Interaction of Stress, Corticotropin-Releasing Factor, Arginine Vasopressin and Behaviour

Eléonore Beurel and Charles B. Nemeroff

Abstract Stress mediates the activation of a variety of systems ranging from inflammatory to behavioral responses. In this review we focus on two neuropeptide systems, corticotropin-releasing factor (CRF) and arginine vasopressin (AVP), and their roles in regulating stress responses. Both peptides have been demonstrated to be involved in anxiogenic and depressive effects, actions mediated in part through their regulation of the hypothalamic-pituitary-adrenal axis and the release of adrenocorticotropic hormone. Because of the depressive effects of CRF and AVP, drugs modifying the stress-associated detrimental actions of CRF and AVP are under development, particularly drugs antagonizing CRF and AVP receptors for therapy in depression.

Keywords Stress · Corticotropin-releasing factor · Arginine vasopressin · Behaviour

Contents

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1 Stress and Its Consequences on Behaviour

Although stress is now considered a common component of life in modern societies (Joels and Baram 2009), its definition remains somewhat vague. Stress is generally considered to involve external challenges to the organism, which can include psychogenic stressors that may be actual or potential adverse situations, as well as physical stressors (e.g. immune challenge, hypovolemia or cold exposure) (Dayas et al. 2001; Pacak and Palkovits 2001). Although these disparate stressors activate different brain circuits, adaptive responses to these stressors often include similar mediators. In the short term, the organism tends to adapt to the stress to maintain homeostasis, for example by eliminating the challenge or by avoidance (McEwen 1998, 2007). Over time, maintaining physiological stability becomes more difficult. It is now well-established that exposure to extraordinary levels of stress, chronic stress or repeated exposures to stress can markedly increase vulnerability to serious mental illness, and cardiovascular disorders (Rosengren et al. 2004).

This subject is a vast one with entire volumes and meeting proceedings dedicated to it. Instead of trying to cover stress neurobiology in any comprehensive manner, we focus on two neuropeptide systems, corticotropin-releasing factor (CRF) and arginine vasopressin (AVP). Nevertheless, it is important to note that two major systems have long been known to play prominent roles in mediating the stress response: the hypothalamic-pituitary-adrenal (HPA) axis (Herman and Cullinan 1997) and the sympatho-adrenal-medullary system. Thus, hypothalamic and extra-hypothalamic CRF is the preeminent example of a stress-related neuropeptide system that promotes withdrawal and attenuates appetitive behaviors, while there is evidence that neuopeptide Y (NPY) exerts the opposite effect. CRF is thought to mediate the acute stress response in cooperation with AVP (Gillies et al. 1982; Jaferi and Bhatnagar 2007; Lightman 2008; Ma et al. 1997; van Gaalen et al. 2002). The latter appears to be contributing to the long term stress response which likely leads to depression (Dinan and Scott 2005). It is important to note in any discussion of stress that different individuals encounter different magnitudes of stress exposures and the perception of stress varies significantly from individual to individual. Two divergent hypotheses have been proposed to explain the variable outcomes of stress in different individuals (Nederhof and Schmidt 2012). The first one states that stress exposure early in life increases the risk of vulnerability to detrimental stress responses later in life (McEwen 1998; Heim et al. 2008). In contrast, the second hypothesis focuses on resilience, suggesting that repeated exposures to adverse situations during development can be beneficial by promoting resilience even if the environment remains aversive (Schmidt 2011). Most studies in laboratory animals have focused on vulnerability rather than resilience (Veenema et al. 2008; Zobel et al. 2000) and have been interpreted from the point of view that the molecular modifications that ensue in response to stress result from changes in vulnerability. This is at least in part due to the difficulty of distinguishing resilient animals from controls (Schmidt et al. 2010;

Stedenfeld et al. 2011). However, resilience mechanisms are now the focus of considerable investigation (Bilbo et al. 2008; Champagne et al. 2008) because they represent an innovative approach to both understanding pathophysiology as well as drug development for a range of stress-related syndromes.

Many behaviors that are assessed in rodents in response to stress have been interpreted to resemble symptoms exhibited by patients with post-traumatic stress disorder (PTSD) or major depressive disorder (MDD). Although emotional and psychological stress are difficult to evaluate in rodents, a variety of stressors have been shown to induce "depressive-like behavior". These behaviors include loss of enjoyment (anhedonia), loss of motivation, sleep disturbances, deficient sociability skills, anxiety, changes in appetitive behavior, or cognitive deficits, which have all been associated with prolonged stress exposure. For example, anhedonia, learned helplessness, and sociability deficiencies in animal models have been induced by a variety of stressors, such as chronic restraint stress, in which rodents are immobilized repeatedly for hours in a tube, the learned helplessness paradigm, where rodents receive inescapable footshock, the chronic social defeat paradigm, where rodents are repeatedly exposed to aggression by dominant animals, or chronic unpredictable stress, where rodents receive different (heterotypic) stressors every day. A number of neurobiological consequences of chronic stress have been observed including dysregulation of the HPA axis, reduced hippocampal neurogenesis and reduction of brain-derived neurotrophic factor (BDNF), which is required for synaptogenesis (Maras and Baram 2012). The composition of the microbiota of the gut is also affected by the HPA axis through the release of stress hormones and the sympatho-adrenal medullary system (Collins et al. 2012; Dinan and Cryan 2012). The microbiota is a major regulator of the immune system and the immune system has now been unequivocally shown to be altered in patients with mood disorders. Indeed, administration of a low dose of the inflammatory stimulant lipopolysaccharide (LPS) is sufficient to induce sickness behavior, which shares many characteristics with human major depressive behavior. We review here the involvement of the HPA and the sympatho-adrenal system in stress related disorders.

2 HPA Axis

Activation of the HPA axis in response to stress results in widespread hormonal, neurochemical and physiological alterations (Herman and Cullinan 1997). Activation of the HPA axis is mediated by the release of neuropeptides, including CRF and vasopressin into the hypothalamo-hypophyseal portal system, which stimulates the release from the anterior pituitary of adrenocorticotropic hormone (ACTH). ACTH in turn promotes the synthesis and secretion of glucocorticoids from the adrenal cortex (Aguilera 1994; Antoni 1986a). Thus, glucocorticoids (cortisol in humans, and corticosterone in most rodents) are released upon activation of the HPA axis. Glucocorticoid receptors or mineralocorticoid receptors,

both of which are activated by glucocorticoids, are expressed in several brain regions (e.g. prefrontal cortex, amygdala, hippocampus and other limbic and midbrain structures). They are steroid receptors that function as transcription factors that regulate cell function even after acute stress is terminated. The magnitude, type, and duration of the stress are important in determining the HPA axis response. The HPA axis has been most scrutinized in PTSD and MDD. Thus, elevated plasma glucocorticoid concentrations have been observed in patients with MDD, particularly those with more severe and/or psychotic symptoms; in contrast a small population of MDD patients show reduced levels of glucocorticoids, which seems to be associated with milder symptoms (Stetler and Miller 2011). In PTSD, in contrast, a tendency for lower levels of glucocorticoids has been reported, but these findings are also mixed (Meewisse et al. 2007). These discordant findings are undoubtedly in part due to the confounding effects of child abuse and neglect on HPA axis activity in adulthood (Heim et al. 2008). This concatenation of findings renders difficult a comprehensive understanding of the role of glucocorticoids in the development of stress-related disorders. It is important to note the broad effects on the brain of glucocorticoids, which are released peripherally in response to stress, which contrasts with the local release of neurotransmitters and neuropeptides that provide a more restricted synaptic modulation. Thus, increased cerebrospinal fluid (CSF) levels of the neuropeptide CRF seem to correlate more closely than do glucocorticoid levels with stress-related disorders (Heim et al. 2000, 2008; Yehuda et al. 2005).

2.1 Corticotropin-Releasing Factor System

Corticotropin-Releasing Factor (CRF), a 41 amino acids peptide was discovered in 1981, and since then three related ligands and two receptors have been identified. The canonical role of CRF is to initiate the endocrine response to stress by releasing ACTH from the anterior pituitary. This neuropeptide is released from cell bodies within the hypothalamic paraventricular nucleus (PVN) to activate the HPA axis (Korosi and Baram 2008), but neurons express CRF in several extrahypothalamic brain regions (amygdala, cerebrocortical areas, septum, hippocampus) where they play a key role in the autonomic, immune and behavioral effects of stress (Chen et al. 2000, 2001, 2004; Korosi and Baram 2008; Sawchenko et al. 1993). CRF is also expressed in the periphery (blood vessels, skin, lung, testes, ovaries or placenta). Its three related ligands, urocortin 1, urocortin 2 (stresscopin-related peptide) and urocortin 3 (stresscopin) are also expressed both in the periphery and in the brain. Although urocortin 1 and urocortin 2 share a hypothalamic distribution with CRF, urocortin 3 seems to have minimal overlapping expression with CRF (Hauger et al. 2003). CRF and urocortin 1 both bind preferentially to CRF-R1 receptors, whereas urocortins 1, 2 and 3 bind to CRF-R2 receptors with a high affinity. CRF-R1 is expressed mainly in the brain (Swanson et al. 1983), while CRF-R2 is expressed mainly in the periphery. CRF-R1 and

CRF-R2 have 70 % amino-acid sequence homology, but diverge greatly in their N-terminal sequences and belong to the class B1 of 7-transmembrane G-protein coupled receptors. CRF receptors also regulate a diverse group of other intracellular signaling pathways that involve intracellular effectors such as cAMP and an array of protein kinases. This allows them to exert unique roles in the integration of homeostatic mechanisms. It is thought that CRF-R1 principally mediates the stress response. The CRF system is also regulated by a CRF-binding protein (CRFBP), which is highly conserved and present in the circulation as a 37 kDa glycoprotein that binds CRF and related peptides, reducing their availability.

Thus, the CRF system has a multitude of physiological functions, all related to the orchestration of the stress response. CRF stimulates ACTH synthesis and release in the pituitary, thus controlling the HPA axis, but also activates the noradrenergic and sympathetic systems. Locally, CRF regulates adrenal steroidogenesis and catecholamine synthesis in the adrenal gland. In addition, CRF acts in limbic areas in modulating alertness and fear, and appetite and libido, all dysregulated in depressive disorders. Direct regional brain-specific injections of CRF in rodents promotes anxiety, reduces slow wave sleep, is associated with psychomotor alterations (less time spent in the center of an open field) (Sutton et al. 1982), increased grooming and anhedonia (Dunn et al. 1987; Heinrichs et al. 1991), enhanced novelty-suppressed feeding (Britton et al. 1982), decreased appetite and libido, and decreased exploratory behavior (Berridge and Dunn 1989). These effects of CRF are not mediated by HPA axis activation. This was confirmed using transgenic mouse models where CRF was either knocked out (Muller et al. 2003; Smith et al. 1998; Timpl et al. 1998) or overexpressed, and by using selective CRF receptor antagonists (Steckler and Holsboer 1999).

The role of the CRF system in depression has been supported by clinical studies showing that depressed patients have higher CSF concentrations of CRF (Nemeroff et al. 1984), and depressed patients who died by suicide exhibit increased expression of CRF mRNA in the hypothalamus and PFC (Austin et al. 2003; Merali et al. 2004; Nemeroff et al. 1988; Raadsheer et al. 1994) as well as a reduction in CRF receptor binding density (Owens et al. 1991) and CRF receptor mRNA expression (Merali et al. 2004). Moreover, CSF concentrations of CRF are reduced by electroconvulsive therapy (Nemeroff et al. 1991) and antidepressant treatments (De Bellis et al. 1993; Heuser et al. 1998; Veith et al. 1993). Early relapse of depression is also associated with elevated concentrations of CSF CRF (Banki et al. 1992). Altogether, these findings as well as the neuroendocrine data clearly suggest an overactive CRF/CRF-R1 system in depressed patients (Merali et al. 2004; Nemeroff et al. 1988).

These findings supported the development of CRF receptor antagonists as a new therapeutic strategy for depression (Grigoriadis 2005). Small molecule inhibitors of CRF-R1 have been developed as potential therapies (Holsboer and Ising 2008), because CRF has a 15 times higher affinity for CRF-R1, than CRF-R2. Some CRF-R1 antagonists have been tested clinically, and although there is some evidence for anti-anxiety and antidepressant effects in a few studies without evidence of adverse effects (Ising et al. 2007; Kunzel et al. 2003; Nickel et al. 2003; Zobel et al. 2000),

the results of the randomized controlled studies have been very disappointing (for review Brothers et al. 2012, Koshimizu et al. 2012). Unfortunately none of the studies enriched their studies with patients who hypersecreted CRF.

2.2 Arginine Vasopressin System

(AVP) and oxytocin are cyclic nonapeptides. There are two major AVP systems in the brain: one responsible for AVP-dependent actions on blood pressure and water conservation, comprising the magnocellular neurons in the paraventricular (PVN) and supraoptic nuclei secreting AVP and oxytocin into the peripheral circulation from the posterior pituitary. The second is responsible for the regulation of the HPA axis via the PVN secreting AVP into the hypothalamo-hypophyseal portal circulation (Aguilera and Rabadan-Diehl 2000; Antoni 1993). AVP-expressing neurons in the amygdala also influence memory and behavior (Alescio-Lautier et al. 2000; Caffe et al. 1987), and in the suprachiasmatic nucleus, AVP regulates circadian rhythms (Arima et al. 2002; Kalsbeek et al. 2010; Li et al. 2009). The actions of AVP are mediated through two main G-protein coupled receptors: V1 receptors (V1a and V1b) are coupled to phospholipase C, which increases intracellular Ca^{2+} and protein kinase C activity (Jard et al. 1987), and V2 receptors are coupled to the adenylyl cyclase/protein kinase A pathway to regulate water homeostasis in the kidney (Frank and Landgraf 2008). The mitogen activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) and the phosphatidylinositol 3 kinase (PI3 K)/Akt pathways are also regulated by AVP during neuronal development and survival, synaptic plasticity and memory formation (Chen and Aguilera 2010; Chen et al. 2008, 2009; de Wied et al. 1993). In addition to protecting neurons against apoptosis, AVP inhibits the production of the pro-inflammatory cytokines interleukin-1 and tumor necrosis factor-α in astrocytes, therefore providing another mechanism to protect neurons (Zhao and Brinton 2004).

Using a variety of experimental approaches, it has been clearly shown that AVP is anxiogenic (Neumann and Landgraf 2012). These approaches include central or peripheral administration of V1 receptor antagonists, siRNA, knockout mice, and adenoviral overexpression of V1 receptors (Landgraf 2006; Mak et al. 2012; Pitkow et al. 2001; Ring 2005; Ryckmans 2010; Simon et al. 2008). Hyperactivity of the AVP system shifts behavior towards hyper-anxiety and passive coping. Indeed, some of the untoward consequences of early-life stress appear to be mediated by AVP (Murgatroyd et al. 2010; Veenema et al. 2006).

Because of the close association of anxiety and depression, AVP has been suggested to mediate both conditions. CNS AVP circuits also promote depressive behavior in rats, and these effects are blocked by the administration of antidepressants (Keck et al. 2003). In postmortem tissue of depressed patients, an increase in mRNA expression of AVP and V1 receptors was observed, as well as an increase in the number of PVN neurons expressing AVP (Bao and Swaab 2010;

Wang et al. 2008). It is also important to note that AVP augments the effects of CRF on ACTH release from the anterior pituitary, thereby increasing HPA axis activity (Holsboer et al. 1984). Thus, this may contribute to the hypercortisolemia observed in depression. These anxiogenic and fear effects are thought to act upon a specific population of neurons in the central amygdala in rats (Huber et al. 2005). Intranasal injection of AVP modulates neurons in the prefrontal cortex-amygdala regions, which are thought to mediate threat perception, social behavior, anxiety, and fear processing (Zink et al. 2010).

AVP also regulates affiliative behaviors (Winslow et al. 1993), in particular paternal behaviors in voles, such as crouching over and contacting or grooming pups (Wang et al. 1994). AVP is important in a variety of species for partner preference and pair bonding (Donaldson and Young 2008; Lim and Young 2004) and is thought to influence social memory in males (Ferguson et al. 2002; Lim and Young 2004). AVP also promotes inter-male aggression (Caldwell et al. 2008) and maternal aggression (Bosch and Neumann 2010).

Intranasal administration of AVP has been shown in men to facilitate the encoding of facial identification (Guastella et al. 2010), to have sex-specific influences on social communication, in particular regarding aggression (Thompson et al. 2006). As in animals, AVP promotes stress responses in humans, increasing the cortisol response to social stressors (Shalev et al. 2011). However, the mechanism whereby AVP affects human behaviors remains unknown (McCall and Singer 2012).

Therefore, targeting the AVP system may open new therapeutic avenues. For example, there is an antagonist of V1 receptors (SSR149415) that has shown anxiolytic, antidepressant and anti-stress effects (Griebel et al. 2002; Hodgson et al. 2007; Iijima and Chaki 2007; Litvin et al. 2011; Overstreet and Griebel 2005; Shimazaki et al. 2006; Simon et al. 2008; Stemmelin et al. 2005; Urani et al. 2011). Unfortunately, the clinical trials in depression have been unsuccessful (for review Brothers et al. 2012, Koshimizu et al. 2012). However, SSR149415 also binds the oxytocin receptor (OXTR) (selectivity ratio of 3.2 V1b/OXTR) (Antoni 1986b; Chadio and Antoni 1989; Griffante et al. 2005; Samson and Schell 1995), which explains certain of the effects of this antagonist; oxytocin is known to antagonize the effects of AVP in anxiety and depression (Neumann and Landgraf 2012). Other V1b receptor antagonists are currently under study. The subjacent strategy is to promote the oxytocin system, which has been shown to exert opposite actions of AVP in anxiety and depression by modulating different neuronal circuitry. Although in development, no lipophilic oxytocin receptor agonists have yet to be developed.

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