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Neuroendocrine pharmacology of stress

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Abstract

Exposure to hostile conditions initiates responses organized to enhance the probability of survival. These coordinated responses, known as stress responses, are composed of alterations in behavior, autonomic function and the secretion of multiple hormones. The activation of the renin–angiotensin system and the hypothalamic–pituitary–adrenocortical axis plays a pivotal role in the stress response. Neuroendocrine components activated by stressors include the increased secretion of epinephrine and norepinephrine from the sympathetic nervous system and adrenal medulla, the release of corticotropin-releasing factor (CRF) and vasopressin from parvicellular neurons into the portal circulation, and seconds later, the secretion of pituitary adrenocorticotropin (ACTH), leading to secretion of glucocorticoids by the adrenal gland. Corticotropin-releasing factor coordinates the endocrine, autonomic, behavioral and immune responses to stress and also acts as a neurotransmitter or neuromodulator in the amygdala, dorsal raphe nucleus, hippocampus and locus coeruleus, to integrate brain multi-system responses to stress. This review discussed the role of classical mediators of the stress response, such as corticotropin-releasing factor, vasopressin, serotonin (5-hydroxytryptamine or 5-HT) and catecholamines. Also discussed are the roles of other neuropeptides/neuromodulators involved in the stress response that have previously received little attention, such as substance P, vasoactive intestinal polypeptide, neuropeptide Y and cholecystokinin. Anxiolytic drugs of the benzodiazepine class and other drugs that affect catecholamine, $GABA_A$, histamine and serotonin receptors have been used to attenuate the neuroendocrine response to stressors. The neuroendocrine information for these drugs is still incomplete; however, they are a new class of potential antidepressant and anxiolytic drugs that offer new therapeutic approaches to treating anxiety disorders. The studies described in this review suggest that multiple brain mechanisms are responsible for the regulation of each hormone and that not all hormones are regulated by the same neural circuits. In particular, the renin–angiotensin system seems to be regulated by different brain mechanisms than the hypothalamic–pituitary–adrenal system. This could be an important survival mechanism to ensure that dysfunction of one neurotransmitter system will not endanger the appropriate secretion of hormones during exposure to adverse conditions. The measurement of several hormones to examine the mechanisms underlying the stress response and the effects of drugs and lesions on these responses can provide insight into the nature and location of brain circuits and neurotransmitter receptors involved in anxiety and stress.

Keywords: Stress; CRF (corticotropin-releasing factor); ACTH (adrenocorticotropin hormone); Corticosterone; Vasopressin; Oxytocin; 5-HT (5-hydroxytryptamine, serotonin); Substance P; Neuropeptide Y; VIP (vasoactive intestinal polypeptide); Amygdala; Hypothalamus

1. Introduction

Stress, a response to aversive stimuli, is a concept that is difficult to define fully because its interpretation tends to vary according to individual disciplines. Hans Selye, a pioneer in addressing general principles of physiology and pathophysiology in the exploration of stress, defined stress as "the nonspecific response of the body to any demand" (Selye, 1976). He emphasized the role of an integrated response of multiple systems rather than isolated reflexes. Although virtually all organs are affected by exposure to a hostile environment, the neuroendocrine, cardiovascular, immune and gastrointestinal systems are the first to experience functional changes. In this review, we will focus on the neuroendocrine responses.

Exposure to hostile conditions (usually referred to as stressors) results in a series of coordinated responses organized to enhance the probability of survival. These coordinated responses, often referred to as "stress responses," are

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composed of alterations in behavior, autonomic function and the secretion of multiple hormones including adrenocorticotropin hormone (ACTH) and cortisol/corticosterone, adrenal catecholamines, oxytocin, prolactin and renin (Van de Kar and Blair, 1999). Some of the physiological changes associated with the stress response include: (1) mobilization of energy to maintain brain and muscle function; (2) sharpened and focused attention on the perceived threat; (3) increased cerebral perfusion rates and local cerebral glucose utilization; (4) enhanced cardiovascular output and respiration, and redistribution of blood flow, increasing substrate and energy delivery to the brain and muscles; (5) modulation of immune function; (6) inhibition of reproductive physiology and sexual behavior; (7) decreased feeding and appetite. In the specialized situation of fluid loss due to hemorrhage, responses also include water retention through both renal and vascular mechanisms (Habib et al., 2001; Sapolsky, 2000; Sapolsky et al., 2000). These orchestrated responses are geared to alter the internal milieu in a way that increases the probability of survival. Stressors can be defined as conditions that endanger, or are perceived to endanger, the survival of an individual (Van de Kar and Blair, 1999). In general, these stressors can be grouped into three broad categories: (a) psychological stressors based on a learned response to the threat of an impending adverse condition (fear, anxiety, exposure to a novel or uncontrollable environment); (b) stressors that consist of a physical stimulus and have a strong psychological component (pain, foot shock, immobilization); (c) stressors which challenge cardiovascular homeostasis (hemorrhage, orthostatic stress/upright tilt, exercise, heat exposure) (Van de Kar and Blair, 1999).

The neuroendocrine responses to stressors are considered important survival mechanisms during exposure to life-threatening stimuli. There is general agreement regarding the role of the hypothalamic–pituitary–adrenal axis and adrenal catecholamines in maintaining energy balance, as well as the role of the renin–angiotensin system in redistributing blood flow towards the brain and other vital organs (Van de Kar and Blair, 1999). However, it is less clear why all three categories of stressors mentioned above increase the secretion of oxytocin and prolactin (but not vasopressin). While both oxytocin and prolactin have well-defined roles in control of female reproductive and nurturing function, the fact that they are secreted in both males and females in response to aversive stimuli implicates them as ‘‘stress hormones,’’ thus suggesting that they play other important roles that are important for survival. Oxytocin has been suggested to play a role in sodium balance and in a central anxiolytic circuit (Gimpl and Fahrenholz, 2001), while prolactin has been suggested to modulate immune function (Neidhart, 1998). However, there is no definitive explanation as to why so much energy is expended during exposure to stressors to release both oxytocin and prolactin into the circulation.

Many brain structures are involved in the response to psychologically and physically stressful stimuli. Activation of the hypothalamic–pituitary–adrenal axis leads to a rapid secretion of ACTH from corticotrophs in the anterior pituitary and to an increase in circulating glucocorticoids (Aguilera et al., 2001). Initially, it was thought that corticotropin-releasing factor (CRF) is the sole means of releasing ACTH from the pituitary gland. Currently, we know that CRF is the primary but not the only regulator of ACTH release from the pituitary gland (Levens, 1990). CRF plays a prominent role in mediating the effect of stressors on the hypothalamic–pituitary–adrenocortical axis, and in coordinating the endocrine, autonomic, behavioral and immune responses to stress (Dunn and Berridge, 1990; de Souza, 1995; Stout et al., 2002; Vale et al., 1981, 1991; Van de Kar and Blair, 1999).

This review will focus on the central pathways, neurotransmitters and receptors involved in mediating the neuroendocrine responses to psychological and physical stressors. A final chapter covering the most relevant drugs is included.

2. Neuroanatomy of the stress response

Fig. 1 summarizes a few of the well-characterized brain circuits that participate in the regulation of the neuroendocrine responses to stressors. Multiple brain structures are involved in the organization of responses to aversive or stressful stimuli. Among them are the hypothalamus, septohippocampal system, amygdala, cingulate and prefrontal cortices, hindbrain regions such as the brainstem catecholamine cell body groups (A2/C2 cell groups in the nucleus of the tractus solitarius; A1/C1 cell groups in the ventrolateral medulla; A6 cell groups in the locus coeruleus), the parabrachial nucleus, cuneiform nucleus and dorsal raphe nucleus (Van de Kar and Blair, 1999). Most sensory inputs pass through either the reticular activating system or the thalamus, which function as relay stations, to the amygdala and sensory cortex (Amiragova, 1985; Korte et al., 1992; Pezzone et al., 1992). The sensory cortex then communicates either directly or via the hippocampus with the lateral amygdala through the perirhinal cortex (Davis et al., 1994a,b; LeDoux, 1995). The amygdala is composed of several nuclei, which perform different functions. The lateral and the basolateral nuclei of the amygdala funnel and integrate sensory input from the thalamus, and cognitive information from the cortex and hippocampus (Van de Kar and Blair, 1999). The central amygdaloid nucleus is involved in behavioral, autonomic and endocrine responses (Van de Kar and Blair, 1999). The amygdala also innervates and is innervated by the dorsal raphe nucleus and catecholaminergic nuclei located in the brainstem, which, in turn innervate CRF neurons in the hypothalamic paraventricular nucleus (Petrov et al., 1994a,b; Wallace et al., 1992). CRF neurons in the paraventricular nucleus receive input from the central amygdala both directly and through the bed nucleus of the stria terminalis (Cullinan et al., 1993; Gray et al., 1989, 1993; Gray, 1993). This amygdalo-

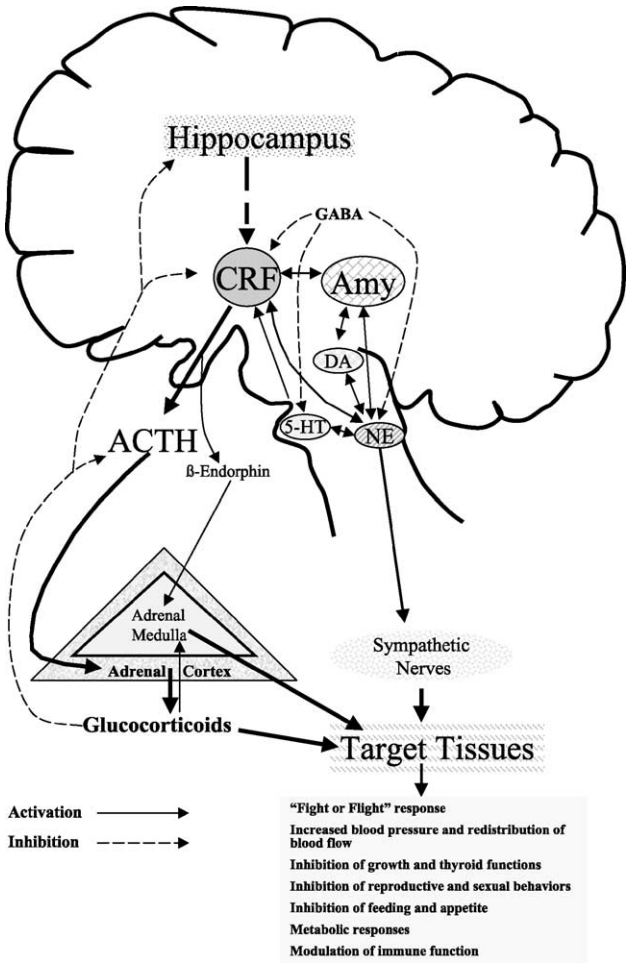

Fig. 1. Brain circuits participating in the regulation of the neuroendocrine stress response. CRF = corticotrophin-releasing factor in the hypothalamic paraventricular nucleus; 5-HT = serotonin in the dorsal raphe nucleus; NE = norepinephrine in the locus coeruleus; DA = dopamine in the mesolimbic system; Amy = amygdala; GABA = gamma-amino-butyric acid.

hypothalamic pathway is believed to play a key role in the adrenocortical response to a number of somatosensory stimuli (Feldman et al., 1975; Gray, 1993; Gray et al., 1993).

The hypothalamic paraventricular nucleus plays a pivotal role in the adaptive response to stressors. It is subdivided into at least eight subdivisions (Swanson, 1987; Swanson and Sawchenko, 1983). One of these subdivisions is the magnocellular part containing large neurons that synthesize oxytocin and vasopressin. These neurons project to the posterior (neural) lobe of the pituitary gland and release oxytocin and vasopressin directly into the circulation (Van de Kar and). CRF, the releasing factor for ACTH, is synthesized by the parvicellular neurons of the hypothalamic paraventricular nucleus and its action is central in the neuroendocrine control of ACTH release from the anterior lobe of the pituitary gland (Cole and Sawchenko, 2002; Penalva et al., 2002). CRF also plays a role in the activation of the sympathetic nervous system (Penalva et al., 2002). Vasopressin is also synthesized in parvicellular neurons in the hypothalamic paraventricular nucleus. Activation of the parvicellular neurons of the paraventricular nucleus increases the release of CRF and vasopressin and initiates the endocrine response to a stressor, stimulating the release of pro-opiomelanocortin (POMC) products, which include ACTH and β-endorphin. The hypothalamic paraventricular nucleus also contains CRF neurons that project to noradrenergic cell bodies in the locus coeruleus, a norepinephrine system that controls the stress-induced stimulation of the sympatho-adrenal system (Koob, 1999; Valentino et al., 1993), and produces an increase in norepinephrine levels in terminal regions such as the frontal cortex (Curtis et al., 1997b; Lavicky and Dunn, 1993). While CRF-containing nerve terminals have been identified in a subregion of the serotonergic dorsal raphe nucleus in the midbrain, their origin probably is in the central nucleus of the amygdala (Kirby et al., 2000; Lowry et al., 2000; Valentino et al., 2001). CRF and noradrenergic neurons are stimulated by serotonin (5-hydroxytryptamine or 5-HT) and acetylcholine, and inhibited by glucocorticoids, gamma-amino-butyric acid (GABA), ACTH and opioid peptides (Aghajanian and VanderMaelen, 1982; Calogero et al., 1988; Stratakis et al., 1995; Stratakis and Chrousos, 1995).

ACTH is the key regulator of glucocorticoid secretion from the adrenal cortex. Glucocorticoid hormones, mainly corticosterone in rats and cortisol in humans, are the final effectors of the hypothalamic–pituitary–adrenocortical axis and participate in the control of homeostasis and the response of the organism to stressors (Habib et al., 2001). Corticosterone effects are mediated by two glucocorticoid receptor subtypes: the mineralocorticoid receptor that has a higher affinity for corticosterone (Kd ≈ 1 nM), and the glucocorticoid receptor that possesses a lower affinity for corticosterone (Kd ≈ 5 nM) (Meijer and Dekloet, 1998; Meijer et al., 1998). These receptors act as ligand-dependent transcription factors (Evans and Arriza, 1989; Gesing et al., 2001). Mineralocorticoid receptors are found in some limbic brain areas such as the hippocampus, whereas glucocorticoid receptors are found in several brain regions, including frontal cortex and hypothalamic paraventricular nucleus (Jacobson and Sapolsky, 1991; Meijer and Dekloet, 1998). Glucocorticoids play a principal role in energy metabolism, growth processes, immune function and brain function, including learning and memory processes underlying behavioral adaptation (Gesing et al., 2001; Stratakis and Chrousos, 1995; Stratakis et al., 1995).

Glucocorticoids also play a key regulatory role in the neuroendocrine control of the hypothalamic–pituitary–adrenocortical axis and on the termination of the stress response by exerting negative feedback at the levels of hypothalamus and pituitary (De Kloet, 1995) and in some supra-hypothalamic structures (De Kloet et al., 1986; Gesing et al., 2001; Meaney et al., 1996; Meijer and Dekloet, 1998; Reul et al., 1990). Activation of mineralocorticoid receptors in the hippocampus inhibits the activity

of the hypothalamic–pituitary–adrenocortical axis (Gesing et al., 2001). These receptors are localized in pyramidal (CA1-4) and granular (dentate gyrus) neurons of the hippocampus (Gerlach and McEwen, 1972; Herman et al., 1989). Hippocampal neuronal inputs activate inhibitory GABA-ergic neurons located in the ventrolateral septal region and the bed nucleus of the stria terminalis, which project to CRF neurons in the parvicellular region of the hypothalamic paraventricular nucleus (Herman and Cullinan, 1997). Some of the evidence supporting this interaction is that intracerebroventricular and intra-hippocampal injection of the synthetic mineralocorticoid receptor antagonist RU 28318 results in an elevation of baseline corticosterone levels in rats (Oitzl et al., 1995; Ratka et al., 1989; van Haarst et al., 1997). Additionally, electrical stimulation of the hippocampus in humans and cats produces a decrease in the plasma levels of glucocorticoids (Rubin et al., 1966).

3. Neuroendocrine control of the stress response

3.1. Introduction

The stress response includes, among others, activation of the renin–angiotensin system and activation of the hypothalamic–pituitary–adrenocortical axis. A typical neuroendocrine response involves initially, within seconds, the increased secretion of catecholamines (epinephrine and norepinephrine) from the sympathetic nervous system and adrenal medulla, the release of CRF and vasopressin from parvicellular neurons into the portal circulation and increased secretion of oxytocin from the neural lobe of the pituitary, and 5–10 s later, the secretion of pituitary ACTH (Sapolsky et al., 2000; Van de Kar and Blair, 1999). This response also involves, some seconds latter, a decreased secretion of pituitary gonadotropins and increased secretion of prolactin and growth hormone (in primates) from the anterior pituitary, increased secretion of renin from the kidneys and the pancreatic secretion of glucagon (Sapolsky et al., 2000). In the case of hemorrhage, this first wave also includes massive secretion of vasopressin from neurons of the magnocellular regions of the hypothalamic paraventricular nucleus and renin from the kidney (Sapolsky et al., 2000). Some minutes latter, there is an increase in the plasma levels of glucocorticoids and an inhibition of the secretion of gonadal steroids. However, the glucocorticoid peak appears between 30 min and 1 h after the onset of the stressor (Paris et al., 1987; Sapolsky et al., 2000).

Several neuropeptides and neurotransmitters other than CRF also regulate the stress response in a coordinate way, each following a determined time course and specificity for a determined stressor. The chapters below summarize the roles of some of these neurotransmitters and neuropeptides in the stress response.

3.2. Corticotropin-releasing factor (CRF)

CRF is a 41-amino-acid peptide that is the primary regulator of the secretion of ACTH from the pituitary gland. It is generated by cleavage of the 196-amino-acid C-terminus of prepro-CRF (Vale et al., 1981). CRF plays a prominent role in mediating the effect of stressors on the hypothalamic–pituitary–adrenocortical axis, and in coordinating the endocrine, autonomic, behavioral and immune responses to stress (de Souza, 1995; Dunn and Berridge, 1990; Owens and Nemeroff, 1993; Vale et al., 1981; Van de Kar, 1991). The cerebral cortex, the parvicellular region of the paraventricular nucleus of the hypothalamus, the amygdala and the hippocampus are the major brain regions containing neurons which express CRF mRNA (Bittencourt and Sawchenko, 2000). CRF is also expressed in the periphery (adrenal gland, testis, placenta, gut, spleen, thymus and skin) (Dautzenberg and Hauger, 2002).

Members of the CRF family include: the 41-amino-acid peptide CRF, the 41-amino-acid peptide urotensin, the 40-amino-acid amphibian peptide sauvagine, the 40-amino-acid peptide urocortin, the 38-amino-acid peptide urocortin II (also known as stresscopin-related peptide) and the 38-amino-acid peptide urocortin III (also known as stresscopin) (Dautzenberg and Hauger, 2002; Reul and Holsboer, 2002). These peptides only share a homology of four amino acids with each other, and the biological activity appears to be determined by the secondary structure of the peptide, rather than the primary structure (Dautzenberg and Hauger, 2002).

The actions of CRF are mediated through three G-protein-coupled receptor subtypes designated CRF_1 (Chang et al., 1993; Chen et al., 1993; Vita et al., 1993), CRF_2 (Chalmers et al., 1995; Perrin et al., 1995; Reul and Holsboer, 2002) and CRF_3 (Arai et al., 2001). The CRF_1 receptor (415–420 amino acids) possesses one functional splice variant and several non-functional splice variants (Dautzenberg and Hauger, 2002). On the other hand, the CRF_2 receptor has three functional splice variants, CRF_{2A-C} (also termed $CRF_{2\alpha-\gamma}$) that apparently do not show major pharmacological differences (Dautzenberg et al., 2001). The CRF_3 receptor presents 85% of sequence homology with the CRF_1 receptor (Arai et al., 2001), and its expression has been detected in the catfish pituitary and brain (Arai et al., 2001). Currently, there is no knowledge of mammalian homologues of the CRF_3 receptor. CRF is relatively selective for CRF_1 over CRF_2 receptors, whereas urocortin II and urocortin III have a higher affinity for CRF_2 receptors than for CRF_1 receptors. Urocortin has a similar high affinity for both CRF_1 and CRF_2 receptors (Reul and Holsboer, 2002). Additionally, CRF and urocortin bind with high affinity to the CRF-binding protein (CRFBP), which modulates the CRF-related activity by limiting CRF receptor activation. Urocortin II and III have a low affinity for CRF-binding protein (Lewis et al., 2001).

CRF_1 and CRF_2 receptors are differentially expressed in the brain; whereas CRF_1 receptors are widely distributed in the central nervous system and are involved in sensory

information processing and motor control, CRF_2 receptors are restricted to sub-cortical structures (Chalmers et al., 1995; Van Pett et al., 2000). CRF_1 receptor mRNA is found in the cortex, anterior pituitary, amygdala, cerebellum, hippocampus and olfactory bulb (Chalmers et al., 1995; Sanchez et al., 1999). The CRF_1 receptor is also found in the hypothalamus and locus coeruleus of primates, but not in rodents (Sanchez et al., 1999). CRF_2 receptor mRNA is expressed in the parvicellular region of the hypothalamic paraventricular nucleus, lateral septum, amygdala, hippocampus and retina (Lovenberg et al., 1995a,b; Palchaudhuri et al., 1999; Sanchez et al., 1999).

3.3. CRF and stress

Since its identification in 1981, CRF has been hypothesized to be an integrator of multiple components of the stress response (Vale et al., 1981). In addition to hypothalamic–pituitary–adrenal regulation, CRF elicits stress-like effects such as the activation of the autonomic nervous system, arousal, anxiety-like behaviors, suppression of the immune system and suppression of eating behavior (Bale et al., 2000; Brown and Fisher, 1985; Dunn and Berridge, 1990; Gully et al., 2002; Irwin et al., 1988; Owens and Nemeroff, 1991; Spina et al., 2000; Sutton et al., 1982). These central actions of CRF are appropriate to facilitate "fight or flight" responses (Kalin et al., 1994; Korte et al., 1993).

Several studies have attempted to elucidate the role played by each CRF receptor in the stress response. Experimental approaches included the use of specific peptide and non-peptide antagonist for CRF receptors, intracerebroventricular injections of antisense oligodeoxynucleotides corresponding to either the CRF_1 or CRF_2 and transgenic animals deficient for CRF_1 and/or CRF_2 receptors.

3.3.1. CRF and cellular activation during stress

Studies examined the correlation between cellular activation, determined by increased levels of c-fos mRNA, and CRF_1 receptor levels in different brain areas highly involved in the neuroendocrine response to stress. Acute restraint stress increased c-fos mRNA and CRF_1 mRNA and protein expression preferentially in CRF-producing neurons of the parvicellular hypothalamic paraventricular nucleus (Imaki et al., 2001). Also, a small number of oxytocin and vasopressin-producing neurons expressed CRF_1 and c-fos mRNA following restraint stress (Imaki et al., 2001). An i.p. injection of CP-154,526, a CRF_1 receptor antagonist, significantly attenuated by 50% the effects of restraint stress on ACTH secretion as well as the expression of c-fos mRNA in the hypothalamic paraventricular nucleus (Imaki et al., 2001).

3.3.2. CRF receptor antagonists in the stress response

Table 1 summarizes binding constants of some antagonist for CRF receptors. Peptide and non-peptide CRF receptor antagonists reduce the behavioral and neuroendocrine effects of different acute and chronic stressors in rodents (Table 2) (Griebel, 1999). However, these antagonists can only produce inhibitory effects when the endogenous tone of CRF is high, pointing to a crucial importance of baseline stress levels (Griebel et al., 2002). Recent studies reported that SSR125543A, a potent and selective CRF_1 receptor antagonist, inhibits the increase in plasma ACTH levels in normal rats elicited by an intracerebroventricular injection of CRF (4 μg/kg) and reduces by 73% the increase in plasma ACTH levels elicited by a 15-min restraint stress (Gully et al., 2002).

3.3.3. CRF and CRF_1 receptor over-expression in the stress response

CRF_1 mRNA expression within the hypothalamic paraventricular nucleus is extremely low, but expression of both CRF and CRF_1 receptor mRNA in the parvicellular neurons of the hypothalamic paraventricular nucleus is substantially and rapidly (within the first 5 min) increased by stress, intracerebroventricular injection of CRF or an immune challenge (lipopolysaccharide or LPS injection) (Imaki et al., 1996, 2001; Lu et al., 1994; Makino et al., 1995; Mansi

Table 1
Binding constants of different antagonists for CRF_1 and CRF_2 receptors

	Antagonists	CRF_1 (nM)	$CRF_{2\alpha}$ (nM)	$CRF_{2\beta}$ (nM)
1	CRA1000	20.6		>10,000
2	CRA1001	22.3		>10,000
3	CP-154,526	1.8		>10,000
4	SC241	14.8		>10,000
5	Antalarmin	1.4		>1000
6	SSR125543A	1.8	>1000	
7	R-121919	3		
8	DMP696	1.6		
9	Astressin	5.7		4.0
10	[DPhe^{12},Nle^{21,38}] h/rCRF-(12–41)	46.4		17.7
11	[DPhe^{12}]oCRF-(12–41)	290.2		153.8
12	α-helical CRF-(9–41)	60.3		6.4
13	[DPhe^{11},His^{12}]Svg-(11–40)	153.6		1.4
14	[DPhe^{11}]Svg-(11–40)	237.3		3.5
15	[DLeu^{11}]Svg-(11–40)	>1000		20.9
16	[DPhe^{11}]rUcn-(11–40)	33.0		5.2
17	[DPhe^{11},Glu^{12}]rUcn-(11–40)	68.2		9.5
18	[DLeu^{11},Glu^{12}]rUcn-(11–40)	91.1		27.9
19	Cyclo(29–32) [DPhe^{11},Glu^{12}, Lys^{32}]rUcn-(11–40)	47.1		22.4

Data for 1–4 were taken from Okuyama et al. (1999a); 5 was taken from Webster et al. (1996); 6–7 were taken from Gully et al. (2002); 8 was taken from Maciag et al. (2002); 9–19 were from Ruhmann et al. (1998). These data correspond to binding competition experiments using ^{125}I-ovine-CRF for CRF_1 and/or ^{125}I-Sauvagine for CRF_2 receptors.

1–5: Ki values were determined in membranes or homogenates prepared from frontal cortex (CRF_1) and heart (CRF_2).

6: Ki values were obtained in CHO cells expressing CRF_1.

9–19: Binding constants were determined in membranes from HEK cells transfected separately for CRF_1 and CRF_2 receptors.

[DPhe^{11},His^{12}]Svg(11–40) is also known as Anti-Sauvagine 30.

Table 2
Drugs that alter the effect of stressors on the secretion of ACTH (or corticosterone), oxytocin, prolactin and renin

Drug	Selectivity	Stressor	ACTH/ corticosterone	Oxytocin	Prolactin	Renin	References
SSR125543A	CRF_1 receptor antagonist	immobilization	↓				Gully et al., 2002
Antalarmin	CRF_1 receptor antagonist	immobilization	↓				Gully et al., 2002
		social stressor	=				Wong et al., 1999
CRA1000	CRF_1 receptor antagonist	endotoxin stress	↓				Pournajafi et al., 2001
		ether	=				Pournajafi et al., 2001
CR-154,526	CRF_1 receptor antagonist	air puff startle	↓				Arborelius et al., 2000
		immobilization	↓				Imaki et al., 2001
Astressin	CRF_1 receptor antagonist	immobilization	↓				Pelleymounter, 2002
Antisauvagine-30	CRF_1 receptor antagonist	immobilization	=				Pelleymounter, 2002
DMP696	CRF_1 receptor antagonist	maternal separation and foot shock	↓				Maciag et al., 2002
		handling and footstock	=				Maciag et al., 2002
α-Helical CRF-(9–41)	CRF receptor antagonist	intracerebroventricular injection	↓				Kim et al., 1998
RP67580	Tachykinin NK_1 receptor antagonist	immobilization	↑				Jessop et al., 2000
SSR149515	V_{1b} receptor antagonist	immobilization	↓				Serradeil-Le Gal et al., 2002
SR48692	Neurotensin antagonist	novelty	↓				Nicot et al., 1997
Devazepide	CCK_1 receptor antagonist	swim	=				Hernando et al., 1996
Ac,Tyr1,D-Phe2-GRF(1–29)	VIP receptor antagonist	cold stress	↓				Nowak et al., 1994
		ether	=				Nowak et al., 1994
Buspirone	5-HT_{1A} receptor agonist	conditioned fear	=		↓		Urban et al., 1986
		conditioned fear				↓	Van de Kar et al., 1985b
		rotation	=				Matheson et al., 1997
Ipsapirone	5-HT_{1A} receptor agonist	conditioned fear	↓		=	↓	Rittenhouse et al., 1992
		immobilization	=		↓	↓	Rittenhouse et al., 1992
		swim	=		=	=	Rittenhouse et al., 1992
		rotation	↑				Matheson et al., 1997
8-OH-DPAT	5-HT_{1A} receptor agonist	conditioned fear	↓				Saphier and Welch, 1995
		immobilization	=				Saphier and Welch, 1995
		conditioned fear				↓	Van de Kar, 1996
Gepirone	5-HT_{1A} receptor agonist	rotation	↑				Matheson et al., 1997
Methysergide	$5\text{-HT}_{1/2}$ receptor antagonist	head-up tilt	=		↓	↓	Matzen et al., 1993b; Matzen, 1995
NAN-190	5-HT_{1A} receptor antagonist	immobilization	=		=		Jorgensen et al., 2001
WAY-100635	5-HT_{1A} receptor antagonist	conditioned fear	=				Groenink et al., 1996a
		immobilization	↓		=		Jorgensen et al., 2001
LY-206130	5-HT_{1A} receptor antagonist	immobilization	=		↓		Jorgensen et al., 2001
Ketanserin	5-HT_2 receptor antagonist	head-up tilt	=		=	=	Matzen et al., 1993b; Matzen, 1995
		immobilization			↓		Jorgensen et al., 1992
		photic stimulus	↓				Feldman et al., 1998
		ether			↓		Jorgensen et al., 1992
LY53857	5-HT_2 receptor antagonist	immobilization			↓		Jorgensen et al., 1992
		conditioned fear				=	Lorens et al., 1986
		ether			↓		Jorgensen et al., 1992
ICS 205-930	5-HT_3 receptor antagonist	immobilization			↓		Jorgensen et al., 1992
		ether			↓		Jorgensen et al., 1992
Ondansetron	5-HT_3 receptor antagonist	head-up tilt	↓				Matzen et al., 1993b
		immobilization			↓		Jorgensen et al., 1992
		ether			↓		Jorgensen et al., 1992
Diisopropyl-fluorophosphate	Inhibitor of cholinesterase	conditioned fear			=	=	Van de Kar et al., 1985a
Morphine	Opiate receptor agonist	immobilization		=			Carter et al., 1986
Naloxone	Opiate receptor antagonist	conditioned fear		↑			Onaka and Yagi, 1990
		conditioned fear			=	=	Van de Kar et al., 1985a
		immobilization		↑	↓		Samson et al., 1985
Naltrexone	Opiate receptor antagonist	motion	↑		↓		Odio and Brodish, 1990
MR2266BS	κ receptor antagonist	immobilization		↑			Carter and Lightman, 1987
ICI 154129	δ receptor antagonist	immobilization		=			Carter and Lightman, 1987

Table 2 (*continued*)

Drug	Selectivity	Stressor	ACTH/ corticosterone	Oxytocin	Prolactin	Renin	References
s-α-Fluoromethyl-histidine	Inhibitor of histamine synthesis	immobilization	↓				Knigge et al., 1991
		immobilization			↓		Kjær et al., 1991
		ether	↓				Knigge et al., 1991
SKF-91488	Inhibitor of histamine-methyl-transferase	immobilization	↑				Knigge et al., 1991
		immobilization			↑		Kjær et al., 1991
Cimetidine	H_2 receptor antagonist	immobilization			↓		Knigge et al., 1991
		immobilization				↓	Matzen et al., 1990
		ether			↓		Knigge et al., 1991
Ranitidine	H_2 receptor antagonist	immobilization			↓		Knigge et al., 1991
		immobilization				↓	Matzen et al., 1990
		ether			↓		Knigge et al., 1991
		foot shock		=			Yagi, 1994
		novelty		=			Yagi, 1994
Fluoxetine	5-HT uptake inhibitor	conditioned fear	=	=		=	Zhang et al., 2000
		swim	=				Stout et al., 2002
Venlafaxine	5-HT/norepinephrine uptake inhibitor	random stress	↓				Stout et al., 2002
		immobilization	=				Stout et al., 2002
		swim	=				Stout et al., 2002
Desipramine	Norepinephrine uptake inhibitor	immobilization	=				Stone and Trullas, 1984
Reboxetine	Norepinephrine uptake inhibitor	swim	=				Stout et al., 2002
Tranylcypromine	MAO-A inhibitor	swim	=				Stout et al., 2002
Nefazodone	Antidepressant	rotation	=				Matheson et al., 1997
Midazolam	Benzodiazepine	conditioned fear	↓		↓	=	Van de Kar et al., 1985a
Alprazolam	Benzodiazepine	stressful interview	↓		=		Rohrer et al., 1994
Chlordiazepoxide	Benzodiazepine	conditioned fear	↓		↓	=	Van de Kar et al., 1985a
		conditioned fear	↓	↓			Yagi and Onaka, 1996b
		foot shock		↓			Yagi and Onaka, 1996a
		maternal separation and foot shock	↓				Maciag et al., 2002
		handling and footstock	=				Maciag et al., 2002
Diazepam	Benzodiazepine	stress-induced hyperthermia	=				Groenink et al., 1996b
		head-up tilt	↓				Matzen et al., 1993a
Muscimol	GABA agonist	air-jet stress	↓				Stotz-Potter et al., 1996
Prazosin	α_1 receptor antagonist	photic stimulus	↓				Feldman and Weidenfeld, 1996
		ether	↓				Szafarczyk et al., 1987
Propranolol	β-adrenoceptor antagonist	conditioned fear			=		Van de Kar et al., 1985a
		immobilization				↓	Golin et al., 1988
		head tilt up				↓	Golin et al., 1988
		ether	↓				Szafarczyk et al., 1987
Sotalol	β-adrenoceptor antagonist	conditioned fear	↓				Richardson Morton et al., 1990
		photic stimulus	=				Feldman and Weidenfeld, 1996
CI628	Estrogen receptor antagonist in intact rats	immobilization	↑				Young et al., 2001
Tamoxifen	Estrogen receptor antagonist in intact rats	immobilization	↑				Young et al., 2001
Estradiol	Estrogen receptor agonist in ovarioctemized rats	immobilization	↓				Young et al., 2001
Estradiol and progesterone	in ovarioctemized rats	immobilization	↓				Young et al., 2001

Explanation of symbols: the effects of different drugs on the hormone response to stressors are expressed as potentiation (↑), inhibition (↓) and no change (=).

et al., 1996; Rivest et al., 1995; Van Pett et al., 2000). Whereas CRF_2 expression is constitutive under these conditions (Rivest and Laflamme, 1995; Rivest et al., 1995), acute (2 h) and repeated (2 h daily for 14 days) immobilization stress significantly increases CRF_1 receptor mRNA in the hypothalamic paraventricular nucleus and decreases it in

the anterior pituitary, without affecting its levels in the basolateral nucleus of the amygdala (Makino et al., 1995). Other studies found that acute immobilization stress also produces an increase in CRF mRNA levels within the central nucleus of the amygdala, whereas chronic foot shock stress significantly increases CRF mRNA in both Barrington's nucleus (a pontine micturition center) and the hypothalamic paraventricular nucleus (Imaki et al., 1991a,b). Additionally, studies in sleep-deprived rats showed a marked increase in CRF levels in the striatum and limbic areas (olfactory tubercle, nucleus accumbens, septum), but the hypothalamic CRF content was reduced (Fadda and Fratta, 1997). Sleep deprivation stress was induced by keeping the rats for 72 h on a small platform (7 cm) surrounded by water (Fadda and Fratta, 1997).

3.3.4. CRF_1 and/or CRF_2 receptor knockout

In male mice lacking the CRF_1 receptor, the release of ACTH and corticosterone after forced swim stress is reduced compared with wild-type mice (Smith et al., 1998; Timpl et al., 1998). The histological analysis of the adrenal gland of the CRF_1 receptor knockout and wild-type mice did not reveal any apparent changes for the adrenal cortex, including the zona fasciculata (the major site of corticosterone production). Nevertheless, there was a 49% reduction in the diameter of the adrenal medulla in homozygous CRF_1 receptor-deficient mice, compared with the wild-type mice (Timpl et al., 1998). Primary cultures of pituitary cells collected from the CRF_1 knockout mice failed to display an increase in c-AMP accumulation and ACTH secretion upon CRF treatment, verifying that the mutation caused a loss of CRF_1 receptor function (Smith et al., 1998).

Less agreement exists regarding the role of CRF_2 receptors in knockout mice. One group of investigators did not find differences between CRF_2 knockout mice and the wild-type control mice (Kishimoto et al., 2000), probably because they analyzed hypothalamic–pituitary–adrenocortical activity at a single time point. On the other hand, other CRF_2 knockout mouse lines showed augmentation of plasma ACTH and corticosterone levels in response to restraint stress (Bale et al., 2000; Coste et al., 2000). Ten minutes after the onset of stress, corticosterone levels continued to rise in the CRF_2 mutant mice reaching higher levels than in the wild type (Bale et al., 2000; Coste et al., 2000). At 90 min after onset of stress, corticosterone levels were still higher in the CRF_2 receptor knockout mice than in the wild-type mice. Apparently, CRF_2 receptors are involved in recovery from stress.

CRF_2 receptor-deficient mice have been reported to be hypersensitive to restraint stress (Bale et al., 2000). When the CRF_2 knockout mice were submitted to a time-course restraint-stress experiment, ACTH and corticosterone levels were higher following 2 min of restraint as compared to the wild type (Bale et al., 2000). Basal ACTH and corticosterone levels were normal for both wild-type and CRF_2 receptor-deficient mice (Bale et al., 2000).

Studies on the hypothalamic–pituitary–adrenocortical axis of double knockout mice lacking both CRF_1 and CRF_2 receptors confirm the data obtained with the single-gene knockout mice (Preil et al., 2001). The CRF_1 receptor knockout has a dominating influence, presumably because of its key position on the anterior pituitary corticotrophs. The neuroendocrine phenotype of mice lacking both CRF_1 and CRF_2 receptors is dominated by the functional loss of CRF_1 receptors, and the CRF_2 receptor does not compensate for the deficiency of CRF_1 receptors (Preil et al., 2001). Currently, there is no information on the role of CRF_3 receptors in the stress response. However, the failure to activate the hypothalamic–pituitary–adrenocortical axis after CRF administration in CRF_1/CRF_2 knockout mice (Preil et al., 2001) suggests that CRF_3 receptors are not likely to be involved in the stress-induced increase in ACTH release, at least via direct effects on pituitary corticotrophs or adrenocortical cells.

In summary, one needs to keep in mind that, because of developmental compensation, a knockout mouse is not equivalent to an experiment using an antagonist. Nevertheless, there seems to be a dual organization of CRF receptors in the stress-induced activation of the hypothalamic–pituitary–adrenal axis. CRF_1 receptors play a critical role initiating the acute phase of the stress-induced hypothalamic–pituitary–adrenocortical response. CRF_2 receptors apparently are involved in the recovery phase of this response. Additionally, the studies in transgenic mice open the possibility that deletion of either CRF receptor may have a compensatory increase in the expression of CRF, vasopressin and urocortin.

3.4. Extra-hypothalamic CRF functions

In addition to its neuroendocrine function, CRF may act as a neurotransmitter or neuromodulator in extra-hypothalamic circuits to integrate brain multi-system responses to stress (Preil et al., 2001). Some of the areas involved in this extra-hypothalamic CRF regulation include cortex, amygdala, bed nucleus of the stria terminalis, nucleus accumbens, dorsal raphe nucleus, hippocampus and locus coeruleus (Curtis and Valentino, 1994; Curtis et al., 1995, 1999).

3.5. CRF receptors in anxiety and depression

3.5.1. Anxiety

Severe anxiety and depression are stress-related disorders and may be neuro-adaptive changes that result from an exacerbated stimulation of one or more of the CRF-regulated pathways. This section will summarize some of the evidence supporting a role for CRF receptors in anxiety and depression.

3.5.2. CRF_1 receptor in anxiety

The anxiety-like behavioral effects of CRF involve the activation CRF_1 receptors (Dautzenberg and Hauger, 2002).

CRF_1 receptor knockout mice show reduced anxiety-related behavior in the elevated plus maze test and in the light–dark box test (Smith et al., 1998; Timpl et al., 1998). Inhibition of CRF_1 expression, by central administration of CRF_1 antisense oligodeoxynucleotides, produces anxiolytic-like effects in different tests, including elevated plus maze, open field and the defensive withdrawal tests (Heinrichs et al., 1997; Liebsch et al., 1995, 1999; Skutella et al., 1998). Also, treatment with non-peptide antagonists that selectively block CRF_1 receptors (NBI27914, CRA1000, CRA1001, CP-145,526, R-121919, antalarmin, DMP904 and DMP696) promotes anxiolytic-like responses in the elevated plus maze test, the light–dark box test, the mouse defense test battery and the fear-potentiated startle test (Deak et al., 1999; Lundkvist et al., 1996; Okuyama et al., 1999b; Schulz et al., 1996; Smagin and Dunn, 2000). CRF has a higher affinity for CRF_1 than for CRF_2 receptors. Transgenic mice overexpressing CRF show increased anxiety-related behavior suggesting a more important role for CRF_1 than CRF_2 in anxiety (Stenzel-Poore et al., 1994).

3.5.3. CRF_2 receptors in anxiety

The role of CRF_2 receptors in anxiety is less clear than that of CRF_1 receptors. In two lines of CRF_2 receptor-deficient mice, an increase in anxiety-related behavior was observed (Bale et al., 2000; Kishimoto et al., 2000). However, other investigators did not find any change in behavior of these mice compared with controls (Coste et al., 2000). Studies using central administration of CRF_2 antisense oligonucleotides reported no effect on anxiety-like behavior of rats in the elevated plus maze test and in the defensive withdrawal tests (Heinrichs et al., 1997; Liebsch et al., 1999).

Experiments using antisauvagine-30, a CRF_2 receptor antagonist, reported blockade of the effects of immobilization stress on anxiety-like behavior in the elevated plus maze test (Radulovic et al., 1999). Other investigators found that this peptide increases anxiety-like behavior (Kishimoto et al., 2000). Recent studies conducted in rats showed that antisauvagine-30 infused into the lateral cerebral ventricles produces a significant dose-dependent reduction in conditioned freezing, an increase in the number of entries and time spent in the open arms of the elevated plus maze, and it also facilitated the exploratory activity in a large illuminated open field (Takahashi et al., 2001). If one accepts the notion that the effects of antisauvagine-30 are primarily mediated by antagonism of CRF_2 receptors, then the data would suggest an anxiolytic-like behavioral effect, without effects on locomotor activity. According to Reul and Holsboer (2002), "the picture is emerging that activation of CRF_2 receptors can result in anxiolysis or anxiogenesis depending on when the animal is tested, and possibly, where the receptor is localized."

3.5.4. Depression

High concentrations of CRF were observed in postmortem samples of cerebrospinal fluid obtained from severely depressed suicide victims, suggesting that chronic hypersecretion of CRF plays a leading role in the etiology of major depression (Arborelius et al., 1999). Additionally, a clinical trial indicated that the non-peptidergic CRF_1 receptor antagonist R-219919 has antidepressant properties in patients with major depression (Zobel et al., 2000). On the other hand, there is contradictory evidence regarding the expression of CRF_1 receptors in the brain of depressed patients. Whereas some authors found a decreased expression in postmortem brains of suicide victims (Nemeroff, 1988) others did not find any difference (Hucks et al., 1997). Also, the levels of mRNA encoding CRF_1 and CRF_2 receptors in the anterior pituitary obtained from depressed suicide victims was similar to the mRNA levels in control patients (Hiroi et al., 2001).

3.6. Clinical studies and CRF

Strong evidence supports a role for CRF in depression (Arborelius et al., 1999). Although an alteration of the hypothalamic–pituitary–adrenocortical axis was described in patients with panic disorders, there was no difference in levels of CRF in the cerebrospinal fluid between these patients and healthy patients (Fossey et al., 1996; Jolkkonen et al., 1993; Roy-Byrne et al., 1986). However, the concentration of CRF in the cerebrospinal fluid is higher in other anxiety disorders, related to post-traumatic stress disorder, drug withdrawal, obsessive compulsive disorders and Tourette's syndrome (a syndrome associated with increased vulnerability to stress and anxiety) (Altemus et al., 1992, 1994; Arborelius et al., 1999; Bremner et al., 1997; Chappell et al., 1996; Smith et al., 1989).

Many, though not all, depressed patients exhibit hyperactivity of the hypothalamic–pituitary–adrenocortical axis (Arborelius et al., 1999; Plotsky et al., 1998; Sherman and Pfohl, 1985). This hyperactivity is expressed in higher CRF levels in the cerebrospinal fluid of drug-free patients with major depression and from suicide victims compared with patients with other psychiatric disorders and healthy controls (Arato et al., 1989; Banki et al., 1992; Hernandez et al., 1984; Widerlov et al., 1988). However, some studies reported no differences in CRF levels in the cerebrospinal fluid between healthy subjects and depressed patients (Geracioti et al., 1997; Kling et al., 1991, 1994; Pitts et al., 1995). Postmortem studies in depressed patients reveal an increased expression of CRF mRNA and CRF levels in the hypothalamic paraventricular nucleus (Raadsheer et al., 1994, 1995). Additionally, many patients with major depressive disorder have higher plasma cortisol concentrations (Arborelius et al., 1999). Interestingly, depressed patients showed a blunted ACTH response after intravenous administration of CRF, which may be explained by a desensitization of pituitary CRF receptors in these patients (presumably secondary to increased hypothalamic CRF release) (Arborelius et al., 1999; Holsboer et al., 1986; Krishnan et al., 1993). After clinical recovery, patients showed no difference

in ACTH levels after CRF injection with healthy controls (Amsterdam et al., 1988). Also, depressed patients with higher plasma cortisol concentrations are less sensitive to the inhibitory effect of dexamethasone in lowering plasma ACTH and cortisol in comparison with healthy patients. These observations suggest a dysfunction of the hypothalamic–pituitary–adrenocortical axis. This blunted response was not found after clinical recovery of the depressed patients (Arborelius et al., 1999).

3.7. Vasopressin

Vasopressin is a nine-amino-acid neuropeptide that is synthesized in different hypothalamic nuclei, including the supraoptic nucleus, paraventricular nucleus and suprachiasmatic nucleus (Dorsa et al., 1988; Miller et al., 1988; Swanson et al., 1983; Swanson and Sawchenko, 1983; Van Leeuwen et al., 1978). Vasopressin is produced from a precursor (prepro-vasopressin) which consists of arginine vasopressin, neurophysin II and a glycoprotein (Brownstein, 1983; Schmale et al., 1983). Prepro-vasopressin is processed in secretory vesicles during axonal transport from the hypothalamus to the posterior pituitary (Brownstein, 1980; Brownstein et al., 1980). Magnocellular neurons located in the hypothalamic paraventricular and supraoptic nuclei project to the neural lobe of the pituitary (posterior lobe), where vasopressin is released directly into the systemic circulation. Stimuli that can induce vasopressin release include hyper-osmotic or hypovolemic stimuli (Majzoub et al., 1983, 1984, 1987; Morris and Alexander, 1989). On the other hand, vasopressin synthesized in parvicellular neurons of the hypothalamic paraventricular nucleus that also express CRF is a regulator of the hypothalamic–pituitary–adrenocortical axis (Mouri et al., 1993; Sawchenko et al., 1984; Whitnall and Gainer, 1985; Whitnall et al., 1985a,b,c). Vasopressin is secreted into the median eminence and is transported via the superior hypophysial artery to the anterior lobe of the pituitary. In the anterior pituitary, vasopressin potentiates the effect of CRF on ACTH release (Swanson and Sawchenko, 1983; Swanson et al., 1983).

The biological effects of vasopressin are mediated by activation of V_{1a} and V_{1b} (also called V_3) receptors that activate phospholipases via $G_{q/11}$ proteins, and V_2 receptor that activate adenylyl cyclase by interacting with G_s proteins (Birnbaumer, 1999, 2000). In Chinese hamster ovary (CHO) cells transfected with the human V_{1b} receptor, other intracellular pathways, such as increased production of c-AMP, have been described (Thibonnier et al., 1997, 1998a,b). The V_2 receptor is mostly found in the kidney where it mediates the antidiuretic effect of vasopressin (Nagasaki et al., 1995, 2002). The V_{1a} receptors are ubiquitously located in brain, platelets, blood vessels, liver, adrenal gland and uterus (Lolait et al., 1995a,b; Rabadan-Diehl et al., 1995; Thibonnier et al., 1998a,b). V_{1b} receptor immunoreactivity has been described in the pituitary gland, hypothalamus, amygdala, cerebellum and in areas close to the circumventricular organs devoid of a blood–brain barrier (Hernando et al., 2001). The V_{1b} receptor is mainly involved in the stimulating effect of vasopressin on ACTH secretion in the pituitary (De Keyzer et al., 1994; Hernando et al., 2001).

Vasopressin is a weak ACTH secretagogue, but it acts synergistically with CRF in the stimulation of ACTH secretion (Antoni, 1984a,b, 1993; Antoni et al., 1984; Dickstein et al., 1996; Gaillard et al., 1984; Gillies et al., 1980; Plotsky, 1991; Rivier and Vale, 1983; Serradeil-Le Gal, 2001, 2002; Whitnall, 1993). Vasopressin seems to be critically involved in a variety of brain functions, such as the generation of emotions, learning and memory (Ebner et al., 2000).

Studies in genetically vasopressin-deficient Brattleboro rats provided substantial and initial evidence for the role of vasopressin in stress. The ACTH response to several stimuli is impaired in Brattleboro rats (Arimura et al., 1967; Conte-Devolx et al., 1982; Kjaer et al., 1993; McCann et al., 1966; Wiley et al., 1974; Yates et al., 1971). The impaired ACTH response in the Brattleboro rats is believed to be due to by their vasopressin deficiency, because the hypothalamic levels of CRF in these rats are similar to those in control rats (Kjaer et al., 1993).

The parvicellular vasopressin neurons play a major role during the stress response (Aguilera and Rabadan-Diehl, 2000a,b). Chronic stress increases the expression of vasopressin in parvicellular neurons of the hypothalamic paraventricular nucleus and its secretion into the pituitary portal circulation, stimulating the hypothalamic–pituitary–adrenocortical axis (Van de Kar and Blair, 1999). Also, stress regulates pituitary V_{1b} receptors, increasing the ACTH-releasing activity of vasopressin (Rabadan-Diehl et al., 1995). In anti-vasopressin-immunized rams, there is a reduced ACTH and cortisol response to insulin stress, restraint stress and CRF injection (Watabe et al., 1987a,b, 1988). Also, an i.p. injection of a vasopressin antiserum reduces the ACTH responses to restraint stress (Linton et al., 1985). SSR149515, a selective non-peptide V_{1b} receptor antagonist inhibits the effects of restraint-stress on ACTH release in rats, and displays anxiolytic-like activity in the four-plate test, a mouse model of anxiety. This was observed both after acute and after 7 days of repeated administrations of SSR149515 (Serradeil-Le Gal et al., 2002).

Studies with transgenic mice support the role of vasopressin in the behavioral stress response. A knockout mouse deficient in the V_{1b} receptor displays behavioral alterations such as reduced aggression and social memory that could be attributed to the absence of the V_{1b} receptors (Aguilera and Rabadan-Diehl, 2000a; Aguilera et al., 2001; Hernando et al., 2001; Rabadan-Diehl et al., 1995). On the other hand, CRF_1 receptor-deficient mice presented higher basal plasma vasopressin levels than controls and increased expression of vasopressin mRNA in the hypothalamic paraventricular nucleus, with a marked immunoreactivity in both the zona interna and the zona externa of the median eminence (Muller et al., 2000). Administration of both a V_1 receptor antagonist and corticosterone decreased the basal levels of

ACTH in CRF_1 receptor-deficient mice (Muller et al., 2000). These authors also reported that, in homozygous CRF_1 receptor-deficient-mice, plasma vasopressin (from hypothalamic magnocellular origin) fell to levels indistinguishable from those in heterozygous mutants or wild-type mice, after forced swim or social defeat stress (Muller et al., 2000).

Finally, it has been suggested that CRF and vasopressin mobilize different pools of pituitary ACTH in the stress response (Hauger and Dautzenberg, 2000). In this way, vasopressin could override the glucocorticoid feedback inhibition of ACTH release, maintaining the responsiveness of corticotrophs to novel stressors, following repeated activation of the hypothalamic–pituitary–adrenocortical axis.

3.8. Serotonin

Serotonin (5-hydroxytryptamine or 5-HT) is a monoamine widely distributed in the brain and involved in mood and impulse control (Fink et al., 1998; Young et al., 1996). Dysfunction of serotonergic neurotransmission has been associated with several mood disorders, including depression, anxiety, panic disorder, obsessive–compulsive disorder and eating disorders (Graeff et al., 1997; Levy and Van de Kar, 1992; Mora et al., 1997). Additionally, serotonergic neurons have a major influence on the regulation of neuroendocrine function. The serotonergic cell bodies are located either in the dorsal or median raphe nuclei, but some are located in the ventrolateral region of the midbrain that is also known as the B9 cell group (Dahlstrom and Fuxe, 1965). Serotonergic neurons located in the midbrain raphe innervate the hypothalamus. Many of these neurons also send collaterals to the amygdala (Petrov et al., 1994b) and possibly to other limbic forebrain regions. Thus, changes in the serotonergic input to several limbic forebrain regions can be reflected in changes in the serotonergic input into the hypothalamus.

Seven families of serotonin receptors have been cloned ($5\text{-}HT_{1-7}$) (Hoyer et al., 1994). Except for $5\text{-}HT_3$ receptors, which are ligand-gated ion channels, all other serotonin receptors are seven transmembrane peptides coupled to G proteins. Members of the $5\text{-}HT_1$ receptor family ($5\text{-}HT_{1A}$, $5\text{-}HT_{1B}$, $5\text{-}HT_{1D}$, $5\text{-}HT_{1E}$, $5\text{-}HT_{1F}$) are mainly coupled to $G_{i/o/z}$ proteins, members of the $5\text{-}HT_2$ family ($5\text{-}HT_{2A}$, $5\text{-}HT_{2B}$, $5\text{-}HT_{2C}$) are coupled to $G_{q/11}$ proteins and all other receptor families are coupled to G_s proteins (Albert and Tiberi, 2001; Hoyer et al., 2002). In the serotonergic synapse, the serotonin receptors are found in pre-synaptic nerve terminals, also called autoreceptors ($5\text{-}HT_{1B/1D}$), and in postsynaptic neurons (most if not all other receptor families, including $5\text{-}HT_{1B/1D}$ receptors). Additionally, the soma and dendrites of serotonergic neurons contain $5\text{-}HT_{1A}$ receptors that function as negative feedback autoreceptors.

$5\text{-}HT_{1A}$ and $5\text{-}HT_{2A}$ receptors have received a great deal of attention in recent years because of their presumed role in mood disorders (Blier, 2001; Du et al., 2000; Massou et al., 1997; Olivier et al., 1999; Sargent et al., 2000; Shapira et al., 2000; Zanardi et al., 2001). The neurons in the hypothalamic paraventricular nucleus express both $5\text{-}HT_{1A}$ and $5\text{-}HT_{2A}$ receptors (Appel et al., 1990; Gundlah et al., 1999; Wright et al., 1995; Zhang et al., 2001). Whereas $5\text{-}HT_{1A}$ receptor are associated with the inhibition of adenylyl cyclase activity and the decrease of cyclic AMP, $5\text{-}HT_{2A}$ receptors are coupled to the activation of phospholipase C and production of inositol trisphosphate and diacylglycerol through $G_{q/11}$ proteins (Hoyer et al., 1994).

Evidence supporting a role for serotonin in stress was obtained in microdialysis studies examining changes in extracellular levels of serotonin in different brain areas, including hypothalamus, amygdala, frontal cortex and raphe nuclei, after exposure to several stressors (Adell et al., 1997; Amat et al., 1998; Fujino et al., 2002; Funada and Hara, 2001; Hashimoto et al., 1999; Kawahara et al., 1993; Maswood et al., 1998; Shimizu et al., 1992). Insulin injection in fasted rats, exercise and immobilization produce an increase in brain tryptophan availability and serotonin levels in the hypothalamus (Chaouloff, 1993; Gordon and Meldrum, 1970). Also, sound stress raises tryptophan hydroxylase activity through glucocorticoid receptors, an effect prevented by adrenalectomy (Singh et al., 1990). Although foot shock also has been associated with rises in serotonin synthesis/metabolism (Dunn, 1998, 2000; Saphier and Welch, 1995), this increase could be an adaptive response to counterbalance neuronal depletion of serotonin during stress (Chaouloff et al., 1999). Also, immobilization or restraint stress has been associated with increased synthesis/metabolism of serotonin in some limbic regions (Dunn, 2000; Shimizu et al., 1989).

Administration of $5\text{-}HT_{2A/2C}$ receptor agonists to rats produces an increase in all the hormones that can be classified as stress hormones, including ACTH, corticosterone, oxytocin, prolactin and renin (Bagdy, 1996; Levy et al., 1994; Rittenhouse et al., 1994; Van de Kar et al., 2001). The effects of one of these drugs, DOI [(±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane-HCl] are blocked by pretreatment with a $5\text{-}HT_{2A}$ receptor antagonist MDL 100,907 [(±)-α-(2,3 dimethoxyphenyl)-1-(2-fluorophenyl)-4-piperidinemethanol] indicating that $5\text{-}HT_{2A}$ receptors are the predominant receptor mediating these neuroendocrine responses (Van de Kar et al., 2001). Additionally, exposure of rats to stress and administration of DOI increase the expression of the immediate early gene c-fos in the CRF and oxytocin neurons of the hypothalamic paraventricular nucleus and also in neurons in the central amygdala (Campeau and Watson, 1997; Senba and Ueyama, 1997; Van de Kar et al., 2001; Viau and Sawchenko, 2002). Injection of the $5\text{-}HT_2$ receptor antagonist ketanserin into the amygdala inhibits the effect of photic stress on ACTH release (Feldman et al., 1998). Thus, it is tempting to speculate that some of the effects of stressors are mediated via serotonergic mechanisms.

We have previously reported that 5-HT_{1A} receptors stimulate the release of ACTH, oxytocin and corticosterone (Serres et al., 2000; Van de Kar, 1997). This effect is mediated by G_z protein, a pertussis toxin-insensitive protein in the hypothalamic paraventricular nucleus (Serres et al., 2000). In this brain region, autoradiographic studies indicate a substantial density of [^{3}H]8-OH-DPAT [(±)-8-hydroxy-2(di-*n*-propylamino)tetralin hydrobromide]-labeled 5-HT_{1A} receptors in the medial parvicellular divisions (containing CRF neurons) and the ventrolateral magnocellular divisions (containing oxytocin neurons) (Li et al., 1997). The mRNA coding for 5-HT_{1A} receptors has also been detected in the paraventricular nucleus (Wright et al., 1995).

In addition to the role of 5-HT_{1A} and 5-HT_{2A} receptors in the release of stress hormones, acute stress either increases or decreases hippocampal and/or cortical 5-HT_{1A} receptor binding in a stressor and subregion-dependent manner (Raghupathi and Mcgonigle, 1997). Also, the sensitivity of 5-HT_{1A} autoreceptors (but not its B_{max}) was decreased by sustained exposure of rats to a novel environment (Laaris et al., 1997). Desensitization of 5-HT_{1A} receptors has been associated with the therapeutic effects of selective serotonin uptake inhibitors (SSRIs) and anxiolytic 5-HT_{1A} receptor agonists (such as buspirone) (Berlin et al., 1998; Bosker et al., 2001; Cowen, 1998; Hensler and Durgam, 2001; Hensler, 2002; Lerer et al., 1999; Lesch, 1991; Li et al., 1996a; Raap et al., 1999a,b; Sim-Selley et al., 2000).

Selective serotonin uptake inhibitors are among the most prescribed medications to treat anxiety disorders. Acute administration of selective serotonin uptake inhibitors reduces both the acquisition and the expression of freezing behavior in rats during exposure to conditioned stress (Hashimoto et al., 1996). However, the relevance of this information to treatment of anxiety is questionable since acute administration of selective serotonin uptake inhibitors to patients does not improve but can actually exacerbate anxiety (Belzung et al., 2001; Nierenberg et al., 2000). Chronic treatment with fluoxetine (Prozac®), a typical selective serotonin uptake inhibitor drug, abolishes the anxiogenic effect of CRF in the social interaction test in rats, while acute fluoxetine produces an anxiogenic effect (To et al., 1999; To and Bagdy, 1999). Our studies reveal that chronic fluoxetine (daily for 14 days) reversed the stress-induced defecation and suppression of exploring behavior and shortened the duration of stress-induced freezing behavior (Zhang et al., 2000). However, the stress-induced increase in plasma levels of ACTH, corticosterone, oxytocin, prolactin and renin was not inhibited by fluoxetine treatment (Zhang et al., 2000). These findings suggest that neuro-adaptive changes induced by sustained inhibition of serotonin reuptake contribute to the mechanism of the anxiolytic effects of fluoxetine. In contrast, the neuroendocrine responses to conditioned stress are not affected by these neuro-adaptive changes, likely due to the importance of these hormones for survival and the multiplicity of neurotransmitters mediating the effects of stressors on hormone secretion.

Serotonergic neurons also interact with CRF neurons. CRF, urocortin, CRF_1 and CRF_2 receptors and CRF-binding protein have been described in raphe nuclei (Chalmers et al., 1995; Cummings et al., 1983; Kirby et al., 2000; Kozicz et al., 1998; Palkovits et al., 1985; Potter et al., 1992; Swanson et al., 1983; Van Pett et al., 2000). Injection of low doses of CRF into the dorsal raphe nucleus predominantly inhibits the firing rate of serotonergic neurons resulting in reduced extracellular levels of serotonin in the rat striatum (Price et al., 1998; Price and Lucki, 2001). A CRF receptor antagonist reverses this effect (Price et al., 1998; Price and Lucki, 2001). Intracerebroventricular injection of higher doses of CRF (3 μg) increases extracellular striatal levels of serotonin (Kirby et al., 2000). Interestingly, CRF_1 receptor knockout mice show a decreased corticosterone response to stress, but enhanced hippocampal serotonergic neurotransmission, as determined by an increase in the release of serotonin in the hippocampus using microdialysis (Penalva et al., 2002). In these experiments, enhanced 5-hydroxyindolacetic acid (the main metabolite of serotonin) was observed using in vivo microdialysis in hippocampus of CRF_1 receptor knockout mice under basal (home cage) and stress (forced swimming) conditions (Penalva et al., 2002). These observations suggest an increased release of serotonin in the hippocampus of CRF_1 knockout mice. Also, microdialysis experiments revealed an inhibitory regulation of extracellular serotonin levels by CRF (Price and Lucki, 2001). The intracerebroventricular injection of CRF (0.3–1.0 μg) decreased extracellular serotonin in the lateral septum, but this effect disappeared when higher CRF concentrations (3.0 μg) were used (Price and Lucki, 2001). These investigators also found that the direct administration of CRF (30 ng) into the dorsal raphe nucleus reduced extracellular serotonin levels in the lateral septum and in the striatum. This effect was inhibited by the previous injection of a CRF_1 receptor antagonist (D-PheCRF-(12–41), 10 ng) (Price and Lucki, 2001). These results agree with previous results of these authors showing that the pretreatment with D-PheCRF-(12–41) in rats submitted to swim stress prevented the reduction of extracellular serotonin in the lateral septum (Price et al., 1998).

In summary, serotonin plays a key role in the stress response. Most of the evidence suggests that depletion of brain serotonin increases anxiety in humans. Conversely, drugs that increase the levels of serotonin, such as selective serotonin uptake inhibitors, have anxiolytic effects, particularly in patients suffering from generalized anxiety and panic disorders (Leonard, 1993; Van Ameringen et al., 1996; Van Megen et al., 1997a,b). Besides its importance in the secretion of stress hormones (ACTH, corticosterone, oxytocin, prolactin and renin) and the co-localization of its receptors in neuroendocrine brain regions, the regulation, by CRF, of serotonergic signaling may be an important mechanism mediating the serotonergic dysfunction reported in several neuro-psychiatric disorders, such as anxiety, depression and stress-related drug withdrawal (Parsons et al., 1995a,b, 1996; Sarnyai et al., 1995; Weiss et al., 1996).

3.9. Norepinephrine

Norepinephrine (also called noradrenaline) is a broadly distributed catecholamine in brain. Other catecholamines that function as neurotransmitters are dopamine, the precursor of norepinephrine and epinephrine, one of its metabolites (Dishman, 1997; Gottfries, 1980; Mongeau et al., 1997; Robinson, 1975; Shih et al., 1999). The noradrenergic locus coeruleus gives rise to divergent efferent pathways that provide the major source of norepinephrine to the forebrain (Curtis and Valentino, 1994; Curtis et al., 1997a; Sawchenko and Swanson, 1982). The hypothalamus as a major integrative center of the neuroendocrine response also receives innervation of norepinephrine-containing neurons (Habib et al., 2001). Noradrenergic neurons that innervate the hypothalamic paraventricular nucleus have their origin in the caudal nucleus of the solitary tract (A2 cell group) in the dorsolateral medulla, with some contributions from the medullary A1 cell group and the locus coeruleus (Cunningham and Sawchenko, 1988; Habib et al., 2001; Palkovits et al., 1999; Palkovits, 1999). The pharmacological classification of noradrenergic receptors includes alpha (α_1 and α_2) and beta (β1, β2 and β3) receptors.

A general activation of the norepinephrine neurons has been described in response to different stressors (sound, restraint, hypoglycemia, swimming) in rats and cats (Abercrombie and Jacobs, 1987a,b, 1988; Cassens et al., 1980, 1981; Curtis et al., 1997b; Morilak et al., 1987). Foot shock stress produces an immediate increase in brain levels of 3-methoxy-4-hydroxyphenylglycol sulfate (MHPG-SO4), a major metabolite of norepinephrine in rat brain (Cassens et al., 1981). An enhanced turnover in norepinephrine metabolism was also described during exposure to stress in rats (Korf et al., 1973). Also, in vivo microdialysis revealed the release of endogenous norepinephrine in the hippocampus of rats submitted to restraint and intermittent tail shock stress (Abercrombie and Jacobs, 1988). Tyrosine hydroxylase activity, the rate-limiting enzyme in norepinephrine synthesis, is increased in response to a repeated intermittent stress paradigm involving foot shock and noise stress (Melia and Duman, 1991). Interestingly, this increase was inhibited by the CRF antagonist alpha-helical CRF (Melia and Duman, 1991). Apparently, the effect of stressors on noradrenergic activity appears to be sensitized by the previous exposure of the subject to different stressors (Cassens et al., 1980, 1981). Cassens et al. (1980) reported that 24 h after foot shock stress (a stressor that stimulates norepinephrine metabolism), an increase in the metabolism of norepinephrine could be elicited by previously neutral environmental stimuli that had been paired with the stress (Cassens et al., 1980). Similar results were obtained when the release and synthesis of norepinephrine in hippocampus were measured in naive and chronically cold-stressed rats, in response to acute tail shock stress (Nisenbaum and Abercrombie, 1993). Using in vivo microdialysis, it was determined that the basal extracellular concentrations of norepinephrine and 3,4-dihydroxyphenylacetic acid (DOPAC, an index of norepinephrine synthesis) in hippocampus were similar in the two groups; however, 30 min of intermittent tail shock produced a greater elevation of extracellular norepinephrine and 3,4-dihydroxyphenylacetic acid in the chronically cold-stressed rats than in the native controls (Nisenbaum et al., 1991; Nisenbaum and Abercrombie, 1993).

Reciprocal neural connections exist between CRF neurons in the hypothalamic paraventricular nucleus and noradrenergic neurons in the locus coeruleus (Habib et al., 2001). Synaptic contacts were observed between CRF-immunoreactive terminals and locus coeruleus dendrites (Curtis et al., 1997a; Van Bockstaele et al., 1998, 1999, 2001). Both α and β adrenergic receptors regulate the secretion of ACTH. A peripheral injection of β receptor agonists stimulates the secretion of ACTH, β-endorphin and pro-opiomelanocortin (al Damluji, 1988; Hary et al., 1984; Whitnall, 1993). Infusion of α adrenergic antagonists inhibits stress-induced ACTH release (Szafarczyk et al., 1987). On the other hand, there is substantial evidence for the regulation of noradrenergic activity by CRF (Curtis et al., 1997a, 1999; Smagin et al., 1999). In halothane-anesthetized rats, intracerebroventricular administration of CRF produces a dose-dependent increase in spontaneous discharge (Valentino and Foote, 1987). Ala_{14}CRF (3 μg), an inactive analogue of CRF, had no effect on locus coeruleus spontaneous discharge rates (Valentino and Foote, 1987; Valentino, 1988). Recently, these authors also reported that intra-locus coeruleus microinfusion of CRF (3–100 ng) increases the neuronal discharge rate in the locus coeruleus (from 28% to 105%, over control values) and increases norepinephrine levels in the frontal cortex in a dose-dependent manner (Curtis et al., 1997a). Microinfusion of a CRF antagonist attenuated, but did not block, the activation of the locus coeruleus (Curtis et al., 1997a). Similar results were reported by others authors (Smagin et al., 1995). Similarly, CRF injection into one side of the locus coeruleus and a contralateral infusion of artificial cerebrospinal fluid into the other side increased norepinephrine levels only in the ipsilateral prefrontal cortex (Asbach et al., 2001).

In summary, brain norepinephrine is a major alarm system that leads to a decrease in neurovegetative functions, such as eating and sleeping (Habib et al., 2001). Most of the evidence, but not all, suggests that CRF acts as a neurotransmitter in the locus coeruleus-mediating noradrenergic activation by different stressors. Interestingly, recent reports add new pieces to this unresolved puzzle, suggesting that endogenous opioids may act as antagonists of the action of CRF in the locus coeruleus, serving to counterbalance the excitatory effects of CRF on the locus coeruleus–norepinephrine system and thereby limiting its activation by stress (Curtis et al., 2001; Valentino and Foote, 1987; Valentino, 1988; Valentino et al., 1993, 1998, 2001; Van Bockstaele, 2000).

3.10. Vasoactive intestinal polypeptide

Vasoactive intestinal polypeptide (VIP) is a 28-amino-acid peptide closely related to other members of the secretin–glucagon family, such as secretin, peptide histidine isoleucine, growth hormone-releasing peptide and gastric inhibitory factor (Malendowicz and Nussdorfer, 1993; Nussdorfer et al., 2000; Strand, 1999a). VIP is also structurally related to PACAP (pituitary adenylyl cyclase-activating peptide) 38 and 27, two bioactive forms of the VIP/secretin/glucagon family (Kozicz et al., 1997). The NH_2-terminal portion of PACAP shows 68% structural homology with VIP (Kozicz et al., 1997; Strand, 1999a).

Receptors for VIP and the two alternatively processed forms of the PACAP precursor (PACAP-27 and PACAP-38) include three G-protein-coupled receptors: the PAC_1 or PACAP receptor, which displays higher affinity for PACAP-27 and PACAP-38 than for VIP (Hashimoto et al., 1993; Strand, 1999a); the VIP_1 or $VPAC_1$ receptor (Ishihara et al., 1992); VIP_2 or $VPAC_2$ receptor (Lutz et al., 1993).VIP_1 and VIP_2 receptors do not display marked selectivity for any of these ligands (Dickinson et al., 1999). These receptors are coupled to adenylyl cyclase and in some cases to phospholipase C signaling (Hezareh et al., 1996a,b; Lutz et al., 1996; MacKenzie et al., 1996).

VIP is widely distributed in all the components of the hypothalamic–pituitary–adrenocortical axis and the limbic system. The highest concentration of VIP in the hypothalamus is in the suprachiasmatic nucleus (Mezey and Kiss, 1985). Also, VIP is co-localized with CRF in the parvicellular region of the hypothalamic paraventricular nucleus (Ceccatelli et al., 1989, 1991b). Nevertheless, there is some controversy regarding the detection of VIP in the parvicellular region of the hypothalamic paraventricular nucleus, because it has only been detected by in situ hybridization 7 days after adrenalectomy (Watanobe, 1990), and only in reserpine- and colchicine-treated rats (Ceccatelli et al., 1991a). Also, in hypothalamic magnocellular neurons, expression of VIP is induced after hypophysectomy (Ceccatelli et al., 1991a,b). Additionally, VIP has been found in the pituitary (Arnaout et al., 1986; Hagen et al., 1986; Maas et al., 1991; Morel et al., 1982), in the zona medularis and glomerulosa of the adrenal gland (Cunningham and Holzwarth, 1988, 1989; Holzwarth et al., 1987; Kondo, 1985; Kondo et al., 1986; Murase et al., 1993) and in the frog chromaffin cells of the adrenal gland (Leboulenger et al., 1983, 1984). VIP immunoreactivity has been described in the lateral nucleus of the amygdala, but the highest VIP concentration was found in the central nucleus of the amygdala (Roberts et al., 1982).

A role for VIP in the stress response was initially proposed by the observation that VIP increases the release of ACTH from cell lines of a tumor of the mouse anterior pituitary and human from pituitary adenoma (Nicosia et al., 1983; Oliva et al., 1982, 1984; Reisine, 1984; Rotsztejn et al., 1980; Westendorf and Schonbrunn, 1985). VIP also potentiates the CRF-induced release of ACTH from superfused rat anterior pituitary fragments (Leonard et al., 1988) and acts synergistically with CRF to stimulate secretion of ACTH from normal pituitary cells (Leonard et al., 1988). However, in normal corticotrophs, VIP alone does not stimulate the release of ACTH (Leonard et al., 1988). In vivo experiments reported that 30 min of intravenous VIP infusion raises (10-fold) plasma ACTH levels (Ceccatelli et al., 1991b) and also stimulates glucocorticoid secretion in hypophysectomized dogs (Bloom et al., 1978, 1987). However, in dexamethasone-treated rats, VIP does not alter plasma ACTH levels (Nussdorfer and Mazzocchi, 1987).

VIP is a potent stimulator of aldosterone and corticosterone secretion, but this effect is not present after chronic VIP administration (Nussdorfer and Mazzocchi, 1987), suggesting tolerance to this effect of VIP. Prolonged VIP administration (1.5 μg/100 g/day) to female rats results in an inhibition of corticosterone secretion after 7 and 14 days (44% and 26% of control values, respectively) (Malendowicz and Nussdorfer, 1993). This treatment did not change adrenal weight and evoked only slight changes in the stereologic parameters of the adrenal cortex (volume of adrenocortical zones, average cell volume and number of cells in the gland) (Malendowicz and Nussdorfer, 1993).

A role for VIP in the stress response has been demonstrated by in vivo experiments in rats subjected to different stressors (immobilization, cold, ether, whole-body vibration, noise and sleep deprivation). (1) Chronic immobilization (2 h/day, for 13 consecutive days) resulted in an increase of VIP in the median eminence, while acute immobilization does not produce any change (Armario et al., 1993). (2) Ac,Tyr1,D-Phe2-GRF(1–29) amide, a specific VIP antagonist markedly lowered aldosterone and ACTH release in rats submitted to cold stress (Nowak et al., 1994). In this experiment, the administration of a VIP antagonist to control rats lowered the plasma levels of aldosterone, without affecting ACTH levels. (3) Studies using the intravenous injection of an VIP antibody demonstrate that VIP increases prolactin release during exposure to ether (Abe et al., 1985; Kaji et al., 1985a,b). This has been corroborated when a VIP antibody solution administered intracerebroventricularly inhibited the ether-induced release of prolactin (Watanobe et al., 2000). Ether also raises plasma ACTH and aldosterone levels, an effect that is inhibited by the prior administration of a VIP antagonist (2 μg Ac,Tyr1,D-Phe2-GRF(1–29) amide, s.c.) (Nowak et al., 1994). On the other hand, VIP release in the median eminence was unaffected by exposure to ether (Gavalda et al., 1993). (4) Whole-body vibration stress experiments reported a significant increase in VIP level in the amygdala and a significant reduction in the hippocampus (Nakamura et al., 1992, 1994). (5) Noise-induced stress (90 min, broad band, 102 dB) significantly increases VIP-like immunoreactivity in the amygdala, without changes in VIP immunoreactivity in the hippocampus (Nakamura et al., 1994). (6) Acute REM (rapid eye movement) sleep deprivation produces an increase in the density

of VIP receptors in the frontal cortex, dorsal raphe and paraventricular thalamic nucleus after 24 h, and even more so after 72 h of REM sleep deprivation (Jimenez-Anguiano et al., 1996). Autoradiographic experiments reported that in rats adapted during 7 days prior to REM deprivation, there is a decrease in the density VIP receptors in some areas of the brain (Jimenez-Anguiano et al., 1996).

In summary, VIP does not appear to be involved in the initial phases of the stress responses, and therefore, it may use a slower mechanism to activate factors responsible for more sustained responses to a stressor. Changes in VIP occur 1–4 h (Gavalda et al., 1993; Nowak et al., 1994), or 24 h (Jimenez-Anguiano et al., 1996), or 2–14 days (Armario et al., 1993; Gavalda et al., 1993) after the onset of the stress stimulus.

3.11. Neuropeptide Y

Neuropeptide Y (NPY) is a 36-amino-acid peptide synthesized in neurons of the arcuate nucleus which project to the paraventricular nucleus of the hypothalamus (Baker and Herkenham, 1995; de Quidt and Emson, 1986a,b,c; Rutkoski et al., 1999; Sawchenko et al., 1985). Neuropeptide Y is known to have diverse functions including regulation of feeding behavior, blood pressure, circadian rhythm, reproductive behavior and the response to stress (Rutkoski et al., 1999). Neuropeptide Y is one of the most abundant and widely distributed peptides in the central and peripheral nervous systems, where it is co-localized with norepinephrine and ATP (Lundberg et al., 1986a,b, 1987, 1988, 1989a,b, 1996). To date, five neuropeptide Y receptors have been characterized (termed neuropeptide Y Y_1–Y_5 receptors). Most of these receptors are associated with pertussis-sensitive G_i/G_o proteins, inhibition of adenylyl cyclase and activation of phospholipase C and Ca^{2+} mobilization from intracellular compartments (Gicquiaux et al., 2002).

Several lines of evidence suggest that neuropeptide Y is a neurotransmitter and neurohormone involved in stress responses and as such should be considered a stress molecule (Zukowska-Grojec et al., 1988, 1991, 1996; Zukowska-Grojec and Vaz, 1988; Zukowska-Grojec, 1995). However, we have to distinguish between the role played by neuropeptide Y in the periphery and in the central nervous system. In the periphery, neuropeptide Y is released from the sympathetic nerves and the adrenal medulla (in some species also from platelets) in addition to norepinephrine during stress, and may contribute to the pressor response to various stimuli (Grundemar and Hakanson, 1993). Neuropeptide Y has a vasopressor effect, reflecting direct vasoconstriction of blood vessels and potentiation of the norepinephrine-evoked response (Grundemar and Hakanson, 1993; Zukowska-Grojec, 1995). The vasoconstrictor activity of blood-borne neuropeptide Y is mediated by vasoconstrictive neuropeptide Y Y_1 receptors and is terminated by the enzyme dipeptidyl peptidase IV (DPPIV), which converts neuropeptide Y to non-vasoconstrictive peptides (Qureshi et al., 1998).

Plasma neuropeptide Y levels rise after exposure to several stressors (Castagne et al., 1987; Zukowska-Grojec et al., 1988; Zukowska-Grojec and Vaz, 1988). Plasma neuropeptide Y is increased by transfer to a new environment (by 52%), exposure to cold water (4 °C, by 117%), hemorrhage (4 ml/300 g body weight, by 231%) and orthostatic hypotension (by 10%) (Puybasset et al., 1993; Zukowska-Grojec et al., 1988; Zukowska-Grojec and Vaz, 1988). Plasma neuropeptide Y levels increase 132% after handling rats, and this effect is also found in adrenalectomized rats (Castagne et al., 1987). Hemorrhagic stress in conscious rats increases plasma neuropeptide Y 100% at 10 min after hemorrhage (Morris et al., 1987, 1997). In pigs, a rise of almost 600% was observed at 60 min after the first bleeding (Rudehill et al., 1987). Pretreatment with BIBP-3226, a neuropeptide Y Y_1 receptor antagonist, abrogated the increased plasma neuropeptide Y levels after hemorrhagic shock (Zukowska-Grojec, 1995). BIBP-3226 had no major influence on blood pressure but attenuated stress-induced hypertension (Zukowska-Grojec, 1995). This information supports the hypothesis that neuropeptide Y is mainly released during stress involving intense sympathetic nervous system activation (Doods et al., 1996). In rats subjected to cold water stress, the administration of the neuropeptide Y Y_1 receptor antagonist BIBP-3226 (3 mg/kg per hour infusion) tended to decrease the stress-induced pressor response and significantly attenuated the post-stress elevation of blood pressure (Zukowska-Grojec et al., 1996). Also, BIBP-3226 attenuates stress-evoked tachycardia in conscious spontaneously hypertensive rats (Zhang et al., 1997).

Adrenal neuropeptide Y gene expression is also increased by different stressors, such as immobilization and cold (Hiremagalur et al., 1994). Adrenal prepro-neuropeptide Y mRNA levels were elevated by a relatively short period of stress, and a single immobilization was sufficient to increase prepro-neuropeptide Y mRNA, which remained elevated for at least 1 day later (Hiremagalur et al., 1994). This rise in adrenal neuropeptide Y mRNA was abolished by the transcriptional inhibitor actinomycin D. Repeated daily immobilization (2 and 7 days) led to a further rise and sustained elevations of adrenal prepro-neuropeptide Y mRNA levels. This increase persisted for 2–3 days after the cessation of repeated stress (Hiremagalur et al., 1994). Cold and shaker stress also significantly increase adrenal neuropeptide Y mRNA (Han et al., 1997, 1998; Levenson and Moore, 1998). The source of neuropeptide Y in the blood is under discussion, and some evidence suggests that stress-induced increase in neuropeptide Y in the adrenal gland does not necessarily produce a hike in plasma neuropeptide Y levels. Additional evidence indicates that neuropeptide Y inhibits both basal and ACTH-stimulated corticosterone secretion in isolated rat adrenocortical cells (Malendowicz et al., 1990).

In the central nervous system, various stressors can induce changes in neuropeptide Y levels in specific brain areas (Nankova et al., 1996; Rybkin et al., 1997). Immobilization stress of rats raises neuropeptide Y levels in the paraventricular nucleus of the hypothalamus (Rybkin et al., 1997). Opposite results have been described for the paraventricular nucleus in rats immobilized for 2 h daily for 6 days and sacrificed 24 h after the last immobilization (Makino et al., 1999, 2000). Forced immobilization of the rats for 4 h each day for 9 consecutive days (repeated stress) also decreased the neuropeptide Y content of the arcuate nucleus by 25%, an effect blocked by the administration of glucocorticoids (Pralong et al., 1993). Also, immobilization stress produces a decrease in neuropeptide Y mRNA levels in the amygdala and the arcuate nucleus, detected by RNAse protection assay and in situ hybridization (Krukoff et al., 1999; Thorsell et al., 1998). A similar effect was seen in the neocortex, but was less pronounced and slower in onset (Thorsell et al., 1998). Striatal and hypothalamic neuropeptide Y levels were not significantly affected (Thorsell et al., 1998). Further studies by this group showed that 1-h restraint increases experimental anxiety in the elevated plus maze through actions within the amygdala, while intra-amygdala administration of neuropeptide Y has the opposite effect (Thorsell et al., 1999). In a repeated immobilization (1 h/day, 9–10 days) experiment, an up-regulation of prepro-neuropeptide Y mRNA and neuropeptide Y peptide was found in the amygdala, but not in hypothalamic or cortical extracts (Thorsell et al., 1999). Others studies found no changes of neuropeptide Y levels in the ventrolateral or dorsomedial medulla, paraventricular and arcuate nucleus of the hypothalamus or frontal cortex of rats 4 h after a 30-min period of restraint stress (Rivet et al., 1989). Rats submitted to short-term restraint (held by the tail for 1 min) did not show any change in neuropeptide Y levels in the periaqueductal gray (Rosen et al., 1992). Also, rats submitted to cold stress showed no effect on neuropeptide Y levels in the brain stem (Schon et al., 1986).

Experiments using transgenic mice and rats resulted in dissimilar results (Inui et al., 1998; Thorsell et al., 2002). Transgenic mice over-expressing neuropeptide Y (115% over the control) displayed behavioral signs of anxiety and hypertrophy of adrenal zona fasciculata cells (Inui et al., 1998). This anxiety-like behavior was reversed, at least in part, by administration of the CRF antagonist, alpha-helical CRF-(9–41) into the third cerebral ventricle. These results suggest that neuropeptide Y has a role in anxiety and behavioral responses to stress partly via the CRF neuronal system (Inui et al., 1998). These investigators previously described evidence that an intraventricular administration of neuropeptide Y antibody significantly inhibited the ACTH and cortisol response to hypoglycemia (Inui et al., 1990). On the other hand, transgenic rats over-expressing high levels of neuropeptide Y in the hippocampus showed a markedly attenuated sensitivity to behavioral consequences of stress (Thorsell et al., 2000, 2002). These results are in agreement with previous data that demonstrate that exogenous administration of neuropeptide Y produces anti-anxiety actions in the elevated plus maze and the social interaction test (Broqua et al., 1995; Heilig and Murison, 1987; Heilig and Thorsell, 2002).

In summary, plasma neuropeptide Y appears to be responsible for stress-induced regional vasoconstriction in response to a stressor. Additional functions would include facilitating platelet aggregation, leukocyte adhesion and macrophage activation (Zukowska-Grojec, 1995). In the central nervous system, the response of neuropeptide Y to different stressors is not clear, but the literature suggests that neuropeptide Y is a powerful anxiolytic substance (Holden and Pakula, 1999) and a protector of stress actions (Heilig and Murison, 1987; Heilig and Thorsell, 2002).

3.12. Cholecystokinin

Cholecystokinin (CCK) is a family of peptides that was purified initially as a CCK-33 amino acid peptide, where 33 corresponds to the number of amino acids forming the peptide molecule (Mutt and Jorpes, 1968; Strand, 1999a). The different variations in length of the active CCK molecule include 5, 7, 8, 18, 25, 33, 39 and 58 amino acids (Keire et al., 1999, 2002; Reeve et al., 1986; Strand, 1999a), where the C-terminal pentapeptide Gly–Trp–Asp–Met–Phe–NH_2 is essential for CCK biological activity (Strand, 1999a). CCK-8 and CCK-22 are the predominant forms in rats and pigs, whereas CCK-33 and CCK-58 are the major forms in humans (Strand, 1999a). In the nervous system, CCK is found predominantly as the C-terminal octapeptide, CCK-8 (Dockray, 1982; Fuxe et al., 1985; Lotstra and Vanderhaeghen, 1987; Strand, 1999a; Vanderhaeghen et al., 1980, 1981, 1992). Neurons containing CCK are widely distributed throughout the brain, mainly in the frontal cortex (Beinfeld, 1983, 1997, 2001; Rehfeld et al., 1985).

Two types of CCK receptors have been identified, CCK_1 and CCK_2 receptors (also named CCK-A and CCK-B receptors, respectively), that belong to the receptor superfamily of G-protein coupled, which stimulate intracellular calcium and inositol phosphate pathways (Dauge et al., 2001; Huang et al., 1994; Jensen et al., 1994; Wank et al., 1992, 1994; Wank, 1995, 1998). These receptors share 50% of homology (Huang et al., 1994; Jensen et al., 1994; Kopin et al., 1994, 2000; Wank, 1995, 1998). The distribution of the CCK_1 receptor is primarily in the periphery, but it is also found in a few discrete brain regions such as the area postrema, interpeduncular nucleus and nucleus of the solitary tract (Becker et al., 2001; Hill et al., 1987a,b, 1988; Moran et al., 1986, 1987; Moran and Schwartz, 1994). On the other hand, CCK_2 receptors are almost exclusively expressed in the central nervous system, especially in cortical and limbic structures (Durieux et al., 1988; Gaudreau et al., 1983, 1987; Moran and Schwartz, 1994; Moran et al., 1986, 1987; Pelaprat et al., 1989; Pommier et al., 1999, 2002).

Pharmacological data indicate that CCK peptides and receptors play an important role in the neurobiological mechanisms of stress- and anxiety-related behaviors (Dauge and Lena, 1998; Dauge et al., 2001). In humans, administration of CCK-4 (Trp–Met–Asp–Phe) produces panic attack in healthy volunteers and in patients with panic disorders (Bradwejn, 1992, 1993; Bradwejn et al., 1994; Bradwejn and Koszycki, 1994, 2001; de Montigny, 1989; Van Megen et al., 1994, 1996a,b,c, 1997a,b). A polymorphism in the CCK promoter has been reported in patients with panic disorders, suggesting that this mutation can increase their vulnerability to panic disorders (Wang et al., 1998). On the other hand, selective CCK_2 receptor antagonists, such as PD135,158, prevents CCK-4 (Trp–Met–Asp–Phe) induction of panic attacks in humans (Bradwejn and Koszycki, 1994) and produces anxiolytic-like effects in various animal paradigms (such as the elevated plus maze and social defeat) (Dauge and Lena, 1998; Tsutsumi et al., 1999, 2001; Van Megen et al., 1994, 1996a,b,c, 1997a,b) and attenuates the anxiogenic influence of CCK (Adamec et al., 1997; Adamec, 1997). Additionally, an increase in CCK and the density of the CCK receptors have been repeatedly reported in some brain areas (arcuate nucleus, frontal cortex) of rats subjected to anxiogenic situations (Giardino et al., 1999; Harro et al., 1996; Siegel et al., 1987). Cortical extracellular CCK concentrations increased in rats subjected to stressful or anxiogenic-like stimuli (Becker et al., 1999, 2001; Nevo et al., 1996). Also, acute intraperitoneal injection of lipopolysaccharide (250 μg/kg) to rats increased its CCK mRNA expression levels (185%) in parvicellular cells of the hypothalamic paraventricular nucleus, occurring in a majority (70%) of CRF neurons (Juaneda et al., 2001). However, for mild stress (such as an i.p. injection of a saline solution), a biphasic pattern was observed in prefrontal cortex, with a decrease 20 min after injection and an increase 8 h after this mild stressor (Radu et al., 2001). Further experiments have shown that the CCK_2 receptor antagonist, CI-988 (2 mg/kg, i.p.) reduced anxiety-like behavior without increasing the CCK outflow in the prefrontal cortex (Becker et al., 2001). In the same experiment, pretreatment with diazepam, but not buspirone, prevented both the anxiety-related behavior and CCK overflow in the prefrontal cortex (Becker et al., 2001).

Studies of the role of CCK using molecular biology tools have reported different results (Dauge et al., 2001; Tsutsumi et al., 2001). Infusion of CCK_2 receptor antisense oligodeoxynucleotides into the lateral ventricle suppressed conditioned fear in rats (Tsutsumi et al., 2001). In this experiment, rats infused in the lateral ventricle at a constant rate during 6 days with CCK_2 receptor antisense, sense or random oligodeoxynucleotides were subject to a 30-min prior inescapable electric foot shock in a chamber with grid floor. In the following days, the rats were placed again in the chamber and observed during 5 min without foot shock. The rats that were injected with the CCK_2 antisense oligodeoxynucleotides showed a reduced freezing behavior, indicating that the CCK_2 receptor plays an important role in anxiety (Tsutsumi et al., 2001). On the other hand, transgenic CCK_2 receptor-deficient mice did not show any behavioral modification compared to wild type in the elevated plus maze and in the motility-conditioned suppression (Dauge et al., 2001). An unknown compensatory mechanism in these transgenic animals have been proposed to occur following CCK receptor knockout (Dauge et al., 2001).

In summary, CCK release and mRNA expression is increased during stress both in limbic and hypothalamic areas (Hernando et al., 1996; Nevo et al., 1996; Rosen et al., 1992). The results obtained with CCK_2 receptor antagonist and antisense oligodeoxynucleotides are consistent with a role of CCK_2 receptors in mediating the stress response in rats (Dauge and Lena, 1998; Tsutsumi et al., 1999, 2001; Van Megen et al., 1996b, 1997a,b). However, the brain regions were this receptor exerts its anxiolytic-like activity are still undefined. Additionally, there is no consistent information about the neuronal circuits involved in the anxiogenic effects of CCK, that it may be through mesolimbic dopamine neurons (Crawley, 1991, 1992, 1994; Crawley and Corwin, 1994).

3.13. Substance P

Substance P (SP) is a decapeptide (Arg–Pro–Lys–Pro–Gln–Gln–Phe–Phe–Gly–Leu–Met NH_2) that, with neurokinin A and neurokinin B, belongs to the tachykinin neuropeptides family (Strand, 1999b). Tachykinins are involved in multiple functions due to their widespread distribution centrally and peripherally (Strand, 1999b). Whereas in the periphery, tachykinins are regulators of blood flow, vascular permeability, salivation, micturition, gastrointestinal motility and intestinal secretions, in the central nervous system, substance P regulates processes involving sensory perception (vision, olfaction and audition) in addition to pain (Strand, 1999b).

Substance P is found in some structures that participate in pain control (midbrain periaqueductal gray, nucleus raphe magnus and the nucleus reticularis giganto cellularis), corpus striatum, spinal cord, median eminence and in the hypothalamic paraventricular nucleus (Jessop et al., 1990, 2000; Jessop, 1999; Li et al., 1996b; Strand, 1999b). Interestingly, substance P and tachykinin NK_1 receptor are expressed in amygdala, septum, hippocampus, hypothalamus and periaqueductal grey (Mantyh et al., 1996; Oyamada et al., 1999). Substance P is co-expressed with serotonin in dorsal raphe neurons in human brain (Baker et al., 1991); by contrast, co-expression of substance P and serotonin in ascending raphe neurons does not appear to occur in the rat brain; therefore, it has been suggested that there might be species differences in the physiology of this system (Rupniak and Kramer, 1999).

Three main receptors mediate the effects of tachykinins, tachykinin NK_1, NK_2 and NK_3 receptors, which show greater affinity for substance P, neurokinin A and neurokinin

B, respectively (Okano et al., 2001; Strand, 1999b); however, substance P, neurokinin A and neurokinin B act as fully agonists in the three receptors (Strand, 1999b). The signaling cascade of the neurokinin receptors includes the activation of G_q proteins, phospholipase C and release of intracellular calcium, as well as opening of calcium channels in the plasma membrane (Otsuka and Yanagisawa, 1990; Otsuka and Yoshioka, 1993; Strand, 1999b).

The role of substance P in the stress response is confusing. The earliest works reported an anxiolytic-like role for substance P, supported by the fact that intracerebroventricular injection of substance P produces decreased plasma levels of ACTH (Chowdrey et al., 1990; Larsen et al., 1993a) and the injection of a substance P receptor antagonist peptide raises plasma ACTH and corticosterone (Larsen et al., 1993b). Also, substance P receptor antagonists increased CRF mRNA in the parvicellular region of the hypothalamic paraventricular nucleus (Chowdrey et al., 1995; Faria et al., 1991). It was proposed that the inhibitory effect of substance P over the CRF secretion could be mediated by GABA and serotonin in the hypothalamic paraventricular nucleus (Culman and Unger, 1995; Culman et al., 1995; Sakuma et al., 1991), because GABA-ergic and serotonergic neurons in the hypothalamus innervate CRF neurons (DiMicco et al., 1996; Herman and Cullinan, 1997). Substance P stimulates the release of GABA and inhibit the release of serotonin in the hypothalamic paraventricular nucleus (Culman and Unger, 1995; Culman et al., 1995; Sakuma et al., 1991). Intracerebroventricular injection of substance P also inhibits the corticosterone release stimulated by serotonin (Saphier et al. 1994).

On the other hand, recent, direct and indirect evidence supports an anxiogenic-like role for substance P and an anxiolytic role for substance P inhibitors (Boyce et al., 2001; Kramer et al., 1998; Santarelli et al., 2001b; Steinberg et al., 2001). Whereas a focal injection of a monoclonal antibody anti-substance P into the ventral tegmental area attenuate stress-induced activation of the mesocortical dopamine pathway (Bannon et al., 1983, 1986), intracerebroventricular injections of substance P agonists produce conditioned place aversion, anxiogenic-like behavior in the elevated plus maze and escape behavior (Aguiar and Brandao, 1996; Kramer et al., 1998). The intra-amygdala injection of L760735, a tachykinin NK_1 receptor antagonist, also showed an anxiolytic effect in guinea pig pups (Boyce et al., 2001). The intracerebroventricular administration of GR 73632 and L733060 (0.1 nmol), tachykinin NK_1 receptor agonists, in guinea pigs produces motor activation and long-lasting audible vocalization (Severini et al., 2002). This effect was attenuated by antidepressant drugs and by L733060 (Severini et al., 2002). CGP49823, another tachykinin NK_1 receptor antagonist, showed anxiolytic-like effects in social interaction test in rats and increased the social interaction following administration of doses of 3–30 mg/kg (File, 1997). Also, anxiolytic and antidepressant drugs might cause down-regulation of substance P synthesis (Brodin et al., 1994; Shirayama et al., 1996, 2000). Additionally, studies of the levels of substance P in different areas of the central nervous system reported an increase of substance P in the depressed patients and a reduction of its levels in the lateral hypothalamic area (Siegel et al., 1987). Also, substance P is released in the basolateral amygdala after neonatal separation stress in guinea pig pups (Kramer et al., 1998). Promising results have been obtained in a randomized double-blind placebo-controlled study conducted to evaluate the safety and efficacy of single daily doses of MK869 (300 mg), a tachykinin NK_1 receptor antagonist, which reported a significant anxiolytic activity in this population of depressed patients (Kramer et al., 1998; Rupniak and Kramer, 1999).

Recent studies in tachykinin NK_1 receptor knockout mice confirmed the anxiogenic role of substance P (Santarelli et al., 2001a). In this study, the tachykinin NK_1 receptor knockout mice showed markedly reduced anxiety-related behaviors in the elevated plus maze, the novelty-suppressed feeding and the maternal separation paradigms (Santarelli et al., 2001a). Pharmacological antagonism of the tachykinin NK_1 receptor, using RP67580, also decreased anxiety-related behaviors in wild-type mice, but has no effect on mice lacking the tachykinin NK_1 receptor (Santarelli et al., 2001a). Santarelli et al. (2001a) also studied whether the antagonism of the tachykinin NK_1 receptors modified the function of the serotonergic system, a neurotransmitter that modulates mood and anxiety, as was described previously. These investigators recorded the firing rate of serotonin in the dorsal raphe neurons in wild-type mice, tachykinin NK_1 receptor knockout mice and wild-type mice pretreated with RP67580 (Santarelli et al., 2001a). The NK1 knockout mice and wild-type mice pretreated with substance P antagonist showed an increased firing activity in the dorsal raphe, which has been described as a common consequence to most antidepressant treatment (Santarelli et al., 2001a). Experiments in the other line of knockout mice for the tachykinin NK_1 receptor reported decreased anxiety in the transgenic mice, in comparison with the wild type, but only using the ultrasonic vocalizations paradigm, which measures the number of ultrasonic vocalizations emitted by 8-day-old pups separated from their mother (Rupniak et al., 2000; Murtra et al., 2000). No differences in the elevated plus maze was detected between the wild controls and the tachykinin NK_1 receptor knockout mice (Murtra et al., 2000; Rupniak et al., 2000).

In recent studies, the antagonism of tachykinin NK_2 receptors have been also involved with anxiolytic responses (Steinberg et al., 2001). Studies with SR48968 (0.3–10 mg/kg, i.p.), a selective tachykinin NK_2 receptor antagonist, reported anxiolytic-like behavior in mice, rats and guinea pig pups (Steinberg et al., 2001). According to the authors, this effect would involve a reduction of stress-induced substance P release because SR48968 reduced the separation-induced increase in the number of neurons displaying tachykinin NK_1 receptor internalization in the amygdala

(Steinberg et al., 2001). Interestingly, in this work the neuronal firing of the locus coeruleus and noradrenergic release in the prefrontal cortex both elicited by an uncontrollable stressor or an intraventricular administration of CRF were reduced by SR48968 (0.3–1 mg/kg, i.p.) (Steinberg et al., 2001).

In summary, most of the evidence points to an anxiogenic role of substance P, where most of the effects currently known are tachykinin NK_1 receptor mediated. However, an important role for tachykinin NK_2 receptor and even tachykinin NK_3 receptor is not discarded. Interestingly, tachykinin NK_1 receptors are located in the paraventricular nucleus of the hypothalamus, where an interaction with CRF and serotonin is plausible, and also a direct regulation of the hypothalamic–pituitary–adrenocortical axis.

3.14. Estrogen and stress

Females, particularly postmenopausal women, have a high incidence of depression and other stress-related disorders (Angold and Worthman, 1993; Martenyi et al., 2001; Piccinelli and Wilkinson, 2000). Neuroendocrine studies suggest that the impact of estrogen over the hypothalamic–pituitary–adrenocortical axis may play a role in these disorders (Dayas et al., 2000; Piccinelli and Wilkinson, 2000). Clinical trials reported that estrogen replacement therapy, which is a risk factor for stroke in postmenopausal women (Grady et al., 2002), is a promising treatment of depression (Dayas et al., 2000; Fink et al., 1996; Gregoire et al., 1996; Soares et al., 2001).

The mechanisms of action of estrogen on the hypothalamic–pituitary–adrenocortical axis are still under debate (Dayas et al., 2000; Paulmyer-Lacroix et al., 1996; Yukhananov and Handa, 1997). Substantial evidence points to an inhibition of estrogen synthesis by CRF and other hypothalamic neuropeptides (Dayas et al., 2000; Parker et al., 2001). The impact of estrogen on CRF and the hypothalamic–pituitary–adrenocortical axis, at least in laboratory animals, is still unclear (Dayas et al., 2000; Parker et al., 2001). CRF, vasopressin and glucocorticoids inhibit the release of luteinizing hormone-releasing hormone (LHRH) and luteinizing hormone (LH) (Akema et al., 1996; Dufau et al., 1993; Gindoff and Ferin, 1987; Heisler et al., 1994; Petraglia et al., 1987). An inhibition of the gonadal steroid production by CRF and glucocorticoids and a ACTH-induced desensitization to luteinizing hormone has been reported (Calogero et al., 1996; Welsh et al., 1983; Young, 1995). These effects may explain some of the anti-reproductive effects of CRF in different species (Ferin, 1995).

Ovariectomized rats, whose plasma estrogen levels were maintained at physiological levels (25 or 100 pg/ml) for 7 days, showed a suppressed stress-induced Fos-like expression in hypothalamic neuroendocrine cells (Dayas et al., 2000). Furthermore, plasma ACTH responses to both an emotional stressor (noise) and a physical stressor (immune challenge by systemic interleukin-1β administration) were also suppressed (Dayas et al., 2000). In intact female rats, the estrogen antagonists tamoxifen and C1628 increased plasma levels of ACTH and corticosterone in response to restraint stress (Young et al., 2001). Additionally, tamoxifen and C1628 decreased the levels of ACTH in rats exposed to restraint stress in ovariectomized female rats maintaining a low dose of estradiol during 7 days (Young et al., 2001). Progesterone had no effect on ACTH or corticosterone responses and the combination of estradiol and progesterone also decreased the ACTH response to stress, and the magnitude of the effect did not differ from that found with estradiol treatment alone (Young, 2001; Young et al., 2001). These results agree with previous observations that in ovariectomized rats, estrogen has a negative effect on CRF mRNA levels in the hypothalamic paraventricular nucleus of rats (Haas and George, 1989; Paulmyer-Lacroix et al., 1996). However, there is evidence of a stimulatory effect of estrogen on CRF mRNA in the hypothalamic paraventricular nucleus of ovariectomized rats (Patchev et al., 1995). Additionally, female rats, in comparison with male rats, have greater ACTH response to stress, higher corticosterone levels and a faster onset of corticosterone secretion, suggesting that estradiol plays an enhancing role over the stress response (Burgess and Handa, 1992; Carey et al., 1995; Le Mevel et al., 1979; Young, 1996). Methodological differences between that mentioned studies could be found in the hormone treatment applied and the doses of estrogen/estradiol used (Dayas et al., 2000; Young et al., 2001). Rats treated with low doses of estradiol, for short periods (7 days) and with physiological levels of estrogen (25–160 pg/ml), show a decreased response to a stressor (Dayas et al., 2000; Redei et al., 1994; Young et al., 2001). However, rats treated with estradiol for 21 days (much longer that a normal hormonal cycle in rats), although with low estrogen levels, reported higher corticosterone levels in response to foot shock. Besides, a single dose of 8 or 10 μg estradiol in rats, which results in estradiol plasma concentration over 500 pg/ml (that is at least four times higher than proestrus levels in rats), produces increased levels of ACTH or corticosterone in stressed rats (Carey et al., 1995; Viau and Meaney, 1991; Young et al., 2001).

Whereas a gradual decline in estrogen levels after the age of 40 may contribute to a higher rate of depression in women, estrogen replacement therapy has been shown to produce cognitive and mood-enhancing effects in women and may facilitate antidepressant activity (Amsterdam et al., 1999). Clinical studies consistently show that estrogen replacement therapy suppresses hypothalamic–pituitary–adrenal axis responses to an emotional stressor in postmenopausal women (Dayas et al., 2000; Lindheim et al., 1992). This effect may lead to combination therapy of estrogen and selective serotonin uptake inhibitors in treating mood disorders (Amsterdam et al., 1999).

However, the mechanisms by which estrogen may affect stress responsiveness are still unclear. One possible mechanism is that estrogen enhances the inhibitory effect of

glucocorticoids on the hypothalamic–pituitary–adrenocortical axis. These mechanisms would include a reduction in corticosterone metabolism, or an increase in corticosterone synthesis (Kitay, 1965; Lo et al., 2000; Young et al., 2001). Other mechanisms could include an estrogen-induced increase in sensitivity and expression or reduced degradation of glucocorticoid receptors (Burgess and Handa, 1992; Ferrini and De Nicola, 1991). Additionally, a direct effect of estrogen on some brain regions that regulate the hypothalamic–pituitary–adrenocortical axis is possible (Haas and George, 1989; Paulmyer-Lacroix et al., 1996; Raap et al., 2000). Interestingly, estrogen β-receptor (ERβ) is co-localized with oxytocin, but not with CRF neuroendocrine cells in the hypothalamic paraventricular nucleus (Alves et al., 1998a,b; Laflamme et al., 1998). Also, treatment with estrogen suppressed stress-induced (interleukin-1β injection) c-fos expression in the central nucleus of the amygdala of ovariectomized rats (Dayas et al., 2000).

In summary, in humans, there is significant evidence suggesting a beneficial effect of estrogen on the stress response, although the sites and mechanisms of action are still under investigation.

4. Drugs that inhibit the neuroendocrine response to stressors

Table 2 summarizes the effects of anxiolytic drugs, CRF receptor antagonists, agonists and antagonists for serotonin, opioid, histamine and adrenergic receptors on the neuroendocrine responses to stressors. The majority of the cited studies are pre-clinical studies that focus on psychological stressors and their effects on laboratory animals, and there is some information about human studies. New information is emerging about drugs affecting peptide neurotransmitters (CRF, CCK, VIP, neuropeptide Y, substance P and others) (Gully et al., 2002; Nicot et al., 1997; Wong et al., 1999); however, their role in stress-induced secretion of hormones remains to be examined. Most of these new studies only determined the ACTH or corticosterone response to stress, and there is no information about other stress hormones.

The insight gained on the neuroendocrine and neurotransmitter role of CRF, particularly the role of CRF_1 receptor, led to the synthesis of different CRF_1 receptor antagonists. These include: CP-154,526 (butylethyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]-amine), BI27914 (5-chloro-*N*-cyclopropylmethyl-2-methyl-*N*-propyl-*N*'-(2,4,6-trichlorophenyl)-pyrimidin-4,6-diamine), DMP904 (4-(3-pentylamino)-2,7-dimethyl-8-(2-methyl-4-methoxyphenyl)-pyrazolo-[1,5-*a*]pyrimidine), CRA1000 (2-[(*N*-(2-methylthio-4-isopropylphenyl)-*N*-ethylamino]-4-[4-(3-fluorophenyl)-1,2,3,6-tetrahydropyridin-1-yl)-6-methylpyrimidine) and SSR125543A (4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]5-methyl-*N*-(2-propynyl)-1,3-thiazol-2-aminehydrochloride) (Arborelius et al., 2000; Griebel et al., 2002; Gully et al., 2002; Habib et al., 2001; Kim et al., 1998; Maciag et al., 2002; Okuyama et al., 1999a; Pelleymounter et al., 2002; Pournajafi et al., 2001; Ruhmann et al., 1998). SSR125543A is one of the latest non-peptide CRF_1 receptor antagonist described with a high affinity for CRF_1 receptor and low affinity for the CRF_2 receptor (Gully et al., 2002). All the antagonist of the CRF_1 receptor inhibit the ACTH/corticosterone response to stressors and have a good anxiolytic score (Arborelius et al., 2000; Gully et al., 2002; Habib et al., 2001; Kim et al., 1998; Maciag et al., 2002; Pelleymounter et al., 2002). Unfortunately, most of the stressors were applied to laboratory animals during 15–60 min, and only plasma ACTH/corticosterone was determined (Arborelius et al., 2000; Gully et al., 2002; Habib et al., 2001; Kim et al., 1998; Maciag et al., 2002; Pelleymounter et al., 2002). Promising exploratory clinical studies have been conducted with R-121919; however, hepatotoxicity has been reported in some patients (Zobel et al., 2000).

$5\text{-}HT_{1A}$ receptor agonists, buspirone and ipsapirone inhibit the effects of stressors on the secretion of prolactin and corticosterone (Matzen et al., 1993b; Matzen, 1995; Rittenhouse et al., 1992; Urban et al., 1986; Van de Kar et al., 1985b) and also inhibit the effect of conditioned fear stress on the secretion of renin (Groenink et al., 1996a; Matheson et al., 1997; Rittenhouse et al., 1992; Van de Kar et al., 1985a; Van de Kar, 1996). It is possible that the mechanism through which buspirone, ipsapirone and 8-OH-DPAT suppress the effects of stress on the secretion of hormones is mediated by reducing the firing rate of serotonergic neurons in the dorsal raphe (Jorgensen et al., 2001; Matheson et al., 1997). Somatodendritic $5\text{-}HT_{1A}$ autoreceptors in the raphe nuclei inhibit the firing of serotonergic neurons (Blier and de Montigny, 1987; Blier et al., 1987; Fletcher et al., 1996; Remy et al., 1996). This hypothesis is also supported by the observations that lesions in the dorsal raphe nucleus inhibit the corticosterone and renin responses to conditioned fear and suggest that serotonergic neurons in this nucleus are important contributors to the mechanisms that increase hormone release during exposure to psychological stressors (Van de Kar and Blair, 1999).

Studies employing serotonergic receptor antagonists indicate that $5\text{-}HT_2$ and $5\text{-}HT_3$ receptors may also mediate the stress-induced increases in hormone release (Van de Kar and Blair, 1999; Van de Kar et al., 2001). The ability of the $5\text{-}HT_2$ receptor antagonists (ketanserin and LY53857) and $5\text{-}HT_3$ receptor antagonists (ondansetron and ICS 205–930) to inhibit the prolactin response to either ether or immobilization stress was not dose dependent (Jorgensen et al., 1992). Another $5\text{-}HT_{2A}$ receptor antagonist, MDL-11939, inhibits the effect of ether plus immobilization on the secretion of the intermediate lobe hormone α-MSH (Goudreau et al., 1993). Similarly, the $5\text{-}HT_3$ receptor antagonist MDL-72222 reduced the corticosterone response to acoustic stimulation (Saphier et al., 1995). Currently, there is discussion whether $5\text{-}HT_2$ and/or $5\text{-}HT_3$ receptors are part of

the mechanisms responsible for the ACTH and prolactin but not renin responses to stressors (Van de Kar and Blair, 1999). The 5-$HT_{2A/2C}$ receptor antagonist LY53857 does not inhibit the renin response to conditioned stress (Lorens and Van de Kar, 1987). Interestingly, we have observed that chronic treatment with the antidepressant drug fluoxetine reduces some of the behavioral manifestations of conditioned fear (freezing behavior and defecation) but does not alter the ACTH, corticosterone, oxytocin, renin and prolactin responses to conditioned fear stress (Zhang et al., 2000). Fluoxetine produces desensitization of somatodendritic and postsynaptic 5-HT_{1A} receptors and also produces a supersensitivity of postsynaptic 5-HT_2 receptors (Stone and Trullas, 1984; Zhang et al., 2000).

Opioid receptors inhibit the secretion of oxytocin (Leng et al., 1987; Summy-Long et al., 1990). Naloxone and the κ opioid receptor antagonist MR2266BS potentiate the oxytocin response to immobilization, while the δ opioid receptor antagonist ICI 154129 does not alter the oxytocin response to this stressor (Carter et al., 1986; Carter and Lightman, 1987; Matheson et al., 1997; Onaka and Yagi, 1990; Samson et al., 1985). Naltrexone inhibits the prolactin response to motion stress and prolongs the ACTH response to this stressor (Odio and Brodish, 1990). However, the data are not consistent, and there is disagreement regarding the role of opioids in mediating the effects of stress on the secretion of ACTH (Buckingham and Cooper, 1987; Ray et al., 1991; Xu and McCann, 1989). Thus, the most consistent effects are an inhibition by opioid receptor antagonists of the prolactin response to several stressors. Opioids may not be part of anxiety circuits impinging on the hypothalamus but instead act directly on the hypothalamic neurons that regulate the secretion of each individual hormone to alter their responses to stress-initiated signals. Recent data also suggest that opioids antagonize CRF stimulatory action on noradrenergic neurons in the locus coeruleus (Valentino and van Bockstaele, 2001).

Central histaminergic neurons participate in mediating the effects of stressors on the secretion of ACTH, prolactin, adrenal catecholamines and renin (Kjær et al., 1991; Knigge et al., 1991; Knigge and Warberg, 1991; Matheson et al., 1997; Matzen et al., 1990; Yagi, 1994). Ranitidine and cimetidine (histamine H_2 receptor antagonists) inhibit the effects of immobilization on prolactin and renin release, suggesting that H_2 receptors mediate the effects of immobilization stress on these hormones (Van de Kar and Blair, 1999). In general, the influence of histamine is indirect and is mediated by intra-hypothalamic neurons (such as inhibition of tuberoinfundibular dopaminergic neurons) or by altering the function of incoming nerve terminals, such as serotonergic inputs (Knigge and Warberg, 1991).

Benzodiazepine drugs such as diazepam, chlordiazepoxide, alprazolam and midazolam have been used for many years as anxiolytic drugs in humans. These drugs act by enhancing GABA-ergic neurotransmission through an allosteric interaction at the benzodiazepine–$GABA_A$–barbiturate–chloride ionophore receptor complex and are effective in inhibiting the secretion of ACTH to several stressors (Groenink et al., 1996b; Le Fur et al., 1979; Rohrer et al., 1994; Yagi and Onaka, 1996a,b). However, chlordiazepoxide and midazolam fail to inhibit the effects of conditioned fear stress on the secretion of renin (Van de Kar et al., 1985a), suggesting that central GABA-ergic neurons do not play a significant role in the neural circuits that mediate the effects of stressors on the secretion of renin. Diazepam inhibits the ACTH but not plasma catecholamine responses to non-hypotensive head-up tilt (Matzen et al., 1993a). Furthermore, diazepam does not inhibit any hormone responses to hypotensive head-up tilt (Matzen et al., 1993a). Interestingly, benzodiazepines do not affect renin secretion, although they inhibit ACTH, oxytocin and prolactin secretion. The ineffective role of benzodiazepines in reducing the renin response to stress further confirms that brain circuit and/or receptor mechanisms that mediate the effects of stressors on the secretion of ACTH, oxytocin and prolactin are different from those who mediated the secretion of renin.

Central catecholamines can influence the release of stress-related hormones. α-Adrenoceptors play a prominent role in mediating the neuroendocrine effects of stress, although the specific brain region(s) and receptor subtype(s) mediating these responses are not clear (Van de Kar and Blair, 1999). During exposure to stress, the release of catecholamines in the hypothalamus increases ACTH secretion by activation of α_1-adrenoceptors, while activation of α_2-adrenoceptors inhibits this effect (Buckingham and Cooper, 1987; Gaillet et al., 1991b; Grino et al., 1994; Haller et al., 1994; Kovacs and Makara, 1993; Plotsky et al., 1989; Szafarczyk et al., 1987). Injection of the α_1-adrenoceptor antagonist prazosin into the central amygdala reduces the corticosterone response to a stressful combination of ether and light flashes (Feldman and Weidenfeld, 1996), suggesting that catecholamines in other parts of the limbic circuit also play a role. These data are consistent with the fact that catecholaminergic neurons send collaterals to both the central amygdala and paraventricular hypothalamic nucleus (Petrov et al., 1993) and that catecholaminergic innervation of the paraventricular nucleus is required for full expression of the ACTH response to several stressors (Gaillet et al., 1991a; Gibson et al., 1986; Richardson Morton et al., 1990).

Antagonists for β-adrenoceptors reduce basal plasma renin levels (Blair and Gengo, 1995; Keeton and Campbell, 1980) and attenuate the renin response to a wide range of stressors both in humans and in experimental animals (Keeton and Campbell, 1980) and do not reduce ACTH stress response in hypoglycemic stress and conditioned stress (Nilsson et al., 1980; Van de Kar et al., 1985a). The β-adrenoceptors that mediate the renin response to conditioned fear are proposed to reside within the hypothalamus (Richardson Morton et al., 1995). The stressors that stimulate the secretion of renin include conditioned

fear (Van de Kar et al., 1985a), immobilization stress (Golin et al., 1989; Matzen et al., 1990), head-up tilt (Golin et al., 1988), hemorrhage (Blair et al., 1991), water deprivation (Chen et al., 1988) and heat exposure (Escourrou et al., 1982). β-Adrenoceptor antagonists are less effective in attenuating the renin response to hemorrhage (Roarty and Raff, 1988), water deprivation (Blair et al., 1997), or heat exposure (Groza et al., 1981) in rats than in human subjects, nonhuman primates, or dogs. On the other hand, direct injection of propranolol or stall into the hypothalamic paraventricular nucleus reduces the effect of ether and conditioned fear, respectively, on the secretion of corticosterone (Richardson Morton et al., 1990; Szafarczyk et al., 1987). While the local effects of these drugs may be due to blockade of β-adrenoceptors, the receptor specificity of their effects on the paraventricular nucleus requires confirmation.

Among the various classes of drugs discussed above, we find that those interacting with CRF_1, neuropeptides, 5-HT_{1A}, $GABA_A$, histaminergic H_2 receptors and α_1-adrenoceptors appear to interact directly with the neural circuits involved in stress-induced hormone release (Van de Kar and Blair, 1999). Promising results have been obtained using the new class of peptide and non-peptide antagonists of CRF receptors. The neuroendocrine information for these drugs is still incomplete and most of the behavioral studies just used acute stressors. However, although these drugs will require a thorough examination, they are a new class of antidepressant and anxiolytic drugs that offer new targets on specific receptors involved in the onset of the stress response.

5. Conclusions

This review has attempted to examine the role of several neurotransmitters in the brain circuits that regulate the functioning of the neuroendocrine system during exposure to several stressors. The hypothalamic paraventricular nucleus plays a central role in the stress-induced increase in the secretion of ACTH, oxytocin, prolactin and renin. If one scrutinizes Table 2, it is clear that no drug can block all hormone responses to stressors. This suggests that multiple brain mechanisms are responsible for the regulation of each hormone and that not all hormones are regulated by the same neural circuits. In particular, the renin–angiotensin system seems to be regulated by different brain mechanisms than the hypothalamic–pituitary adrenal system. This could be an important survival mechanism to ensure that dysfunction of one neurotransmitter system will not endanger the appropriate secretion of hormones during exposure to adverse conditions. The measurement of several hormones to examine the mechanisms underlying the stress response and the effects of drugs and lesions on these responses can provide insight into the nature and location of brain circuits and neurotransmitter receptors involved in anxiety and stress.

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