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Interaction of stress, corticotropin-releasing factor, arginine vasopressin and behaviour

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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 adrenocorticotrophic 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.

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I. 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 neuropeptide 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.

II. 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 adrenocorticotrophic 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; Heim et al., 2008; Yehuda et al., 2005).

II. 1. Corticotrophin releasing factor (CRF) system

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., 2001; Chen et al., 2004; Chen et al., 2000; 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.

II.2. Arginine vasopressin (AVP) 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; Caffé 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 (PI3K)/Akt pathways are also regulated by AVP during neuronal development and survival, synaptic plasticity and memory formation (Chen and Aguilera, 2010; Chen et al., 2009; Chen et al., 2008; 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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References

- Aguilera G. Regulation of pituitary ACTH secretion during chronic stress. *Frontiers in neuroendocrinology*. 1994; 15:321–350. [PubMed: 7895891]
- Aguilera G, Rabadan-Diehl C. Vasopressinergic regulation of the hypothalamic-pituitary-adrenal axis: implications for stress adaptation. *Regulatory peptides*. 2000; 96:23–29. [PubMed: 11102648]
- Alescio-Lautier B, Paban V, Soumireu-Mourat B. Neuromodulation of memory in the hippocampus by vasopressin. *Eur J Pharmacol*. 2000; 405:63–72. [PubMed: 11033315]
- Antoni FA. Hypothalamic control of adrenocorticotropin secretion: advances since the discovery of 41-residue corticotropin-releasing factor. *Endocr Rev*. 1986a; 7:351–378. [PubMed: 3023041]
- Antoni FA. Oxytocin receptors in rat adenohypophysis: evidence from radioligand binding studies. *Endocrinology*. 1986b; 119:2393–2395. [PubMed: 3021442]
- Antoni FA. Vasopressinergic control of pituitary adrenocorticotropin secretion comes of age. *Frontiers in neuroendocrinology*. 1993; 14:76–122. [PubMed: 8387436]
- Arima H, House SB, Gainer H, Aguilera G. Neuronal activity is required for the circadian rhythm of vasopressin gene transcription in the suprachiasmatic nucleus in vitro. *Endocrinology*. 2002; 143:4165–4171. [PubMed: 12399408]
- Austin MC, Janosky JE, Murphy HA. Increased corticotropin-releasing hormone immunoreactivity in monoamine-containing pontine nuclei of depressed suicide men. *Mol Psychiatry*. 2003; 8:324–332. [PubMed: 12660805]
- Banki CM, Karmacsi L, Bissette G, Nemeroff CB. CSF corticotropin-releasing hormone and somatostatin in major depression: response to antidepressant treatment and relapse. *European*

neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 1992; 2:107–113. [PubMed: 1352999]

- Bao AM, Swaab DF. Corticotropin-releasing hormone and arginine vasopressin in depression focus on the human postmortem hypothalamus. *Vitamins and hormones*. 2010; 82:339–365. [PubMed: 20472147]
- Berridge CW, Dunn AJ. CRF and restraint-stress decrease exploratory behavior in hypophysectomized mice. *Pharmacol Biochem Behav*. 1989; 34:517–519. [PubMed: 2623010]
- Bilbo SD, Yirmiya R, Amat J, Paul ED, Watkins LR, Maier SF. Bacterial infection early in life protects against stressor-induced depressive-like symptoms in adult rats. *Psychoneuroendocrinology*. 2008; 33:261–269. [PubMed: 18164556]
- Bosch OJ, Neumann ID. Vasopressin released within the central amygdala promotes maternal aggression. *Eur J Neurosci*. 2010; 31:883–891. [PubMed: 20374286]
- Britton DR, Koob GF, Rivier J, Vale W. Intraventricular corticotropin-releasing factor enhances behavioral effects of novelty. *Life Sci*. 1982; 31:363–367. [PubMed: 6983018]
- Caffe AR, van Leeuwen FW, Luiten PG. Vasopressin cells in the medial amygdala of the rat project to the lateral septum and ventral hippocampus. *J Comp Neurol*. 1987; 261:237–252. [PubMed: 3305600]
- Caldwell HK, Lee HJ, Macbeth AH, Young WS 3rd. Vasopressin: behavioral roles of an "original" neuropeptide. *Progress in neurobiology*. 2008; 84:1–24. [PubMed: 18053631]
- Chadio SE, Antoni FA. Characterization of oxytocin receptors in rat adenohypophysis using a radioiodinated receptor antagonist peptide. *The Journal of endocrinology*. 1989; 122:465–470. [PubMed: 2549159]
- Champagne DL, Bagot RC, van Hasselt F, Ramakers G, Meaney MJ, de Kloet ER, Joels M, Krugers H. Maternal care and hippocampal plasticity: evidence for experience-dependent structural plasticity, altered synaptic functioning, and differential responsiveness to glucocorticoids and stress. *J Neurosci*. 2008; 28:6037–6045. [PubMed: 18524909]
- Chen J, Aguilera G. Vasopressin protects hippocampal neurones in culture against nutrient deprivation or glutamate-induced apoptosis. *J Neuroendocrinol*. 2010; 22:1072–1081. [PubMed: 20673301]
- Chen J, Liu Y, Soh JW, Aguilera G. Antiapoptotic effects of vasopressin in the neuronal cell line H32 involve protein kinase Calpha and beta. *Journal of neurochemistry*. 2009; 110:1310–1320. [PubMed: 19519660]
- Chen J, Young S, Subburaju S, Sheppard J, Kiss A, Atkinson H, Wood S, Lightman S, Serradeil-Le Gal C, Aguilera G. Vasopressin does not mediate hypersensitivity of the hypothalamic pituitary adrenal axis during chronic stress. *Ann N Y Acad Sci*. 2008; 1148:349–359. [PubMed: 19120128]
- Chen Y, Bender RA, Frotscher M, Baram TZ. Novel and transient populations of corticotropin-releasing hormone-expressing neurons in developing hippocampus suggest unique functional roles: a quantitative spatiotemporal analysis. *J Neurosci*. 2001; 21:7171–7181. [PubMed: 11549728]
- Chen Y, Brunson KL, Adelman G, Bender RA, Frotscher M, Baram TZ. Hippocampal corticotropin releasing hormone: pre- and postsynaptic location and release by stress. *Neuroscience*. 2004; 126:533–540. [PubMed: 15183503]
- Chen Y, Brunson KL, Muller MB, Cariaga W, Baram TZ. Immunocytochemical distribution of corticotropin-releasing hormone receptor type-1 (CRF(1))-like immunoreactivity in the mouse brain: light microscopy analysis using an antibody directed against the C-terminus. *J Comp Neurol*. 2000; 420:305–323. [PubMed: 10754504]
- Collins SM, Surette M, Bercik P. The interplay between the intestinal microbiota and the brain. *Nature reviews Microbiology*. 2012; 10:735–742.
- Dayas CV, Buller KM, Crane JW, Xu Y, Day TA. Stressor categorization: acute physical and psychological stressors elicit distinctive recruitment patterns in the amygdala and in medullary noradrenergic cell groups. *Eur J Neurosci*. 2001; 14:1143–1152. [PubMed: 11683906]
- De Bellis MD, Gold PW, Geraciotti TD Jr, Listwak SJ, Kling MA. Association of fluoxetine treatment with reductions in CSF concentrations of corticotropin-releasing hormone and arginine vasopressin in patients with major depression. *The American journal of psychiatry*. 1993; 150:656–657. [PubMed: 8465888]

- de Wied D, Diamant M, Fodor M. Central nervous system effects of the neurohypophyseal hormones and related peptides. *Frontiers in neuroendocrinology*. 1993; 14:251–302. [PubMed: 8258377]
- Dinan TG, Cryan JF. Regulation of the stress response by the gut microbiota: implications for psychoneuroendocrinology. *Psychoneuroendocrinology*. 2012; 37:1369–1378. [PubMed: 22483040]
- Dinan TG, Scott LV. Anatomy of melancholia: focus on hypothalamic-pituitary-adrenal axis overactivity and the role of vasopressin. *Journal of anatomy*. 2005; 207:259–264. [PubMed: 16185250]
- Donaldson ZR, Young LJ. Oxytocin, vasopressin, and the neurogenetics of sociality. *Science*. 2008; 322:900–904. [PubMed: 18988842]
- Dunn AJ, Berridge CW, Lai YI, Yachabach TL. CRF-induced excessive grooming behavior in rats and mice. *Peptides*. 1987; 8:841–844. [PubMed: 3501576]
- Ferguson JN, Young LJ, Insel TR. The neuroendocrine basis of social recognition. *Frontiers in neuroendocrinology*. 2002; 23:200–224. [PubMed: 11950245]
- Frank E, Landgraf R. The vasopressin system--from antidiuresis to psychopathology. *Eur J Pharmacol*. 2008; 583:226–242. [PubMed: 18275951]
- Gillies GE, Linton EA, Lowry PJ. Corticotropin releasing activity of the new CRF is potentiated several times by vasopressin. *Nature*. 1982; 299:355–357. [PubMed: 6287293]
- Griebel G, Simiand J, Serradeil-Le Gal C, Wagnon J, Pascal M, Scatton B, Maffrand JP, Soubrie P. Anxiolytic- and antidepressant-like effects of the non-peptide vasopressin V1b receptor antagonist, SSR149415, suggest an innovative approach for the treatment of stress-related disorders. *Proceedings of the National Academy of Sciences of the United States of America*. 2002; 99:6370–6375. [PubMed: 11959912]
- Griffante C, Green A, Curcuruto O, Haslam CP, Dickinson BA, Arban R. Selectivity of d[Cha4]AVP and SSR149415 at human vasopressin and oxytocin receptors: evidence that SSR149415 is a mixed vasopressin V1b/oxytocin receptor antagonist. *British journal of pharmacology*. 2005; 146:744–751. [PubMed: 16158071]
- Grigoriadis DE. The corticotropin-releasing factor receptor: a novel target for the treatment of depression and anxiety-related disorders. *Expert Opin Ther Targets*. 2005; 9:651–684. [PubMed: 16083336]
- Guastella AJ, Kenyon AR, Alvares GA, Carson DS, Hickie IB. Intranasal arginine vasopressin enhances the encoding of happy and angry faces in humans. *Biol Psychiatry*. 2010; 67:1220–1222. [PubMed: 20447617]
- Hauger RL, Grigoriadis DE, Dallman MF, Plotsky PM, Vale WW, Dautzenberg FM. International Union of Pharmacology. XXXVI. Current status of the nomenclature for receptors for corticotropin-releasing factor and their ligands. *Pharmacological reviews*. 2003; 55:21–26. [PubMed: 12615952]
- Heim C, Newport DJ, Miller AH, Nemeroff CB. Long-term neuroendocrine effects of childhood maltreatment. *JAMA : the journal of the American Medical Association*. 2000; 284:2321. [PubMed: 11066180]
- Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology*. 2008; 33:693–710. [PubMed: 18602762]
- Heinrichs SC, Britton KT, Koob GF. Both conditioned taste preference and aversion induced by corticotropin-releasing factor. *Pharmacol Biochem Behav*. 1991; 40:717–721. [PubMed: 1667823]
- Herman JP, Cullinan WE. Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. *Trends in neurosciences*. 1997; 20:78–84. [PubMed: 9023876]
- Heuser I, Bissette G, Dettling M, Schweiger U, Gotthardt U, Schmider J, Lammers CH, Nemeroff CB, Holsboer F. Cerebrospinal fluid concentrations of corticotropin-releasing hormone, vasopressin, and somatostatin in depressed patients and healthy controls: response to amitriptyline treatment. *Depression and anxiety*. 1998; 8:71–79. [PubMed: 9784981]
- Hodgson RA, Higgins GA, Guthrie DH, Lu SX, Pond AJ, Mullins DE, Guzzi MF, Parker EM, Varty GB. Comparison of the V1b antagonist, SSR149415, and the CRF1 antagonist, CP-154,526, in

- rodent models of anxiety and depression. *Pharmacol Biochem Behav.* 2007; 86:431–440. [PubMed: 17291571]
- Holsboer F, Ising M. Central CRH system in depression and anxiety--evidence from clinical studies with CRH1 receptor antagonists. *Eur J Pharmacol.* 2008; 583:350–357. [PubMed: 18272149]
- Huber D, Veinante P, Stoop R. Vasopressin and oxytocin excite distinct neuronal populations in the central amygdala. *Science.* 2005; 308:245–248. [PubMed: 15821089]
- Iijima M, Chaki S. An arginine vasopressin V1b antagonist, SSR149415 elicits antidepressant-like effects in an olfactory bulbectomy model. *Progress in neuro-psychopharmacology & biological psychiatry.* 2007; 31:622–627. [PubMed: 17229509]
- Ising M, Zimmermann US, Kunzel HE, Uhr M, Foster AC, Learned-Coughlin SM, Holsboer F, Grigoriadis DE. High-affinity CRF1 receptor antagonist NBI-34041: preclinical and clinical data suggest safety and efficacy in attenuating elevated stress response. *Neuropsychopharmacology.* 2007; 32:1941–1949. [PubMed: 17287823]
- Jaferi A, Bhatnagar S. Corticotropin-releasing hormone receptors in the medial prefrontal cortex regulate hypothalamic-pituitary-adrenal activity and anxiety-related behavior regardless of prior stress experience. *Brain Res.* 2007; 1186:212–223. [PubMed: 18001698]
- Jard S, Barberis C, Audigier S, Tribollet E. Neurohypophyseal hormone receptor systems in brain and periphery. *Prog Brain Res.* 1987; 72:173–187. [PubMed: 3039574]
- Joels M, Baram TZ. The neuro-symphony of stress. *Nat Rev Neurosci.* 2009; 10:459–466. [PubMed: 19339973]
- Kalsbeek A, Fliers E, Hofman MA, Swaab DF, Buijs RM. Vasopressin and the output of the hypothalamic biological clock. *J Neuroendocrinol.* 2010; 22:362–372. [PubMed: 20088910]
- Keck ME, Welt T, Muller MB, Uhr M, Ohl F, Wigger A, Toschi N, Holsboer F, Landgraf R. Reduction of hypothalamic vasopressinergic hyperdrive contributes to clinically relevant behavioral and neuroendocrine effects of chronic paroxetine treatment in a psychopathological rat model. *Neuropsychopharmacology.* 2003; 28:235–243. [PubMed: 12589376]
- Korosi A, Baram TZ. The central corticotropin releasing factor system during development and adulthood. *Eur J Pharmacol.* 2008; 583:204–214. [PubMed: 18275957]
- Kunzel HE, Zobel AW, Nickel T, Ackl N, Uhr M, Sonntag A, Ising M, Holsboer F. Treatment of depression with the CRH-1-receptor antagonist R121919: endocrine changes and side effects. *J Psychiatr Res.* 2003; 37:525–533. [PubMed: 14563384]
- Landgraf R. The involvement of the vasopressin system in stress-related disorders. *CNS & neurological disorders drug targets.* 2006; 5:167–179. [PubMed: 16611090]
- Li JD, Burton KJ, Zhang C, Hu SB, Zhou QY. Vasopressin receptor V1a regulates circadian rhythms of locomotor activity and expression of clock-controlled genes in the suprachiasmatic nuclei. *American journal of physiology Regulatory, integrative and comparative physiology.* 2009; 296:R824–R830.
- Lightman SL. The neuroendocrinology of stress: a never ending story. *J Neuroendocrinol.* 2008; 20:880–884. [PubMed: 18601712]
- Lim MM, Young LJ. Vasopressin-dependent neural circuits underlying pair bond formation in the monogamous prairie vole. *Neuroscience.* 2004; 125:35–45. [PubMed: 15051143]
- Litvin Y, Murakami G, Pfaff DW. Effects of chronic social defeat on behavioral and neural correlates of sociality: Vasopressin, oxytocin and the vasopressinergic V1b receptor. *Physiol Behav.* 2011; 103:393–403. [PubMed: 21397619]
- Ma XM, Levy A, Lightman SL. Emergence of an isolated arginine vasopressin (AVP) response to stress after repeated restraint: a study of both AVP and corticotropin-releasing hormone messenger ribonucleic acid (RNA) and heteronuclear RNA. *Endocrinology.* 1997; 138:4351–4357. [PubMed: 9322950]
- Mak P, Broussard C, Vacy K, Broadbear JH. Modulation of anxiety behavior in the elevated plus maze using peptidic oxytocin and vasopressin receptor ligands in the rat. *Journal of psychopharmacology.* 2012; 26:532–542. [PubMed: 21890582]
- Maras PM, Baram TZ. Sculpting the hippocampus from within: stress, spines, and CRH. *Trends in neurosciences.* 2012; 35:315–324. [PubMed: 22386641]

- McCall C, Singer T. The animal and human neuroendocrinology of social cognition, motivation and behavior. *Nat Neurosci.* 2012; 15:681–688. [PubMed: 22504348]
- McEwen BS. Stress, adaptation, and disease. Allostasis and allostatic load. *Ann N Y Acad Sci.* 1998; 840:33–44. [PubMed: 9629234]
- McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev.* 2007; 87:873–904. [PubMed: 17615391]
- Meewisse ML, Reitsma JB, de Vries GJ, Gersons BP, Olff M. Cortisol and post-traumatic stress disorder in adults: systematic review and meta-analysis. *The British journal of psychiatry : the journal of mental science.* 2007; 191:387–392. [PubMed: 17978317]
- Merali Z, Du L, Hrdina P, Palkovits M, Faludi G, Poulter MO, Anisman H. Dysregulation in the suicide brain: mRNA expression of corticotropin-releasing hormone receptors and GABA(A) receptor subunits in frontal cortical brain region. *J Neurosci.* 2004; 24:1478–1485. [PubMed: 14960621]
- Muller MB, Zimmermann S, Sillaber I, Hagemeyer TP, Deussing JM, Timpl P, Kormann MS, Droste SK, Kuhn R, Reul JM, et al. Limbic corticotropin-releasing hormone receptor 1 mediates anxiety-related behavior and hormonal adaptation to stress. *Nat Neurosci.* 2003; 6:1100–1107. [PubMed: 12973355]
- Murgatroyd C, Wu Y, Bockmuhl Y, Spengler D. Genes learn from stress: How infantile trauma programs us for depression. *Epigenetics : official journal of the DNA Methylation Society.* 2010; 5
- Nederhof E, Schmidt MV. Mismatch or cumulative stress: toward an integrated hypothesis of programming effects. *Physiol Behav.* 2012; 106:691–700. [PubMed: 22210393]
- Nemeroff CB, Bissette G, Akil H, Fink M. Neuropeptide concentrations in the cerebrospinal fluid of depressed patients treated with electroconvulsive therapy. Corticotrophin-releasing factor, beta-endorphin and somatostatin. *The British journal of psychiatry : the journal of mental science.* 1991; 158:59–63. [PubMed: 1673078]
- Nemeroff CB, Owens MJ, Bissette G, Andorn AC, Stanley M. Reduced corticotropin releasing factor binding sites in the frontal cortex of suicide victims. *Arch Gen Psychiatry.* 1988; 45:577–579. [PubMed: 2837159]
- Nemeroff CB, Widerlov E, Bissette G, Walleus H, Karlsson I, Eklund K, Kilts CD, Loosen PT, Vale W. Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. *Science.* 1984; 226:1342–1344. [PubMed: 6334362]
- Neumann ID, Landgraf R. Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors. *Trends in neurosciences.* 2012; 35:649–659. [PubMed: 22974560]
- Nickel T, Sonntag A, Schill J, Zobel AW, Ackl N, Brunner A, Murck H, Ising M, Yassouridis A, Steiger A, et al. Clinical and neurobiological effects of tianeptine and paroxetine in major depression. *J Clin Psychopharmacol.* 2003; 23:155–168. [PubMed: 12640217]
- Overstreet DH, Griebel G. Antidepressant-like effects of the vasopressin V1b receptor antagonist SSR149415 in the Flinders Sensitive Line rat. *Pharmacol Biochem Behav.* 2005; 82:223–227. [PubMed: 16181667]
- Pacak K, Palkovits M. Stressor specificity of central neuroendocrine responses: implications for stress-related disorders. *Endocr Rev.* 2001; 22:502–548. [PubMed: 11493581]
- Pitkow LJ, Sharer CA, Ren X, Insel TR, Terwilliger EF, Young LJ. Facilitation of affiliation and pair-bond formation by vasopressin receptor gene transfer into the ventral forebrain of a monogamous vole. *J Neurosci.* 2001; 21:7392–7396. [PubMed: 11549749]
- Raadsheer FC, Hoogendijk WJ, Stam FC, Tilders FJ, Swaab DF. Increased numbers of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of depressed patients. *Neuroendocrinology.* 1994; 60:436–444. [PubMed: 7824085]
- Ring RH. The central vasopressinergic system: examining the opportunities for psychiatric drug development. *Current pharmaceutical design.* 2005; 11:205–225. [PubMed: 15638758]
- Rosengren A, Hawken S, Ounpuu S, Liwa K, Zubaid M, Almahmeed WA, Blackett KN, Sitthi-amorn C, Sato H, Yusuf S. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet.* 2004; 364:953–962. [PubMed: 15364186]

- Ryckmans T. Modulation of the vasopressin system for the treatment of CNS diseases. *Current opinion in drug discovery & development*. 2010; 13:538–547. [PubMed: 20812145]
- Samson WK, Schell DA. Oxytocin and the anterior pituitary gland. *Advances in experimental medicine and biology*. 1995; 395:355–364. [PubMed: 8713991]
- Sawchenko PE, Imaki T, Potter E, Kovacs K, Imaki J, Vale W. The functional neuroanatomy of corticotropin-releasing factor. *Ciba Foundation symposium*. 1993; 172:5–21. discussion 21–29. [PubMed: 8491094]
- Schmidt MV. Animal models for depression and the mismatch hypothesis of disease. *Psychoneuroendocrinology*. 2011; 36:330–338. [PubMed: 20674180]
- Schmidt MV, Scharf SH, Sterlemann V, Ganea K, Liebl C, Holsboer F, Muller MB. High susceptibility to chronic social stress is associated with a depression-like phenotype. *Psychoneuroendocrinology*. 2010; 35:635–643. [PubMed: 19857931]
- Shalev I, Israel S, Uzefovsky F, Gritsenko I, Kaitz M, Ebstein RP. Vasopressin needs an audience: neuropeptide elicited stress responses are contingent upon perceived social evaluative threats. *Hormones and behavior*. 2011; 60:121–127. [PubMed: 21554881]
- Shimazaki T, Iijima M, Chaki S. The pituitary mediates the anxiolytic-like effects of the vasopressin V1B receptor antagonist, SSR149415, in a social interaction test in rats. *Eur J Pharmacol*. 2006; 543:63–67. [PubMed: 16843459]
- Simon NG, Guillon C, Fabio K, Heindel ND, Lu SF, Miller M, Ferris CF, Brownstein MJ, Garripa C, Koppel GA. Vasopressin antagonists as anxiolytics and antidepressants: recent developments. *Recent patents on CNS drug discovery*. 2008; 3:77–93. [PubMed: 18537767]
- Smith GW, Aubry JM, Dellu F, Contarino A, Bilezikjian LM, Gold LH, Chen R, Marchuk Y, Hauser C, Bentley CA, et al. Corticotropin releasing factor receptor 1-deficient mice display decreased anxiety, impaired stress response, and aberrant neuroendocrine development. *Neuron*. 1998; 20:1093–1102. [PubMed: 9655498]
- Steckler T, Holsboer F. Corticotropin-releasing hormone receptor subtypes and emotion. *Biol Psychiatry*. 1999; 46:1480–1508. [PubMed: 10599478]
- Stedenfeld KA, Clinton SM, Kerman IA, Akil H, Watson SJ, Sved AF. Novelty-seeking behavior predicts vulnerability in a rodent model of depression. *Physiol Behav*. 2011; 103:210–216. [PubMed: 21303678]
- Stemmelin J, Lukovic L, Salome N, Griebel G. Evidence that the lateral septum is involved in the antidepressant-like effects of the vasopressin V1b receptor antagonist, SSR149415. *Neuropsychopharmacology*. 2005; 30:35–42. [PubMed: 15367924]
- Stetler C, Miller GE. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. *Psychosomatic medicine*. 2011; 73:114–126. [PubMed: 21257974]
- Sutton RE, Koob GF, Le Moal M, Rivier J, Vale W. Corticotropin releasing factor produces behavioural activation in rats. *Nature*. 1982; 297:331–333. [PubMed: 6978997]
- Swanson LW, Sawchenko PE, Rivier J, Vale WW. Organization of ovine corticotropin-releasing factor immunoreactive cells and fibers in the rat brain: an immunohistochemical study. *Neuroendocrinology*. 1983; 36:165–186. [PubMed: 6601247]
- Thompson RR, George K, Walton JC, Orr SP, Benson J. Sex-specific influences of vasopressin on human social communication. *Proceedings of the National Academy of Sciences of the United States of America*. 2006; 103:7889–7894. [PubMed: 16682649]
- Timpl P, Spanagel R, Sillaber I, Kresse A, Reul JM, Stalla GK, Blanquet V, Steckler T, Holsboer F, Wurst W. Impaired stress response and reduced anxiety in mice lacking a functional corticotropin-releasing hormone receptor 1. *Nat Genet*. 1998; 19:162–166. [PubMed: 9620773]
- Urani A, Philbert J, Cohen C, Griebel G. The corticotropin-releasing factor 1 receptor antagonist, SSR125543, and the vasopressin 1b receptor antagonist, SSR149415, prevent stress-induced cognitive impairment in mice. *Pharmacol Biochem Behav*. 2011; 98:425–431. [PubMed: 21356230]
- van Gaalen MM, Stenzel-Poore MP, Holsboer F, Steckler T. Effects of transgenic overproduction of CRH on anxiety-like behaviour. *Eur J Neurosci*. 2002; 15:2007–2015. [PubMed: 12099906]

- Veenema AH, Blume A, Niederle D, Buwalda B, Neumann ID. Effects of early life stress on adult male aggression and hypothalamic vasopressin and serotonin. *Eur J Neurosci*. 2006; 24:1711–1720. [PubMed: 17004935]
- Veenema AH, Reber SO, Selch S, Obermeier F, Neumann ID. Early life stress enhances the vulnerability to chronic psychosocial stress and experimental colitis in adult mice. *Endocrinology*. 2008; 149:2727–2736. [PubMed: 18308845]
- Veith RC, Lewis N, Langohr JI, Murburg MM, Ashleigh EA, Castillo S, Peskind ER, Pascualy M, Bissette G, Nemeroff CB, et al. Effect of desipramine on cerebrospinal fluid concentrations of corticotropin-releasing factor in human subjects. *Psychiatry research*. 1993; 46:1–8. [PubMed: 8464952]
- Wang SS, Kamphuis W, Huitinga I, Zhou JN, Swaab DF. Gene expression analysis in the human hypothalamus in depression by laser microdissection and real-time PCR: the presence of multiple receptor imbalances. *Mol Psychiatry*. 2008; 13:786–799. 741. [PubMed: 18427561]
- Wang Z, Ferris CF, De Vries GJ. Role of septal vasopressin innervation in paternal behavior in prairie voles (*Microtus ochrogaster*). *Proceedings of the National Academy of Sciences of the United States of America*. 1994; 91:400–404. [PubMed: 8278401]
- Winslow JT, Hastings N, Carter CS, Harbaugh CR, Insel TR. A role for central vasopressin in pair bonding in monogamous prairie voles. *Nature*. 1993; 365:545–548. [PubMed: 8413608]
- Yehuda R, Golier JA, Kaufman S. Circadian rhythm of salivary cortisol in Holocaust survivors with and without PTSD. *The American journal of psychiatry*. 2005; 162:998–1000. [PubMed: 15863805]
- Zhao L, Brinton RD. Suppression of proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha in astrocytes by a V1 vasopressin receptor agonist: a cAMP response element-binding protein-independent mechanism. *J Neurosci*. 2004; 24:2226–2235. [PubMed: 14999073]
- Zink CF, Stein JL, Kempf L, Hakimi S, Meyer-Lindenberg A. Vasopressin modulates medial prefrontal cortex-amygdala circuitry during emotion processing in humans. *J Neurosci*. 2010; 30:7017–7022. [PubMed: 20484643]
- Zobel AW, Nickel T, Kunzel HE, Ackl N, Sonntag A, Ising M, Holsboer F. Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. *J Psychiatr Res*. 2000; 34:171–181. [PubMed: 10867111]