induced feedback, evidence suggests that forebrain 5-HT_{1A} receptors are involved in the negative feedback regulation of serotonergic neurons in the midbrain raphé nuclei. Negative feedback interaction has been demonstrated with 5-HT_{1A} receptors expressed by neurons in the amygdala (Bosker *et al.*, 1997, 2001). Similarly, postsynaptic 5-HT_{1A} receptors in the frontal cortex (Ceci *et al.*, 1994; Peyron *et al.*, 1998; Casanovas *et al.*, 1999a; Hajós *et al.*, 1999; Haddjeri *et al.*, 2000; Celada *et al.*, 2001) as well as the striatum (Romero *et al.*, 1994) but not the hippocampus (Hjorth *et al.*, 1996) mediate a negative feedback regulation of serotonergic neurons in the midbrain raphé nuclei.

An antidepressant-induced increase in synaptic 5-HT results in the desensitization of postsynaptic 5-HT_{1A} receptors (Goodwin *et al.*, 1987; Hensler *et al.*, 1991; Serres *et al.*, 2000b; Bosker *et al.*, 2001). In the amygdala, desensitization of postsynaptic 5-HT_{1A} receptors by the SSRI citalopram is linked to an increase in extracellular levels of 5-HT in the amygdala in rats (Bosker *et al.*, 2001). Therefore, the release from negative feedback induced by the autoreceptors and specific postsynaptic 5-HT_{1A} receptors results in an increase in synaptic 5-HT levels in the forebrain. The elevated levels of 5-HT can then act on other 5-HT receptors, some of which may be involved in the therapeutic effect of some antidepressants.

The paraventricular nucleus might also play an integral role in the regulation of 5-HT release from the midbrain raphé to the forebrain by way of postsynaptic 5-HT_{1A} receptors. As in the amygdala, postsynaptic 5-HT_{1A} receptors in the paraventricular hypothalamus become desensitized after treatment with antidepressants such as fluoxetine, paroxetine, and venlafaxine (Li *et al.*, 1996a, 1997b; Raap *et al.*, 1999; Newman *et al.*, 2000; Serres *et al.*, 2000b). The paraventricular nucleus innervates the dorsal

and median raphé nuclei (Conrad and Pfaff, 1976; Behzadi *et al.*, 1990; Peyron *et al.*, 1998). In addition, the dorsal raphé sends collateral innervation to both the amygdala and the paraventricular nucleus (Petrov *et al.*, 1992b, 1994). Together, the evidence of reciprocal innervation gives anatomical context for the possibility of paraventricular nucleus-induced negative feedback on serotonin release from the raphé nuclei.

B. ANXIETY DISORDERS

Anxiety disorders, like depression, are symptoms underlying several neuropathological disorders. Just as stress is linked to the development or occurrence of depression (see Section V.A), anxiety disorders can either lead to depressive disorders or be expressed with depression (Kessler *et al.*, 1996). Anxiety disorders currently comprise a number of similar disorders including generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, and social phobia (Nutt, 1996).

Although fear is considered a normal response to a threatening situation, anxiety is considered to be an unfounded response or inappropriate fear (Ninan, 1999). The key area in the brain associated with the emotional experience of anxiety is the amygdala (LaBar *et al.*, 1995; LeDoux, 1995; Ninan, 1999). Stimulation of the amygdala in humans leads to the expression of emotions associated with fear and anxiety (Davis and Whalen, 2001). A commonality among anxiety disorders is their distorted output from the central nucleus of the amygdala (Ninan, 1999).

1. The Serotonergic System and Anxiety

Benzodiazepines are the most common and popular treatment for several anxiety disorders. Although they provide robust and swift amelioration of anxiety symptoms, their potential for tolerance, physical dependence, and motor and cognitive impairment (Ninan, 1999; Argyropoulos *et al.*, 2000) makes them more of a problem than a solution for anxiety disorders. Benzodiazepines potentiate the effects of the neurotransmitter GABA at GABA-A receptors (Sigel, 2002). The acute actions of benzodiazepines may be due in part to a reduction of 5-HT neuronal firing in the raphé induced by local GABA-ergic neurons as demonstrated by electrophysiological studies (Gallager, 1978; Ferraro *et al.*, 1996; Gervasoni *et al.*, 2000; Varga *et al.*, 2001), *in vivo* microdialysis (Forchetti and Meek, 1981; Tao *et al.*, 1996; Tao and Auerbach, 2000), and behavioral studies (Levine and Jacobs, 1992; Maier *et al.*, 1995a,b; Inoue *et al.*, 1996).

Treatment with serotonergic drugs such as 5-HT_{1A} agonists and SSRIs is therapeutically effective in the treatment of anxiety (Zohar and Westenberg, 2000). Chronic treatment with 5-HT_{1A} agonists such as buspirone, gepirone, ipsapirone, and tandospirone results in the desensitization of both somatodendritic 5-HT_{1A} autoreceptors and postsynaptic 5-HT_{1A} receptors

(Blier and de Montigny, 1987; Blier *et al.*, 1990; Godbout *et al.*, 1991; Bohmaker *et al.*, 1993; Matheson *et al.*, 1996; Berlin *et al.*, 1998; Sim-Selley *et al.*, 2000). Similarly, chronic treatment with SSRIs desensitizes both somatodendritic 5-HT_{1A} autoreceptors and postsynaptic 5-HT_{1A} receptors (Anderson *et al.*, 1996; Li *et al.*, 1997b; Berlin *et al.*, 1998; Lerer *et al.*, 1999; Bosker *et al.*, 2001; Dawson *et al.*, 2002; Hensler, 2002; Pejchal *et al.*, 2002). The actions of these serotonergic drugs suggest that their therapeutic mechanism of action is the desensitization of 5-HT_{1A} receptors (Yocca, 1990).

2. The Hypothalamic–Pituitary–Adrenal Axis and Anxiety

Researchers have proposed that stress activates the HPA axis to counteract glucocorticoid inhibition to subsequent stressors (Dallman and Jones, 1973; Akana *et al.*, 1992; Cassano and D'Mello, 2001). The effects of repeated stress on the neuroendocrine system have characteristics similar to those encountered in chronic anxiety (Boyer, 2000).

Although most patients with anxiety or depression exhibit an increase in CRH levels within the cerebrospinal fluid, the neuroendocrine response associated with anxiety is as a whole the opposite of that of depression (Fang *et al.*, 1981; Bremner *et al.*, 1997b; Arborelius *et al.*, 1999; Boyer, 2000; Kasckow *et al.*, 2001). For example, patients with depression generally have an elevated level of cortisol, and most patients with stress disorders have a lower level of cortisol (Boyer, 2000). Likewise, in depression dexamethasone treatment fails to suppress cortisol levels (Holsboer, 2001), whereas in anxiety disorders not associated with depression, there is a dexamethasone-induced suppression or exaggerated suppression of cortisol levels, particularly in obsessive-compulsive, panic, and posttraumatic stress disorders (Lieberman *et al.*, 1983, 1985; Sheehan *et al.*, 1983; Coryell *et al.*, 1989; Yehuda *et al.*, 1993, 1995; Orlikov *et al.*, 1994; Stein *et al.*, 1997). Furthermore, most depressed patients have a blunted ACTH release following CRH administration, whereas some patients with anxiety disorders, such as panic and posttraumatic stress, primarily have a normal to exaggerated response to CRH administration (Curtis *et al.*, 1997; Heim *et al.*, 2001). However, a few studies report a blunted ACTH response to CRH administration in patients with panic and posttraumatic stress disorders (Roy-Byrne *et al.*, 1986; Smith *et al.*, 1989).

The anxiety-induced hyposecretion of glucocorticoids is thought to be a potentiated feedback due to sensitized glucocorticoid receptors (Boyer, 2000). Animal studies reported an association between neuronal glucocorticoid receptors and lymphocyte glucocorticoid receptors (Lowy, 1989, 1990). Lymphocyte glucocorticoid receptor number is increased with anxiety disorders in humans, suggesting an upregulation of neuronal glucocorticoid receptors (Yehuda *et al.*, 1991, 1995; Boyer, 2000). This upregulation would lead to an increase in negative feedback regulation of ACTH and cortisol

release, thereby resulting in hypocortisolemia. Boyer (2000) hypothesized a "neuroendocrine continuum" to explain the discrepancy between the neuroendocrine responses seen with depression and anxiety. This hypothesis proposes that anxiety occurs prior to major depression. The hypersecretion of CRH observed in anxiety leads to HPA hyperregulation. In people with genetic vulnerability to depression, the hypersecretion of CRH leads to the desensitization of CRH receptors, thereby resulting in dysregulation of the HPA axis.

3. Serotonin and Hypothalamic–Pituitary–Adrenal Axis Interactions in Anxiety

Pharmacological challenge tests are used to study anxiety disorders by precipitating an anxiety attack. Sodium lactate infusion induces panic attacks in patients with panic disorder or generalized anxiety disorder (Cowley and Dunner, 1988; Cowley *et al*., 1988). Inhalation of 5.5% carbon dioxide for 15 min also brings about panic attacks in many patients with anxiety disorders (Rapee *et al*., 1992). Acute depletion of the 5-HT precursor L-tryptophan had little effect on the level of anxiety in patients with panic disorder, but it was able to potentiate carbon dioxide-induced anxiety (Anderson and Mortimore, 1999; Miller *et al*., 2000; Schruers *et al*., 2000). The tryptophan depletion studies would suggest that 5-HT does not play a major role in anxiety attacks, but rather the lack of 5-HT may potentiate other factors that can trigger anxiety attacks. However, administration of *d*-fenfluramine resulted in the precipitation of an anxiety attack in patients with panic disorder, although it was able to reduce a carbon dioxide (7%)-induced panic attack (Mortimore and Anderson, 2000). Administration of the nonspecific 5-HT_1 and 5-HT_2 receptor agonist *m*-CPP induces a greater amount of anxiety in patients with generalized anxiety, obsessive-compulsive or panic disorders as compared with control subjects (Zohar *et al*., 1987; Charney *et al*., 1988; Germine *et al*., 1992; Broocks *et al*., 2000). The 5-HT_{1A} receptor agonist ipsapirone will elicit a panic attack in patients with panic disorder as well (Broocks *et al*., 2000). Together, these studies suggest that there is a dual role for 5-HT in anxiety disorders, in which an acute increase in 5-HT function could lead to an anxiety attack and continued treatment with SSRIs may reduce panic attacks.

As mentioned earlier, patients with anxiety disorders are believed to have desensitized 5-HT_{1A} receptors. When ipsapirone was administered to patients with panic disorder, there was a decreased cortisol response (Broocks *et al*., 2000); however, panic disorder patients given *m*-CPP had an increased cortisol response (Charney *et al*., 1988; Kahn *et al*., 1988; Broocks *et al*., 2000). This study not only further demonstrates that 5-HT_{1A} receptors are desensitized, it also indicates that 5-HT_2 receptors may be supersensitized.

C. CHRONIC FATIGUE

Chronic fatigue is a disorder defined as a disabling fatigue associated with other symptoms such as low-grade fever, sleep disturbances, and myalgias lasting 6 months or longer with no defined medical cause (Demitrack *et al.*, 1992; Fukuda *et al.*, 1994). Although depression is found in nearly half of the patients with chronic fatigue, patients state that their fatigue is due to physical rather than psychological causes (Kruesi *et al.*, 1989; Broocks *et al.*, 2000).

1. The Hypothalamic–Pituitary–Adrenal Axis and Chronic Fatigue

A dysfunctional HPA axis has been cited as a possible contributing factor in chronic fatigue. The main thrust of this theory was based on the fact that many of the symptoms associated with chronic fatigue mirror those of patients with glucocorticoid insufficiency (Demitrack *et al.*, 1991; O'Riordain *et al.*, 1994; Parker *et al.*, 2001). In line with this view, studies involving patients with chronic fatigue report a decrease in cortisol in some subjects (Poteliakhoff, 1981; Demitrack *et al.*, 1991) but not all subjects (Yatham *et al.*, 1995; Scott *et al.*, 1998; Scott and Dinan, 1998; Hudson and Cleare, 1999). The differences observed may relate to the mean length of disease in the patients observed, method of cortisol measurement, as well as the comorbidity of depression (see Parker *et al.*, 2001). Most studies observed a blunted ACTH response to CRH but an exaggerated cortisol response to low doses of ACTH in patients with chronic fatigue (Demitrack *et al.*, 1991; Scott *et al.*, 1998). However, low doses of synthetic ACTH did not result in an exaggerated cortisol response (Hudson and Cleare, 1999).

In chronic fatigue, disruption of the HPA axis may be a result of a deficiency in CRH (Demitrack, 1997). The lack of CRH can result in fatigue indirectly through decreased activation of the HPA axis or directly by decreasing behavioral arousal given that CRH administration leads to behavioral arousal (Sutton *et al.*, 1982; Vgontzas *et al.*, 2001). The attenuation of ACTH secretion is not reflected by a change in net cortisol release, which may demonstrate a supersensitization of the ACTH receptors. As mentioned earlier, subjects with depression also have an attenuated response to CRH. However, in depression the attenuation is believed to exist as a result of the high plasma levels of glucocorticoids associated with depression, which is not the case for chronic fatigue syndrome given that there is a hyposecretion of cortisol.

2. Serotonin and Hypothalamic–Pituitary–Adrenal Axis Interactions in Chronic Fatigue

Given that 5-HT plays such a close role in the regulation of the HPA axis, it would seem natural that 5-HT is involved in chronic fatigue syndrome. Two studies indicate that the prolactin response to administration of the

5-HT-releasing drug, *d*-fenfluramine, is significantly potentiated in patients with chronic fatigue (Cleare *et al*., 1995; Sharpe *et al*., 1997). However, another study found no change in prolactin response to *d*-fenfluramine as compared with control (Bearn *et al*., 1995). Interestingly, the investigators who did not demonstrate an elevated prolactin response did nevertheless observe an increased ACTH response to *d*-fenfluramine with no associated change in cortisol levels, suggesting an impairment of the adrenal cortex (Bearn *et al*., 1995). Another study, which used the racemic mixture of fenfluramine, which is less potent, did not observe a potentiation of the prolactin response as compared with controls (Yatham *et al*., 1995).

Further studies utilized 5-HT_{1A} or 5-HT_{2C} receptor agonists. Neuroendocrine challenge tests with 5-HT_{1A} receptor agonists have reported conflicting results. In patients with chronic fatigue, administration of buspirone resulted in a significant increase in plasma prolactin levels with no report on cortisol levels (Bakheit *et al*., 1992; Sharpe *et al*., 1996). However, the prolactin response to buspirone is mediated by antagonism of dopamine D_2 receptors in the pituitary gland. Ipsapirone administration was less effective in producing an increase in plasma ACTH in chronically fatigued subjects as compared with controls, which would suggest that 5-HT_{1A} receptors are desensitized (Dinan *et al*., 1997).

Although the majority of studies have found an increase in serotonergic activity associated with chronic fatigue, the results are still equivocal. Given that the majority of studies involving chronic fatigue also find a hypoactive HPA axis, which opposes findings in patients with depression, the most parsimonious interpretation would be that the serotonergic activity would be the opposite of that found in depression. Therefore, chronic fatigue most likely involves a hypoactive HPA axis combined with a hyperactive serotonergic system.

VI. CONCLUDING REMARKS

To summarize, the serotonergic system and the HPA axis are closely entwined. Serotonergic innervation regulates the HPA axis under stressful conditions as well as nonstressful conditions such as the circadian rhythm. As illustrated by pathophysiological disorders, a slight change in one system can alter the other. Although it seems unclear which is the underlying cause of disturbances in either system, the fact that serotonergic drugs are of therapeutic use suggests that regulation of the serotonergic system can lead to a normalization of the hypothalamic–pituitary–adrenal axis. Although both systems are known to be dysregulated in pathological conditions, a greater understanding of these interactions would be useful in the understanding and treatment of these disorders.

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