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Gonadal Steroid Hormones and the Hypothalamo-Pituitary-Adrenal Axis

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Abstract

The hypothalamo-pituitary-adrenal (HPA) axis represents a complex neuroendocrine feedback loop controlling the secretion of adrenal glucocorticoid hormones. Central to its function is the paraventricular nucleus of the hypothalamus (PVN) where neurons expressing corticotropin releasing factor reside. These HPA motor neurons are a primary site of integration leading to graded endocrine responses to physical and psychological stressors. An important regulatory factor that must be considered, prior to generating an appropriate response is the animal's reproductive status. Thus, PVN neurons express androgen and estrogen receptors and receive input from sites that also express these receptors. Consequently, changes in reproduction and gonadal steroid levels modulate the stress response and this underlies sex differences in HPA axis function. This review examines the make up of the HPA axis and hypothalamopituitary-gonadal (HPG) axis and the interactions between the two that should be considered when exploring normal and pathological responses to environmental stressors.

Keywords

androgen receptor; estrogen receptor; glucocorticoid; CRF; sex difference; HPA; HPG; dihydrotestosterone; estradiol; testosterone

Introduction

The origins of the study of stress physiology are rooted in the contributions of the early physiologists, Walter Cannon and Hans Selye. It was Cannon who originally coined the term, "fight or flight", when referring to the physiological responses to acute stressors (Cannon, 1915). He later described the concept of homeostasis as a steady state condition that requires active mechanisms to maintain (Cannon, 1932). These pioneering concepts were further explored by Hans Selye who examined the effect of chronic stressors on an

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organism's physiology. Selye's studies into the body's reactions to chronic stressors led to his development of the General Adaptation Syndrome (GAS), a set of nonspecific responses to a stressor which could give rise to pathology after continuous, unrelieved stress.

The pioneering work of Cannon and Selye were closely followed by studies focused on teasing out the biological mechanisms underlying the stress response. These included the demonstration that an anterior pituitary hormone (i.e. adrenocorticotropic hormone; ACTH) can stimulate adrenal glucocorticoid release (Sayers, 1950) and the development of the postulate that pituitary gland function was under neural control (Harris, 1951a; Harris, 1951b). The latter hypothesis was based on Harris' observations of the capillary system that existed connecting the ventral hypothalamus with the anterior lobe of the pituitary. In these pioneering studies, Harris demonstrated that disrupting blood flow from the hypothalamus to the pituitary by pituitary stalk section would impair ACTH release (Fortier et al., 1957), whereas electrical stimulation of the rabbit hypothalamus triggered the release of ACTH into the general circulation (De Groot and Harris, 1950). Harris also showed that pituitary explants were non-functional, yet viable (Harris and Jacobsohn, 1952). Such studies confirmed the importance of the hypothalamus in controlling anterior pituitary function and helped establish the field of neuroendocrinology as a discipline. Further studies by McCann (McCann, 1953) and Porter (Porter, 1953) demonstrated that hypothalamic lesions prevented ACTH release thereby establishing the hypothalamus as the source of the alleged 'releasing factors' that affected pituitary function.

The initial attempts to isolate the putative corticotropin releasing factor (CRF) proved difficult, although initially, the ability of an alternate "CRF", vasopressin, to induce ACTH release was described (McCann and Brobeck, 1954). Hypothalamic releasing factors, such as thyrotropin releasing hormone (TRH), and luteinizing hormone releasing hormone (LHRH, or gonadotropin releasing hormone, GnRH, (Schally et al., 1971a)) were initially isolated in the late '60s and early '70s (Amoss et al., 1971; Burgus et al., 1970; Nair et al., 1970; Schally et al., 1971b; Schally et al., 1971c), yet, it was a decade later when Wylie Vale (Vale et al., 1981) isolated, characterized, and described the biological activity of a hypothalamic peptide that caused the release of ACTH from the anterior pituitary gland. Since then, the 41 amino acid CRF, has been shown to be expressed in many brain areas and has been implicated in a wide variety of behaviors and neurobiological functions (Bale and Vale, 2004). We now know that CRF and vasopressin can be co-localized in some neurons of the paraventricular nucleus of the hypothalamus (Sawchenko et al., 1984; Whitnall and Gainer, 1988), that they can be co-released, and that vasopressin acts to enhance the secretogogue properties of CRF at the anterior pituitary gland (Bilezikjian and Vale, 1987; Gillies et al., 1982; Rivier and Vale, 1983).

Of importance for this discussion are the findings that a number of human neuropsychiatric disorders are accompanied by a dysregulation of the HPA axis and that many of these disorders exhibit profound sex differences in risk implicating a modulatory role for gonadal steroid hormones (Kessler et al., 1993; Kessler, 2003). For example, the incidence of major depressive disorder is at least two fold greater in women than in men (Angold and Worthman, 1993; Kessler et al., 1993; Weissman et al., 1993) and this is associated with enhanced HPA activity associated with a reduced ability to feedback regulate the system

(Ising et al., 2007; Strohle and Holsboer, 2003). In this review, we first examine the HPA axis and its regulatory elements and follow with a discussion of pre-clinical studies showing sex differences in the function of the HPA axis and the well-described role of gonadal steroid hormones in modulating HPA axis responsivity to stress and stress-related behaviors in adulthood.

1. The Hypothalamo-Pituitary-Adrenal (HPA) Axis

1.1 An overview of the HPA axis

Animals respond to real or perceived threats to their welfare by activating neurons that control neuroendocrine responses (e.g. the HPA axis) and the sympathetic autonomic response. For HPA axis activation, the net response is the secretion of glucocorticoids from the adrenal cortex into the general circulation. In humans and many mammals, the main adrenal glucocorticoid is cortisol, whereas corticosterone is the primary glucocorticoid in most rodents. Circulating corticosteroids act on a variety of tissues to mobilize energy stores, induce lipolysis and proteolysis, potentiate vasoconstriction driven by the autonomic nervous system, suppress reproductive function, and alter a number of stress related behaviors; all in an attempt to maintain homeostasis (Herman et al., 2008; Papadimitriou and Priftis, 2009). It is generally thought that many of the responses to acute elevations in glucocorticoids that occur following stressors, such as enhanced cognition and metabolism and inhibition of immune function, are beneficial in the short term as they permit the fight or flight response. By contrast, these same beneficial responses can turn detrimental when the stressor is maintained over long periods of time. Indeed, chronic activation of the HPA axis results in deleterious effects on immune, cardiovascular, metabolic and neural functions and may decrease the viability of neurons and glia to subsequent neurotoxic insults (Jauregui-Huerta et al., 2010; McEwen, 1998; Rajkowska and Miguel-Hidalgo, 2007).

1.2. Anatomy of the paraventricular nucleus (PVN)

The neurons responsible for controlling HPA axis activity reside in the paraventricular nucleus of the hypothalamus (PVN). The PVN represents a collection of neurons in the rostral hypothalamus that is positioned to coordinate neuroendocrine, autonomic and behavioral responses to stressors as well as to maintain energy and water balance (Herman et al., 2008; Levy and Tasker, 2012). The PVN has been most comprehensively studied in the rat brain and reportedly consists of approximately 100,000 neurons in a volume of about $0.5mm^3$. The PVN is arranged in a wing shape structure along the dorsal portion of the third ventricle in the anterior region of the hypothalamus. The initial description of the cytoarchitectural organization of the anterior hypothalamus was made by E.S. Gurdjian (1927). Based upon Nissl stained material, he described a medial group of neurons with small cell bodies, a dense lateral group with medium to large cell bodies, and a dorsal group with unique Nissl staining properties in the area that was later included in the hypothalamic paraventricular nucleus. Bargmann (1949; 1951) later identified the densely packed neurons with large cell bodies (i.e. magnocells) as projecting to the posterior pituitary gland.

Later studies described the PVN based on cytoarchitecture and chemoarchitecture using results from tract tracing, Golgi impregnation, and immunocytochemical approaches

(Armstrong et al., 1980; Swanson and Kuypers, 1980). Based on such parameters, the neurons of the rodent PVN were grouped into subdivisions with each subdivision associated with specific functions (Biag et al., 2012). Furthermore, while there is some controversy regarding the parcellation of the PVN in humans, it seems likely that similar subdivisions also exist based on criteria used for the rat brain (Koutcherov et al., 2000). Moreover, the neurons of the PVN can be further divided by function into three main types. 1) *Neurosecretory parvocellular* neurons which send their axons to the external zone of the median eminence where they secret releasing factors (e.g. CRF, vasopressin, thyrotropin releasing hormone (TSH), somatostatin) into the hypothalamo-hypophyseal portal vasculature to control the secretion of anterior pituitary hormones such as ACTH, TSH and growth hormone (GH). 2) *Neurosecretory magnocellular* neurons which send projections to fenestrated capillaries in the posterior pituitary where they secrete hormones (e.g. oxytocin, vasopressin) directly into the general circulation. 3) *Long-projecting* neurons which send their axons to brainstem and spinal cord regions involved in controlling autonomic and somatosensory function. Moreover, although PVN neurons are largely classified by output, they can further be subdivided by phenotype, afferent input, cell size, density and dendritic morphology (Armstrong et al., 1980; Ju et al., 1986; Kiss et al., 1991; Rho and Swanson, 1989; Swanson et al., 1986; van den Pol, 1982).

The magnocellular neurons of the PVN are largely distributed into two distinct but adjoining areas. The *medial* magnocellular division lies anteromedially within the PVN and contains mostly oxytocin expressing neurons. The *lateral* magnocellular division is comprised largely of a sphere shaped mass of vasopressin expressing neurons that is surrounded by a loop of oxytocin neurons. The majority of these neurons project to the neurohypophysis and are neurosecretory (Rhodes et al., 1981; Swanson and Sawchenko, 1983; Vandesande and Dierickx, 1975).

The parvocellular group of small to medium sized neurons in the PVN send axonal projections to the median eminence. These neurons reside in two main areas of the PVN. The *anterior* parvocellular division extends from the rostral boundary of the PVN to the rostral boundary of the medial magnocellular division, just lateral to the periventricular area. The *medial* parvocellular division lies lateral to the periventricular area and medial to the medial magnocellular division. Neurons in the anterior and medial parvocellular groups project to the median eminence or other hypothalamic and extrahypothalamic regions, with the majority of the CRF peptide found in the median eminence originating from parvocellular PVN neurons (Koegler-Muly et al., 1993; Lind et al., 1985).

Whether in the anterior or medial groups, parvocellular neurons are chemically very diverse and have been shown to express a large list of neuropeptides including, but not limited to: oxytocin, vasopressin, TRH, CRF, angiotensin II, cholecystokinin, cocaine and amphetamine-regulated transcript, enkephalin, galanin, and somatostain (Ceccatelli et al., 1989; Healy and Printz, 1984; Kiss, 1985; Plotsky and Sawchenko, 1987; Suzuki et al., 2001b; Vrang et al., 1999). Although arginine vasopressin (AVP) expression is relatively low in the parvocellular PVN, compared to its expression in magnocellular neurons, it is reportedly co-localized in a majority of CRF neurons, especially after adrenalectomy (Kiss et al., 1984; Sawchenko et al., 1984.; Whitnall and Gainer, 1988)

Most non-neurosecretory neurons of the PVN are found in three main regions: the dorsomedial cap, the ventral PVN, and the posterior PVN (Blair et al., 1996; Ferguson et al., 2008; Swanson, 1977; Swanson and Kuypers, 1980). These neurons largely project to autonomic preganglionic neurons and associated nuclei. The dorsomedial cap sends the majority of its fibers to the lateral gray horn of the spinal column (intermediolateral cell columns), whereas the ventral and posterior regions project to a wide array of brainstem and spinal cord regions including the dorsal vagal motor nucleus, nucleus of the solitary tract, periaqueductal gray, dorsal raphe, locus coeruleus, parabrachial nucleus and ventrolateral reticular nucleus (Hosoya et al., 1991; Luiten et al., 1985; Pyner and Coote, 2000; Saper et al., 1976; Shafton et al., 1998; Shapiro and Miselis, 1985). These descending connections utilize glutamate, gammaaminobutyric acid (GABA) or the various neuropeptides for communication. Of note, the non-neurosecretory neurons of the PVN express a number of neuropeptides including CRF, AVP and oxytocin (Jansen et al., 1995; Milner et al., 1993; Sawchenko, 1987b; Sofroniew and Schrell, 1982). More CRF than AVP neurons of the PVN are long projecting neurons (Sawchenko, 1987b) when detected following colchicine treatment to inhibit axonal transport, and substantially more oxytocin than vasopressin cells were found with long-projecting projections (Sawchenko and Swanson, 1982). Moreover, although the presence of interneurons within the PVN have not been described, axon collaterals from PVN neurons terminate within the PVN and project to other forebrain areas (van den Pol, 1982). Recurrent collaterals from CRF neurons could explain the existence of CRF positive synapses on neurons of the medial parvocellular region and as well as magnocellular and periventricular areas (Hisano et al., 1993; Liposits et al., 1985; Silverman et al., 1989), however, the PVN also receives a dense CRF innervation from neurons in the bed nucleus of the stria terminalis (BnST) (Dong et al., 2001b).

1.3. Regulation of the HPA axis

Acute stress exposure activates the HPA axis resulting in the secretion of corticotropin releasing factors from the PVN (Dunn and Berridge, 1990). CRF causes the release of pituitary ACTH (Antoni, 1986) by binding to CRF-R1 receptors on corticotrophs (Aguilera et al., 2004). ACTH in turn stimulates the biosynthesis and release of glucocorticoids (cortisol in human, corticosterone in rat) by the adrenal cortex (Axelrod and Reisine, 1984; de Kloet, 1984). Ultimately, glucocorticoids bind to their receptors (glucocorticoid receptors, GR) in various tissues including the tissues regulating the HPA axis, thereby reducing the secretion of CRF and ACTH. This negative feedback mechanism (*see below*) is essential for keeping the balance of the HPA axis activity during basal conditions and in response to stress (Tsigos and Chrousos, 2002). Moreover, the changes in glucocorticoids that arise following environmental perturbations can also impact numerous behaviors through actions at other brain regions (Weiser and Handa, 2009, for review see: (Shansky and Lipps, 2013)).

CRF is the primary regulator of ACTH secretion by the anterior pituitary gland. Nonetheless, supporting roles of vasopressin and oxytocin as co-secretagogues have been also demonstrated (Herman et al., 1990; Ring, 2005). Although vasopressin has been originally described as a regulator of osmotic balance, and oxytocin has been considered a principal hormone for parturition, both of these peptides have been now shown to co-localize

with CRF in discrete PVN neuronal populations and are coreleased with CRF (Bondy et al., 1989; Raadsheer et al., 1993; Whitnall and Gainer, 1988) thereby potentiating CRF's secretogogue activity at the level of the corticotroph (Rivier and Vale, 1983; Schlosser et al., 1994). Nonetheless, both vasopressin and oxytocin can stimulate ACTH secretion even in the absence of CRF (Gillies et al., 1982; Schlosser et al., 1994) through the activation of the V1b receptor expressed by corticotrophs (Schlosser et al., 1994). In contrast, when applied directly to the PVN, or following intracerebroventricular injection, oxytocin and vasopressin inhibit HPA responses (Landgraf and Neumann, 2004; Neumann et al., 2000a; Windle et al., 1997), thereby indicating that these neuropeptides can modify PVN function in a paracrine action, perhaps through local release. This is thought to occur through dendritic release of the peptide (Neumann, 2007) resulting in regulatory effects on the PVN that are very different from their actions on the anterior pituitary.

Recent studies have also demonstrated that other regulatory factors are expressed by PVN neurons that can modulate CRF responses. For example, the endocannabinoids, endogenous arachidonate-like lipids, are ligands for cannabinoid receptors (CB_1 and CB_2) that are expressed in brain (Bellocchio et al., 2008). Studies have demonstrated that the CB1 receptor is involved in modulating HPA axis function (Cota et al., 2007). The CB1 receptor is expressed on axon terminals of glutamatergic, GABAergic and monoaminergic neurons and its activation causes suppression of neurotransmitter release to the synapse (Freund et al., 2003). Within the PVN, glucocorticoids cause the release of endocannabinoids which suppress the excitatory inputs to CRF neurons, and this can be blocked with CB1 receptor antagonists (Evanson et al., 2010). Because the endocannabinoids are widely distributed throughout the hypothalamic and limbic circuitries (*see below*), they occupy a unique niche to regulate both excitatory and inhibitory transmitter release, the net result being constraint on HPA activity (Hill et al., 2010). Of particular importance for this discussion, endocannabinoid systems also overlap considerably with receptors for gonadal steroid hormones (for review see: (Gorzalka and Dang, 2012) raising the possibility that this represents an important neuromodulatory system that can be utilized for sex steroid hormone regulation of HPA axis function.

1.4. Stress Integration: neurocircuitry of the HPA axis

The hypophysiotrophic neurons of the parvocellular PVN receive stress-related neuronal input from a variety of sources and integrate that information to produce a relevant response. In addition to neural inputs, it is important to note that these neurons can also respond to the systemic hormonal milieu. The PVN is one of the most vascularized regions of the brain (Herman et al., 2005; Menendez and Alvarez-Uria, 1987; van den Pol, 1982) and the neurovascular development of this area may be influenced by GABA signaling (Frahm et al., 2012). Changes in the neurovascular component of the PVN may reflect functional changes underlying altered neuronal responses to blood-born substances that could modulate autonomic and neuroendocrine function (Tobet et al., 2013). Indeed, it has been shown that glucocorticoid exposure can alter angiogenesis in areas such as the hippocampus and prefrontal cortex (Ekstrand et al., 2008; Neigh et al., 2010). Further, the terminals of PVN neurosecretory neurons are also in place to sample the hypophyseal portal vasculature that is thought to be blood brain barrier deficient (Antoni, 1986; Whitnall, 1993). In contrast, the

dendritic arbors of neurons of the PVN are confined to the boundaries of the PVN (Rho and Swanson, 1989; van den Pol, 1982), thereby restricting the synaptic regulation of PVN neurons to within the PVN whereas the influence of blood-born substances may be more widespread than that of synaptic sampling alone.

Although PVN neurons receive a rather limited number of direct inputs, they receive substantial inputs from neurons in the immediate surround (peri-PVN) and it is this design that may allow greater integration potential. The shell of neurons in the peri-PVN contain substantial numbers of PVN projecting GABA neurons (Roland and Sawchenko, 1993). This architecture raises the possibility that inputs to the PVN are first processed, or filtered, locally prior to contact with the PVN neurons themselves. Application of glutamate to the peri-PVN region results in GABA-dependent inhibition of PVN neurons (Boudaba et al., 1996) indicating that these neurons are inhibitory to CRF neurons. Similarly, the microinjection of glutamate receptor antagonists to the peri-PVN increases the corticosterone response to restraint (Ziegler and Herman, 2000). Peri-PVN neurons show robust c-fos mRNA expression following restraint stress indicating that they are active during the stress response and likely represent an important gating mechanism for signals originating in forebrain and brainstem regions (Herman et al., 2002).

There are a select group of direct inputs to the parvocellular PVN from brainstem neurons that are integral to initiating responses to systemic stressors. The parvocellular PVN is densely innervated with noradrenergic and adrenergic fibers (Cunningham et al., 1990; Hornby and Piekut, 1989; Kitazawa et al., 1987; Liposits et al., 1986; Mezey et al., 1984; Plotsky et al., 1989; Sawchenko and Swanson, 1981) and many of these arise from the locus coeruleus, nucleus of the solitary tract (NTS) and ventrolateral medulla. CRF neurons of the medial parvocellular PVN receive dense noradrenergic innervation primarily from A2 adrenergic cell groups in the NTS (Hornby and Piekut, 1989; Kitazawa et al., 1987; Liposits et al., 1986; Plotsky et al., 1989). A wide array of stressful stimuli increase norepinephrine (NE) release in the PVN, a phenomenon that is negatively correlated with CRF content of the median eminence (indicative of increased CRF release) and positively correlated with ACTH plasma levels (Chen et al., 2004; McIntyre et al., 1999; Pacak et al., 1993; Pacak et al., 1995; Pacak, 2000; Terrazzino et al., 1995). Furthermore, catecholaminergic denervation of the PVN results in an attenuated ACTH response to numerous stressors (Gaillet et al., 1991; Gibson et al., 1986). Accordingly, direct microinfusion of NE into the PVN results in rapid induction of the CRF gene (Cole and Sawchenko, 2002; Itoi et al., 1994; Itoi et al., 1999; Khan et al., 2007). Expression of adrenergic receptors in the PVN is limited to alpha adrenergic receptors, and both alpha(1) and alpha(2) receptors are co-expressed with CRF in the medial parvocellular PVN (Cummings and Seybold, 1988; Day et al., 1997; Day et al., 1999; Sands and Morilak, 1999). However, it appears that alpha(1a) receptors are responsible for the stimulatory effects of NE on CRF (Cummings and Seybold, 1988; Itoi et al., 1994; Khan et al., 2007; Kiss and Aguilera, 1992; Szafarczyk et al., 1987; Whitnall et al., 1993; Windle et al., 1997). The NTS is critical for mediating reflex control of the cardiovascular system and in relaying information on visceral illness and systemic infection (Ericsson et al., 1994; Lawrence and Jarrott, 1996; Seeley et al., 2000). Such perturbations are thought to also recruit the secretion of glucocorticoids to assist in restoring homeostasis.

In addition, glucagon-like peptide-1 (GLP-1) neurons from the NTS have recently been shown to participate in direct activation of parvocellular CRF neurons. These GLP-1 synthesizing neurons in the NTS make direct and dense synaptic connections with a majority of parvocellular CRF neurons (Sarkar et al., 2003; Tauchi et al., 2008), and the GLP-1 receptor is highly expressed in the parvocellular PVN (Gu et al., 2013; Merchenthaler et al., 1999; Shughrue et al., 1996b). Interestingly, the psychogenic stressor, restraint, causes a rapid and substantial decrease in GLP-1 fiber immunoreactivity in the PVN, indicating recent GLP-1 release (Zhang et al., 2009). Intracerebroventricular (ICV) administration of GLP-1 results in the rapid induction of c-Fos immunoreactivity in a majority (>80%) of CRF neurons in the PVN, and a corresponding robust increase in plasma corticosterone concentrations (Larsen et al., 1997). This effect is blocked with ICV pretreatment with a selective GLP-1 antagonist. Furthermore, microinfusion of GLP-1 directly into the PVN results in a dose-dependent increase in plasma corticosterone to levels commonly observed with potent stressors (Kinzig et al., 2003). Recently, GLP-1 has been shown to induce CRF and AVP gene expression in the hypothalamic 4B cell line (Kageyama et al., 2012). These data suggest that stress-activated GLP-1 inputs from the NTS may induce CRF and AVP release from the parvocelluar PVN although this important correlative phenomenon has not yet been directly tested (for a recent review of the role of GLP-1 in stress regulation see (Ghosal et al., 2013)). Other brainstem regions that are critical in autonomic integration and send direct projections to the PVN include the parabrachial nucleus (cardiovascular) and periaqueductal grey (visceral pain) (Behbehani, 1995; Saper, 1995; Sawchenko and Swanson, 1983).

The median and dorsal raphe nuclei of the brainstem also send direct dense serotonergic projections to the parvocellular PVN (Sawchenko et al., 1983). Serotonin (5-HT) receptors are expressed by parvocellular neurons (Zhang et al., 2002) and serotonin's effects are largely stimulatory to PVN output (Van de Kar and Blair, 1999). The 5-HT 2C receptor has been shown to be necessary for 5-HT induced activation of the HPA axis (Heisler et al., 2007). However, activation of 5-HT1A receptors in the PVN also increases ACTH secretion (Rossi et al., 2010), and this effect is desensitized by estradiol treatment. Restraint induced elevations in corticosterone and ACTH can also be inhibited by blocking the 5HT-7 receptor (Garcia-Iglesias et al., 2013). A network of serotonin fibers also surrounds the PVN as well, and serotonin has been shown to inhibit GABAergic synaptic transmission in the PVN (Lee et al., 2008). Therefore, the effect of serotonin on PVN neuron function likely varies depending on where afferent fibers terminate as well as the presence or absence of gonadal steroid hormones.

The parvocellular PVN receives substantial input from other limbic areas. The bed nucleus of the stria terminalis (BnST), a complex group of several related subnuclei, have extensive projections to the PVN (Cullinan et al., 1993; Dong et al., 2001b). These neurons also express estrogen and androgen receptors (Simerly, 1993) and may be critically involved in the modulation of HPA function by sex steroid hormones (*vide infra*). The majority of these PVN-projecting neurons are GABAergic (Cullinan et al., 1993). Lesion studies indicate that these projections inhibit CRF mRNA levels and corticosterone responses to stress (Dunn, 1987; Herman et al., 1994). However, not all of the BnST neurons send inhibitory projections since selective lesions of the anterior or lateral portions of the BnST decrease

ACTH secretion (Gray et al., 1993; Herman et al., 1994). The neurons of the BnST also receive collateral afferents from neurons in the PVN (Dabrowska et al., 2011) thus raising the possibility of extensive feedback loops between the PVN and BnST. Indeed, there is a significant population of CRF producing neurons in the BnST that send projections to the PVN (Dong et al., 2001b; Dong and Swanson, 2006). Moreover, these CRF projections are functional since they have been shown to enhance GABAergic neurotransmission through the activation of CRF receptor 1 in the bed nucleus of the stria terminalis (Kash and Winder, 2006).

Most limbic brain regions such as the hippocampus, prefrontal cortex, medial amygdala and lateral septum that have been shown to modulate HPA axis activity do not directly innervate parvocellular PVN neurons and must act through an intermediary synapse. In general, these areas project to areas like the BnST and peri-PVN which have direct GABAergic input to the PVN (Dong et al., 2001a; Prewitt and Herman, 1998). Thus, the largely glutamatergic output of the hippocampus and prefrontal cortex (Walaas and Fonnum, 1980) is translated into an inhibitory tone on the HPA axis (Diorio et al., 1993; Figueiredo et al., 2003; Herman et al., 1998). On the other hand, amygdaloid projections to the BnST and peri-PVN are largely GABAergic and can work to decrease the inhibition, essentially turning up the gain of the system (Swanson and Petrovich, 1998). By parsing incoming information through direct inputs or by funneling through inhibitory interneurons, the ability to distinguish and grade levels of information in a spatial and context dependent fashion appears to be an effective method of integration by the PVN.

2. Mineralocorticoid and Glucocorticoid Receptors

Following secretion from the adrenal cortex, corticosteroids regulate numerous functions throughout the body, including those of the central nervous system. The actions of glucocorticoids are mediated by two receptors, the type I corticosteroid receptor or mineralocorticoid receptor (MR; also designated NR3C2), and the type II corticosteroid receptor or glucocorticoid receptor (GR, also designated NR3C1). Both of these receptor types are expressed in multiple regions of the mature and developing rat brain (Ahima et al., 1991; Ahima and Harlan, 1990; Cintra et al., 1994; Lawson et al., 1991; McGimsey et al., 1991; Morimoto et al., 1996; van Eekelen et al., 1991). Glucocorticoid receptor and MR actions in the adult and postnatal brain are often in opposition, an example of this can be seen when examining corticosteroid effects on cell death mechanisms in the CNS. In both rodents (Almeida et al., 2000) and in primary cultures of hippocampal neurons (Crochemore et al., 2005) the activation of the GR has been shown to cause a neuroendangering phenotype (a situation where cells are put at risk for subsequent insults that might further impair metabolism), whereas MR activation has been shown to be neuroprotective. Typical of all members of the nuclear receptor superfamily, the classical mechanisms employed by the GR and MR to alter cellular physiology are through the regulation of gene transcription. Since these two receptors share common ligands, the relative binding affinities for the various natural and synthetic glucocorticoids confer a portion of receptor specificity for the initiation of downstream events (Coirini et al., 1985; Sutanto and De Kloet, 1987), in addition to location and circuit specific effects due to distinct receptor localization.

2.1 Glucocorticoid receptor localization

Studies employing autoradiographic binding, in situ hybridization (ISH) and immunohistochemical analyses have identified GR binding, mRNA and protein expression throughout the adult and developing rat brain. In the adult rat brain, both GR mRNA and protein are expressed in the cortex, hippocampus, thalamus, hypothalamus, amygdala, septum, striatum and cerebellum (Ahima and Harlan, 1990; Cintra et al., 1994; McGimsey et al., 1991; Morimoto et al., 1996). The cortex and hippocampus both express the highest levels of GR mRNA and protein. Within the adult rat cortex, GR mRNA and protein expressing neurons are concentrated in the anterior cingulate cortex and retrosplenial cortex (also known as the posterior cingulate cortex). The cingulate cortex laminar layers II, III, and VI have been reported to have the greatest concentration of GR with more than 70% of the cells expressing either the mRNA or protein (Ahima and Harlan, 1990; Aronsson et al., 1988; Cintra et al., 1994; Morimoto et al., 1996). In the adult rat hippocampus, GR is expressed the highest in the hippocampal regions CA1 and CA2 and to a lesser extent in the granule cell layer of the dentate gyrus, with lowest levels in CA3 (Ahima and Harlan, 1990; Aronsson et al., 1988; Cintra et al., 1994; McGimsey et al., 1991; Morimoto et al., 1996). Neurons in the PVN also express GR, perhaps at the highest level of all nuclei in the hypothalamus. Importantly, GR expressing PVN neurons have been shown to express CRF, vasopressin, and most other neuropeptides (Ceccatelli et al., 1989; Liposits et al., 1987; Sawchenko, 1987a; Uht et al., 1988).

The subcellular localization of GR protein has also been established in neurons of the rat brain. Immunoreactive GR predominantly localizes to the cell nucleus with weak cytoplasmic localization (Ahima and Harlan, 1990; Lawson et al., 1991; Morimoto et al., 1996). However, following adrenalectomy, GR is localized to the cytoplasm (Ahima and Harlan, 1990; Morimoto et al., 1996). These localization patterns indicate that circulating corticosterone in the intact animal causes receptor trafficking of the ligand-bound GR to the nucleus whereas, in the absence of ligand, as in the adrenalectomized animal, the unbound GR is found in the cytoplasm.

2.2 Mineralocorticoid Receptor localization

The distribution of MR mRNA and protein in the developing and adult rat brain overlaps with GR expression (Ahima et al., 1991; Lawson et al., 1991; van Eekelen et al., 1991). *In vivo* binding studies using the MR selective ligand, H^3-aldosterone suggested that a majority of MR binding sites in the adult rat brain are found in the hippocampus (Coirini et al., 1985). Similar to GR, MR protein is highly expressed in the adult hippocampus, in regions CA1 and CA2 and to a much lesser extent in the CA3 and dentate gyrus. Curiously, the greatest expression of MR is found in CA2 neurons. Furthermore, MR protein is also expressed at moderate levels in the cortex, including the cingulate cortex, the hypothalamus and subcortical regions. Despite the apparent complete overlap in MR and GR protein in the cingulate cortex, studies have shown that MR protein is confined to only the region of the cingulate cortex located dorsal to the triangular septal nucleus (Ahima et al., 1991).

In addition to the overlap in GR and MR expression within hippocampus and cortex, GR and MR can be co-expressed within individual cells (van Steensel et al., 1996). Further, the brain

regions or cells that express both receptor types are capable of mediating varied responses to the endogenous glucocorticoid. Finally, the expression levels of MR and GR are autologously regulated and are subject to further modulation by gonadal steroid receptors. For example, removal of corticosterone by adrenalectomy increases expression of both MR and GR mRNA in the rat CA1 and dentate gyrus regions of the hippocampus (Burgess and Handa, 1993). The adrenalectomy-induced changes in receptor expression can subsequently be modified by concomitant treatment with the MR selective agonist aldosterone or with estrogen but not androgen treatment (Burgess and Handa, 1993; Kerr et al., 1996). Additionally, GR activation by the selective agonist, RU28362, also attenuates the adrenalectomy induced expression of GR and MR mRNA in the CA1 region, but not the dentate gyrus (Chao et al., 1998).

The main endogenous ligands for GR and MR are the glucocorticoids, cortisol and corticosterone. Both of these hormones bind MR preferentially to GR. The dissociation constants (Kd) of corticosterone for the MR are in the <0.5 nM range whereas the Kd for GR are 4 to 10 times higher (indicative of a lower affinity) than that of MR (Reul and de Kloet, 1985; Sutanto and De Kloet, 1987). The GR and MR are also both able to bind the synthetic glucocorticoid, dexamethasone (DEX). However, unlike the endogenous glucocorticoids, DEX has greater preference for binding for the GR over the MR (Allen et al., 1988; Brinton and McEwen, 1988; Burgess and Handa, 1992). RU28362 is another synthetic glucocorticoid, but it is a selective agonist for the GR, with no apparent binding affinity for the MR (Coirini et al., 1985; Philibert and Moguilewsky, 1983; Quirk and Funder, 1988), and a Kd for the GR in the low nanomolar range.

2.3. Negative feedback regulation of the HPA axis

The HPA axis is governed by a closed-loop negative feedback system typical of most neuroendocrine axes. Glucocorticoid-dependent negative feedback control is essential for the termination of the stress response and reduces the potential for deleterious high amplitude swings in circulating glucocorticoids. Normal HPA function is dependent upon glucocorticoid-mediated negative feedback which is dose and duration dependent (Abe et al, 1980; Sapolsky et al, 2000). Removal of negative feedback by adrenalectomy, for example, results in higher PVN neuropeptide expression and secretion in both the basal and stimulated states (Imaki et al., 1991; Kovacs et al., 1986; Sawchenko, 1987b). Furthermore, negative feedback can inhibit the system by acting at the level of the CRF and AVP neurons of the PVN, through corticotrophs of the anterior pituitary, or indirectly through GR and MR containing brain regions that project to the PVN (Akana et al., 1986; Bradbury et al., 1994; Dallman et al., 1987a; Sawchenko, 1987a). The influence of corticosteroids on the anterior pituitary secretion of ACTH is variable and dependent upon the ligand examined. Corticosteroid effects may further be minimized by the presence of a corticosteroid-binding globulin-like molecule present in corticotrophs (de Kloet et al., 1977), whereas for some synthetic glucocorticoids, the action is largely at the pituitary (Meijer et al., 1998).

Since circulating glucocorticoids can bind either GR or MR, both have been implicated in the negative feedback regulation of the HPA axis, where differential sensitivity to a common ligand appears to allow selective actions. MR has a particularly high affinity for endogenous

glucocorticoids and these receptors are predominantly bound under baseline levels of corticosterone (Reul and de Kloet, 1985; Reul et al., 1990). The hypothesis that MR regulates HPA axis activity during the non-stressed state, is supported by studies showing that adrenalectomy increases basal CRF and ACTH levels (Dallman et al., 1985; Dallman et al., 1987b; Rabadan-Diehl et al., 1997) whereas corticosterone replacement at doses that selectively bind MR returns ACTH levels to normal (Bradbury et al., 1994). Moreover, the hippocampus expresses MR at high levels (Coirini et al., 1985), an observation that suggests that this is a predominant site for HPA regulation during the basal state. Consistent with this, MR antagonists administered directly to the hippocampus elevated basal ACTH and corticosterone levels in a fashion similar to adrenalectomy (Van Haarst et al., 1997). In contrast, in transgenic mice that overexpress MR in the forebrain there is a reduction in the corticosterone response to restraint stress and concomitant decreases in anxiety like behaviors in both males and females (Rozeboom et al., 2007). Thus, collectively, these results suggest that the ratio of MR to GR may be important for regulating HPA reactivity as well as stress related behaviors.

The relatively lower affinity of GR for corticosterone (compared to MR) is thought to direct its actions toward negative feedback following stressors. The GR appears to be largely unoccupied during basal glucocorticoid conditions, but rapidly becomes occupied when glucocorticoid levels increase following stress (Reul and de Kloet, 1985, Reul et al, 1990). Therefore, GR activation allows the return of HPA activity to baseline following high amplitude excursions in corticosteroids, such as following a stressor. Similar to MR, the hippocampal neurons express high concentrations of GR, as does the PVN and the anterior pituitary gland (Ahima and Harlan, 1990; Cintra et al., 1994; McGimsey et al., 1991; Morimoto et al., 1996). HPA axis regulation following a stressor is thought to be mediated through GR in the hippocampus (Sapolsky et al., 1984), amygdala (Shepard et al., 2003) and the hypothalamus (Feldman and Weidenfeld, 2002), with the stress-related increase in corticosterone acting predominantly upon vasopressin neurons of the PVN to initiate the negative feedback regulation of the HPA axis (Kovacs et al., 2000). The importance of GR in negative feedback regulation and behaviors is further emphasized by studies using transgenic mice. Conditional knockout of GR in the forebrain of mice that spare the PVN, causes an increase in basal and stress-responsive corticosterone levels (Kolber and Muglia, 2009) indicating the importance of GR in forebrain sites such as the hippocampus. In contrast, GR overexpression in forebrain did not alter basal ACTH and corticosterone levels, nor their response to mild stress, thus the level of forebrain GR alone is not the only requirement setting the basal tone of the HPA axis (Wei et al., 2004). Selective genetic disruption of GR in the PVN causes enhanced CRH immunoreactivity in the PVN and correspondingly increased levels of ACTH and corticosterone (Jeanneteau et al., 2012), which would be predicted since GR is involved in inhibitory feedback.

Glucocorticoid actions on HPA function occur in several time domains. Fast feedback can occur within seconds to minutes, whereas delayed feedback occurs in the minutes to hours timeframe. The fast feedback component occurs independent of protein synthesis and is mediated at the cell membrane level and may involve endocannabinoids (Dallman, 2005; Hill and Tasker, 2012; Tasker and Herman, 2011) whereas delayed negative feedback is driven by changes in gene expression through classical actions of GR (Pecoraro et al., 2006).

This latter type of feedback has been shown to modulate Ca^{2+} dynamics through DNA dependent alteration in voltage gated Ca^{2+} channels (Joels et al., 2009; Joels and Karst, 2012; Joels et al., 2012). Moreover, in areas like the hippocampus, corticosteroids can influence both excitatory and inhibitory neurotransmission. For example, following corticosterone treatment, CA1 hippocampal neurons have been shown to respond within minutes by increasing miniature excitatory postsynaptic current (mEPSC) frequency (Karst and Joels, 2005) suggesting spontaneous release of glutamate. These effects of corticosterone appear to involve an MR rather than a GR (for review see Joels et al., 2012) and are linked to the ERK1/2 pathway (Olijslagers et al., 2008).

2.4. Circadian influences on the HPA axis

The HPA axis operates under a circadian timing mechanism that is both diurnal and ultradian in nature. Basal levels of corticosteroids undergo daily fluctuations with peak levels attained near the time of lights out in rodents, thereby predicting the onset of activity and feeding (Kalsbeek et al., 2012). At its peak, the diurnal elevations of corticosterone can reach levels that are 5 to 10 times that found at its nadir. In rodents and other nocturnal animals, the nadir in corticosterone secretion is found in the morning, after lights on, whereas this is reversed in diurnal animals and humans. Of importance, ACTH shows a similar, but lower amplitude rhythm throughout the day that can vary by up to several fold when measured from trough to peak (Akana et al., 1986; Dallman et al., 1978; Kalsbeek et al., 1996). It is thought that this dampened rhythm of ACTH compared to corticosterone is partly due to a rhythm in adrenal sensitivity to ACTH (Dallman et al., 1978; Kaneko et al., 1980; 1981). The diurnal rise in glucocorticoids is allowed through a reduction in inhibitory tone from the suprachiasmatic nuclei through projections to the PVN (Kalsbeek et al., 1996; Kalsbeek et al., 2012; Szafarczyk et al., 1983), coupled with an increased adrenal sensitivity to ACTH driven by autonomic inputs, thereby enhancing corticosterone secretion (Oster et al., 2006). Indeed, this concept is supported by studies showing that splanchnic nerve transection can alter adrenal sensitivity to ACTH (Jasper and Engeland, 1997; Ulrich-Lai and Engeland, 2002).

Evidence that CRF plays a role in the diurnal rhythm of corticosterone comes from studies showing that the afternoon increase in corticosterone is absent in CRF-deficient mice (Muglia et al., 1997). However, the rhythm is dependent upon the suprachiasmatic nucleus (SCN) since lesions of the SCN eliminate the daily rhythm in corticosterone (Cascio et al., 1987; Ibuka and Kawamura, 1975). Projections from the SCN that allow it to regulate diurnal function of the neuroendocrine and pre-autonomic neurons in the PVN are thought to be through a vasopressinergic phenotype to the PVN and peri-PVN regions. However, this is still somewhat controversial since AVP gene deletion does not seem to affect the daily corticosterone rhythm (Abel and Majzoub, 2005). However, vasopressin from the SCN inhibits corticosterone release in a nocturnal species (rat) whereas it stimulated corticosterone in a diurnal rodent (Kalsbeek et al., 2008). This may be through differential targets of SCN efferent projections carrying vasopressin. Thus, although there is a close association between the SCN and PVN, the exact mechanisms underlying these interactions have not been completely teased apart.

Glucocorticoids are also secreted in a pulsatile fashion throughout the day with an interpulse interval of approximately 1hr (Lightman et al., 2000). However, these ultradian secretory patterns do not appear to be dependent on the circadian pacemaker since pulsatile secretion is maintained under constant light conditions or after SCN lesions (Waite et al., 2012). Nonetheless, the ultradian pattern is also thought to be dependent upon hypothalamic CRF. In this case, CRF activates a pituitary-adrenal network responsible for the oscillations. Corresponding pulses of CRF are not necessary for the ultradian pattern and elevated levels of CRF appear to disrupt the network. Thus, unlike other neuroendocrine systems, it is the level, not the pattern of CRF secretion that sets the pulsatile dynamics of glucocorticoid secretion (Walker et al., 2012). In turn, the GR has been shown to have an extremely rapid association and dissociation from DNA following activation (Conway-Campbell et al., 2007) and its loss from the nucleus reflects the timing of the 1h pulse of corticosteroid secretion, whereas that of the MR did not. Thus, this MR and GR difference further provides for different patterns of MR and GR binding to sites on DNA and allows multiple cell specific responses (Conway-Campbell et al., 2012).

3. Overview of the Hypothalamo-Pituitary-Gonadal (HPG) Axis

Reproduction, the physiological process that is all-important for the survival of the species, is regulated by a neuroendocrine axis that is parallel to the HPA axis and involves the hypothalamus, anterior pituitary gland and gonads. This hypothalamopituitary-gonadal (HPG) axis is comprised, at its most fundamental element, of GnRH expressing neurons that, in the rodent, are located in the rostral forebrain (medial septum, diagonal band of broca, medial preoptic area, anteroventral preoptic (Jennes and Conn, 1994)). These neurons, through several routes (King et al., 1982; Merchenthaler et al., 1980), send processes to the median eminence to release GnRH into the hypothalamo-hypophyseal portal vasculature where it ultimately acts upon the gonadotropes of the anterior pituitary to stimulate the release of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH). GnRH secretion is pulsatile in nature and this is mirrored by the pulsatile release of luteinizing hormone from the gonadotrophs of the anterior pituitary (Levine et al., 1982; Levine et al., 1991) but this pattern is different from that of ACTH since it possesses an interpulse interval of approximately 30 min. in the rat (Levine and Duffy, 1988) compared to 1 hr for ACTH (Sarabdjitsingh et al., 2010). The pulsatile pattern of GnRH is controlled through the upstream actions of a group of neurons that reside in the arcuate nucleus and express the neuropeptide, kisspeptin (Li et al., 2009), Kisspeptin has been shown to be a potent activator of GnRH secretion affecting both the surge and pulse modes of secretion (Maeda et al., 2010). The pulsatile nature of GnRH is essential for normal gonadotrope function since studies show that the continuous administration of GnRH is unable to stimulate LH secretion (Lincoln et al., 1986; Southworth et al., 1991).

In both sexes, circulating LH stimulates the secretion of steroid hormones from the gonads, although the pulses of LH do not necessarily correspond to elevations in steroid on a one-to-one basis (Ellis and Desjardins, 1982). In the testis, the receptors for LH are found on Leydig cells which synthesize testosterone (T) following LH stimulation.

In the ovary, steroidogenic cells of the follicle are primarily under control of pituitary LH and FSH, which act by binding to their respective high affinity receptors on granulosa and thecal cell membranes. FSH actions are restricted to the granulosa cells where FSH receptors work to activate the aromatase enzyme and allow synthesis of estrogens from aromatizable androgens (testosterone and androstenedione). However, granulosa cells rely upon the thecal cell, whose primary mission appears to be the production of androgens that act as a substrate for estrogen biosynthesis by the granulosa cells. Thecal cell production of androgens is under regulatory control by LH and this forms the basis of the ‘two cell, two gonadotropin” theory of estrogen secretion by the follicle (Gore-Langton and Armstrong, 1994)

4. Gonadal Steroid Receptors

Classical gonadal steroid receptors belong to a “superfamily” of intracellular receptors that act as ligand-activated transcription factors (Evans, 1988). The steroid/thyroid hormone receptor superfamily consists of three main classes (for reviews see (Evans, 1988; Mangelsdorf et al., 1995)). Class 3 comprises the estrogen receptor (ER), androgen receptor (AR), progesterone receptor (PR), GR, and MR. In addition, gonadal steroids have rapid effects through classic and non-classic receptors at the membrane or in the cytosol to influence second messenger pathways and ion channel function which in turn regulates neuronal excitability, regulates cell death, and influences transcriptional activity (Foradori et al., 2008; Vasudevan and Pfaff, 2008) (Figure 1).

4.1 Androgen Receptors

Androgen receptors are responsible for many of the peripheral and central actions of testosterone and its 5-alpha reduced metabolite, dihydrotestosterone (DHT). The androgen receptor (NR3C4: Nuclear Receptor subfamily 3, group C, member 4) is a ligand-activated transcription factor that belongs to the nuclear receptor superfamily. It is activated after binding by either testosterone or DHT, although DHT binds with greater affinity and has a more powerful transcription activation function (Brinkmann, 2011). Subfamily 3 also includes the estrogen, glucocorticoid and progesterone receptors as well. Receptors in this subfamily are characterized by their binding to hormone response elements (HREs) on DNA consisting of two half-sites separated by a three nucleotide spacer. The two half-sites represent inverted repeats, or palindromes, of each other (Denayer et al., 2010). Androgen receptors have also been shown to recognize other non-classical androgen response elements (Denayer et al 2010).

In the unbound state, androgen receptors are found in the cytoplasm of cells (Tyagi et al., 2000), and in neurons they have been described in other cellular locations as well (DonCarlos et al., 2003; DonCarlos et al., 2006; Sarkey et al., 2008). Upon binding to ligand, the cytoplasmic androgen receptor translocates to the nucleus and can be identified in discrete subnuclear compartments, similar to that described for estrogen receptors (Htun et al., 1999; Stenoien et al., 2000).

4.2. Androgen receptor distribution in brain

Early studies utilized *in vivo* autoradiographic approaches with radiolabeled T and DHT to demonstrate specific binding sites in the brain of rodents following administration of a bolus of radiolabelled hormone to the animal. These autoradiographic approaches were able to distinguish high affinity, selective binding sites in the hypothalamus which corresponded with androgen's ability to regulate reproductive neuroendocrine function and behaviors (Sar and Stumpf, 1973; 1977). Later studies using binding assays (Handa et al., 1986; 1987; McGinnis et al., 1983; Roselli, 1991) and in situ hybridization (Simerly et al., 1990) or immunocytochemistry (Kritzer, 2004) demonstrated a unique distribution for AR in the limbic brain. Highest levels of expression are found in hypothalamic areas involved in regulating reproduction, such as the medial preoptic area, ventromedial n. and arcuate n. Moreover, AR was also found in extrahypothalamic regions with implications for regulating neuroendocrine stress responses, stress-related behaviors and autonomic function, such as the BnST, lateral septum, medial amygdala, hippocampus and cortex. Indeed, a role for androgens has been shown for a number of non-reproductive behaviors including cognition and mood, (Hawley et al., 2013) as well as modulating HPA axis reactivity to stress.

4.3. Estrogen Receptors

The genomic actions of estrogens are mediated by two distinct intracellular receptors that function as ligand activated transcription factors. The classical estrogen receptors have been shown to exist in two types, termed estrogen receptor alpha (ERα, NR3A1) and estrogen receptor beta (ERβ, NR3A2). These two estrogen receptor subtypes are encoded by different genes (designated ESR1 and ESR2, respectively), and they are classified together with glucocorticoid and mineralocorticoid receptors based on their signaling pathways through DNA binding.

Similar to other receptors in subfamily 3, the occupancy by estradiol causes estrogen receptor dimerization and subsequent binding to estrogen response elements (ERE) on DNA. ERα and ERβ share similarity in the DNA binding domains (96% homology) and ligand binding domains (56% homology) and bind to the same response elements on DNA (Kuiper et al., 1996). In addition, non-classical mechanisms have been described where ERs can enhance transcription through tethering to other transcription factors. An example of this is the differential interactions of ERα and ERβ with c-Fos, a protein that modulates transcription through the Activator Protein complex (AP-1). Using a simple promoter containing multiple EREs, Paech et al (1997) were able to show that ERα can activate promoters through an adjacent AP-1 site following binding by ER agonists such as estradiol and diethylstilbestrol (DES). In contrast, after estradiol binding, ERβ inhibited transcription through the AP-1 site. Furthermore, when bound by an antagonist, ERβ was a potent transcriptional activator at an AP-1 site. For ERβ, this is also a function of the splice variant expressed (Handa et al., 2012; Price et al., 2001). Thus, the selectivity of the ER signal is dependent, not only upon receptor subtype, but also the ligand and DNA element(s) involved. Similar effects have been shown (*vide infra*) for endogenous promoters such as CRF (Chen et al., 2008; Lalmansingh and Uht, 2008; Miller et al., 2004), vasopressin (Pak et al., 2007), GnRH (Pak et al., 2006), and Oxytocin (Hiroi et al., 2013).

4.4. Estrogen receptor distribution in brain

Estrogen receptors are expressed throughout the rostral-caudal extent of the brain and spinal cord (Simerly and Young, 1991). ERα and ERβ possess overlapping patterns of expression. Brain regions important for HPA and autonomic circuitry that express both forms of ER include the BnST, medial and cortical amygdaloid nuclei, preoptic area, arcuate n.,, parabrachial nucleus, locus ceruleus, nucleus of the solitary tract,. Striking differences in expression patterns between ERα and ERβ are seen in other brain areas. For example, ERα alone is found in the subfornical organ and ERα is more abundant in the arcuate n. and ventromedial n. In contrast, ERβ is found exclusively in the supraoptic n., paraventricular n., suprachiasmatic n., and pineal gland. ERβ appears to be greater in the hippocampus and adult cortex (Chu and Fuller, 1997; Laflamme et al., 1998; Shughrue et al., 1996a). Several studies have also demonstrated that astrocytes and oligodendrocytes can express ERα and ERβ (Azcoitia et al., 1999; Mhyre and Dorsa, 2006; Platania et al., 2003; Santagati et al., 1994; Zhang et al., 2004) although the function of these receptors remain unknown. Recent studies examining ERβ in microglia and astrocytes have suggested an anti-inflammatory property (Saijo et al., 2011; Wu et al., 2013). Thus, the widespread distribution of ERs within limbic brain regions suggests the possibility that they can interact in a number of ways with neuropeptide and glucocorticoid receptors in the regulation of the HPA axis.

4.5. G-protein coupled sex steroid receptors

In addition to its actions in regulating transcription, it has become increasingly clear that estradiol has rapid cellular effects that are mediated by interactions with the cell membrane. To date, although rapid effects of estrogens have been explored in reproductive systems, the examination of membrane mediated gonadal steroid signaling related to the HPA axis is largely missing from the literature. The effects of estradiol to induce rapid changes in second messenger pathways and changes in intracellular Ca2+ concentrations have been described (Chaban et al., 2011; Kelly and Ronnekleiv, 2012) and these non-genomic actions may actually work to potentiate the transcriptional effects of estradiol (Vasudevan et al., 2001). Evidence for membrane sites of estradiol action come from studies showing rapid effects of estradiol that are present even when it is made membrane impermeable by conjugation to bovine serum albumin (BSA), (Schmidt et al., 2000; Vasudevan and Pfaff, 2008). Estradiol treatment has also been shown to potentiate NMDA receptor excitation in hypothalamic neurons (Kow et al., 2005), augment kainate-induced inward currents (Gu and Moss, 1996) and initiate Src/ERK signaling pathway cascades in hippocampal neurons in vitro (Wu et al., 2005). Such data demonstrate that estradiol has actions too rapid to be dependent upon *de novo* protein synthesis, a concept first pioneered by Szego and Davis (1967) in uterine tissues and later by Kelly et al, (1977) for hypothalamus.

The identity of the estrogen receptors that mediate the rapid effects of estradiol are currently being elucidated. A membrane localization of the classical estrogen receptors has been demonstrated by some investigators (Levin, 2005) and the non-selective ER antagonist, ICI 182,780, can block estradiol's rapid induction of calmodulin/kinase activity in hippocampal neurons (Chaban et al., 2004). Further evidence that classical estrogen receptors can have membrane actions comes from studies using a double ER knockout, which do not express ERα or ERβ, and which lose the ability to respond to estradiol with the phosphorylation of

ERK (Abraham et al., 2004). However, these types of responses in knockout animals should be interpreted cautiously since ERs control the expression of a number of genes that may help initiate the membrane responses. Lastly, recent evidence has also demonstrated that ERα can be physically associated with metabotropic glutamate receptors (Micevych and Mermelstein, 2008). ERs are organized with metabotropic glutamate receptors into membrane signaling domains via caveolin proteins in hippocampus (Luoma et al., 2008). Estradiol binding to these membrane ERs can thereby affect metabotropic glutamate signaling independent of glutamate (Grove-Strawser et al., 2010; Meitzen and Mermelstein, 2011; Mermelstein, 2009) thus providing additional evidence for membrane sites of estrogen action.

That estradiol can also have effects on homeostatic mechanisms through modulation of G-protein coupled receptors (GPCRs) has been suggested. Effects of estradiol on autonomic responses, such as control of feeding and core body temperature, can be mimicked by Gαq-signaling ligands like the diphenylacrylamide compound, STX, further implicating specific estradiol effects through G-protein coupled receptors in controlling hypothalamic function (for review see (Kelly and Ronnekleiv, 2013).

Studies have also described an orphan member of the G-protein coupled receptor family, GPR-30 or G-protein coupled estrogen receptor (GPER) that is an integral membrane protein with a high affinity for estradiol (Brailoiu et al., 2007; Filardo et al., 2002). GPER has been shown to couple with Gαs to activate adenylyl cyclase (Prossnitz et al., 2008; Thomas et al., 2005). GPER has also been localized to the endoplasmic reticulum which puts it into an excellent location for regulating intracellular calcium mobilization and synthesis of phosphatidylinositol 3,4,5-triphosphate (Revankar et al., 2005). GPR30 agonists can mimic the desensitizing effects of estradiol on the corticosterone response to the 5-HT1A receptor agonist (+)8-OH-DPAT, and knockdown of GPR30 prevents the estradiol induced decreases in 5-HT1A protein in PVN neurons that accompany this response (McAllister et al., 2012).

Androgens have also been reported to have rapid membrane mediated actions on a number of neuronal cell phenotypes (Foradori et al., 2008; Tabori et al., 2005), and a membrane associated AR similar to the classic AR has been reported in the GT1-7 hypothalamic cell line (Shakil et al., 2002). Androgens and androgen metabolites, such as 3α-diol have been shown to rapidly affect some behaviors, although whether this is through an androgen receptor mediated mechanism is currently debatable (Frye et al., 2010). At present, there is only sporadic evidence for a membrane androgen receptor in brain, whereas a membrane androgen receptor has been described in prostate, colon and breast tumor cells (Gu et al., 2011; Papadopoulou et al., 2009), and BSA conjugated DHT has been shown to have a number of actions on the ERK/MAPK and Akt signaling pathways in these tissues as well as in brain (Gatson and Singh, 2007; Sato et al., 2010). Thus, evidence exists for rapid membrane-initiated signals that may be mediated by a membrane AR (Schmidt et al., 2012) but the protein has yet to be clearly elucidated (for review, see (Foradori et al., 2008)).

5. Gonadal Steroid Control of the HPA Axis

5.1 Sex difference in HPA axis function

Numerous reports have indicated that the function of the HPA axis is different between the sexes, although the direction of this difference is sometimes dependent upon the species being examined. In rodents, basal and stress-induced adrenal glucocorticoid secretion has been reported to be greater in females than in males (Critchlow et al., 1963; Handa et al., 1994a; Kitay, 1963). Activation of the stress response and of PVN neurons is reported to be higher in females than males (Larkin et al., 2010; Seale et al., 2004; Viau et al., 2005), and this could be due to variations in estradiol levels that occur across the estrous cycle of females (Iwasaki-Sekino et al., 2009; Rhodes et al., 2004; Viau and Meaney, 1991). This has been further supported in studies examining the pulsatile patterns of corticosterone secretion, where females show a higher amplitude, frequency and number of corticosteroid pulses compared to males (Seale et al., 2004). Moreover, these sex differences appear to be modulated, not only by the adult gonadal steroid environment, but also after neonatal treatment with testosterone suggesting an organizational effect of gonadal steroids on the neural substrate controlling corticosteroid pulses (Seale et al., 2005a; 2005b). To date, the mechanism(s) by which gonadal steroid hormones may act to influence HPA function have not been completely resolved. Evidence for androgens and estrogens acting in part, by modulating adrenal (Kitay, 1965), anterior pituitary (Coyne and Kitay, 1969; 1971; Viau and Meaney, 2004) and hypothalamic functions (Handa et al., 1994b; Viau and Meaney, 1996; Viau et al., 2001) have been shown. This is exemplified by the considerable overlap in gonadal and adrenal steroid hormone receptor expression within the neural circuitry of the PVN (Figure 2). Its proximity to the third ventricle, dense vascularization, and expression of adrenal and gonadal steroid receptors enable the PVN to weigh stress-related neural input with current endogenous glucocorticoid levels and reproductive status of the animal.

In addition to these direct effects of estrogen on HPA function, the stress response can be indirectly influenced through changes in the expression of circulating proteins that modulate corticosteroid bioavailability following secretion by the adrenal gland. Corticosteroid binding globulin (CBG) is a glycoprotein produced in liver. It has a relatively high binding affinity for corticosteroids and as a result, most corticosteroids in the circulation are found bound to CBG (Westphal, 1983). Only free unbound hormone is available for binding the intracellular receptor or subject to hepatic degradation (Rosner, 1990). Thus, a reported sex difference in the levels of CBG, where males have greater CBG concentrations than females (Westphal, 1971) could act to modulate tissue availability of corticosteroids to brain and thereby influence HPA axis function.

5.2 HPA axis function across the reproductive cycle

Early studies examining sex differences in HPA axis function in rodents described elevated levels of corticosterone in females compared to males (Critchlow 1963). This difference is in part due to the presence of gonadal steroid hormones since there are differences in HPA axis function across the estrous cycle of female rats where the ACTH and corticosterone responses are greatest on proestrus, when estradiol levels are greatest, compared with estrus and diestrus (Viau and Meaney, 1991; Walker et al., 2001). Moreover, estradiol and estradiol

plus progesterone treated animals secreted more corticosterone after stress termination (Viau and Meaney, 1991). Therefore, it appears that enhanced responses to stress are most prevalent in the early part of proestrus when estradiol levels are greatest. Progesterone may reduce the effects of estradiol on HPA axid function as illustrated by studies showing that it prevents E-induced increases in CRH mRNA in the PVN of female monkeys (Roy et al., 1999) and inhibits ACTH release in ewes (Keller-Wood, 1998). Moreover, the neurosteroid, tetrahydroprogesterone can act to prevents the adrenalectomy (ADX) -induced upregulation of AVP mRNA in the PVN of rats (Patchev et al., 1996). Thus, it appears that progesterone functions to inhibit HPA function at certain times of the cycle. Whether or not these effects are mediated by progesterone receptors, or are neurosteroid-like effects of progesterone metabolites (Brunton and Russell, 2011) remains to be determined.

5.3 Estrogen regulation of the HPA axis and mechanisms of action

In female rodents, ovariectomy reduces stress-induced CORT and ACTH secretion and this effect is reversed by estradiol treatment (Burgess and Handa, 1992; Handa et al., 1994a; Serova et al., 2010; Suzuki et al., 2001a; Weiser and Handa, 2009). Consistent with this, implants of a specific estrogen receptor antagonist reduce levels of CORT following restraint stress (Isgor et al., 2003), whereas infusion of estradiol into the brain increases corticosterone responses (Liu et al., 2012; Lund et al., 2006). However, this effect of estrogen is not always consistent and several groups have reported that estrogen can inhibit neuroendocrine responses to stress (Figueiredo et al., 2002; Ochedalski et al., 2007; Young et al., 2001) or have no effect (Babb et al., 2013). Such variation is likely due to the dose and duration of estradiol treatment or the length of time the animal is ovariectomized prior to estradiol treatment (Young et al., 2001). Finally, recent studies indicate that the effect of estradiol can also be influenced by the ER signaling pathway involved since ERα and ERβ can have opposing actions in regulating HPA axis function (*vide infra*).

Insight into the mechanism whereby estradiol modulates HPA axis activity can be deduced by identifying the locations and phenotypes of neurons that express the various forms of ER. ERβ is expressed in some populations of CRF, vasopressin, oxytocin containing neurons in the hypothalamus (Hrabovszky et al., 2004; Laflamme et al., 1998; Suzuki and Handa, 2004). Approximately 85% of oxytocin immunoreactive (-ir) neurons in the PVN have been shown to co-express ERβ (Hrabovszky et al., 2004; Suzuki and Handa, 2004). ERβ is also expressed by a smaller population of CRF –ir neurons in the medial parvocellular PVN and in much larger numbers of CRF expressing neurons in the caudolateral PVN (60–80%; (Laflamme et al., 1998)). Most of these CRF/ERβ expressing neurons appear to be pre-autonomic neurons, however. ERβ is also expressed in vasopressin-ir neurons of the PVN (Sladek and Somponpun, 2004; Somponpun and Sladek, 2002; Suzuki and Handa, 2004). Such data implicate ERβ as a cellular mediator of the direct actions of estradiol on PVN function.

In contrast to ERβ, ERα is not expressed at very high levels by PVN neurons (Laflamme et al., 1998; Simonian and Herbison, 1997; Suzuki and Handa, 2005; Weiser and Handa, 2009), but rather is found at high levels in brain regions that send direct and indirect projections to the PVN such as the peri-PVN, BnST, medial preoptic area, lateral septum,

and hippocampus (Shughrue et al., 1998; Suzuki and Handa, 2005). The limbic distribution of ERα overlaps considerably with ERβ. Moreover, under certain circumstances, such as following chronic food restriction, immunoreactive ER (presumably ERα) has been shown to be expressed by some PVN neurons (Estacio et al., 1996). Therefore, the differing distribution patterns between ERα and ERβ suggest that regulation of the function of the PVN by estradiol can occur through diverse pathways.

The role for ERβ in HPA axis regulation has been explored by the use of ER subtype selective compounds. Treatment of ovariectomized females with the ERβ selective agonist, diarylpropionitrile (DPN), significantly decreases the CORT and ACTH response to stressors (Lund et al., 2005). This effect can also be seen when DPN is placed directly adjacent to the PVN (Lund et al., 2006), an effect that is blocked by the ER antagonist, tamoxifen, thus suggesting a direct action through ERβ containing neurons in the PVN. The effects of systemic administered DPN on the CORT and ACTH response to stress are also present in wild type, but not in ERβ knockout female mice (Oyola et al., 2012), and the effects of DPN can be replicated following treatment with other ERβ selective agonists (Weiser et al., 2009). Taken together, these data demonstrate that the actions of ERβ activation are to reduce the gain of the HPA axis response to an acute stressor.

It is also worthwhile noting that adrenal steroids can influence the expression of ERβ, thereby altering the effect of ERβ signaling on the HPA axis in a parallel feedback fashion. For example, dexamethasone treatment of ovariectomized rats increases ERβ expression in the PVN (Suzuki and Handa, 2004). Similarly, removal of endogenous glucocorticoids by adrenalectomy reduces ERβ mRNA levels in the PVN of female rats, and CORT replacement reverses this effect (Isgor et al., 2003). However, up-regulation of ERβ mRNA was observed only during proestrous when estradiol levels are high. These data suggest that elevated adrenal steroid levels following a stressor may act to increase ERβ expression within the PVN thereby dampening HPA axis reactivity to a subsequent stressor.

In contrast to the effects of ERβ agonists on stress-induced glucocorticoid secretion, treatment with the ERα agonist, propylpyrazoletriol (PPT) increases the CORT and ACTH response to restraint stressors (Liu et al., 2012; Lund et al., 2005; Lund et al., 2006; Serova et al., 2010; Weiser and Handa, 2009). Similarly, treatment with PPT increases stress-induced c-fos mRNA expression in the PVN, an effect that is also blocked by concomitant treatment with tamoxifen (Lund et al., 2006). The effects of ERα activation on HPA axis activity have been explored in much less detail than that of ERβ. However, the results of studies by Weiser and Handa, (2009), indicate that ERα is found in GABAergic peri-PVN neurons and that estradiol can work at the level of the peri-PVN to block the negative feedback regulation of the HPA axis by dexamethasone. These data raise the intriguing possibility that ERα acts to inhibit the negative tone on HPA axis that is provided by GABAergic neurons in the peri-PVN, thereby effectively enhancing the gain of the HPA axis. Such a mechanism (reduction of GABAergic inhibition) is consistent with the mechanism proposed for the increase in hippocampal spine density seen following estradiol treatment (Murphy et al., 1998).

5.4 Androgen regulation of the HPA axis and mechanisms of action

Evidence from physiological studies using gonadectomized and hormone replaced male rodents indicates that androgens provide an inhibitory influence on HPA axis activity (Handa et al., 1994b; Viau and Meaney, 2004). Gonadectomy of male rats results in elevated stress induced CORT and ACTH secretion and this effect is reversible with testosterone or DHT treatment (Handa et al., 1994b; Viau and Meaney, 2004). Androgen treatment has consistently been shown to inhibit HPA axis reactivity in rodents, monkeys and humans (Handa et al., 1994b; Kalil et al., 2013; Rubinow et al., 2005; Toufexis and Wilson, 2012; Williamson and Viau, 2008). Further, treatment with the non-aromatizable androgen, DHT, can also inhibit stress-induced activation of c-fos mRNA in the PVN (Lund et al., 2004b; Seale et al., 2004) suggesting that androgens reduce the gain of the system. The changes in restraint-induced CORT secretion are not accompanied by changes in pituitary sensitivity to CRF (Handa et al., 1994b) nor are there changes in circulating corticosteroid binding globulin (Lund et al., 2004a), thus indicating that these effects of androgen are centrally mediated.

Accompanying the suppression of HPA axis reactivity by androgens is a reduction in CRF-immunoreactivity (ir) in the PVN (Bingaman et al., 1994). Again, by focusing on the distribution of androgen receptors (AR) one can rule in or out some potential sites of androgen action. Androgen receptors are not localized in neuroendocrine neurons within the PVN (Bingaman et al., 1994; Bingham et al., 2006), but rather, AR-ir neurons are found in the dorsal and the ventral medial parvocellular parts of the PVN, which are non-neuroendocrine neurons that project to spinal cord and brainstem pre-autonomic nuclei (Bingham et al., 2006). Studies show that the implantation of testosterone (T) into the medial preoptic area (MPOA) and BnST can reduce the CORT response to acute stress (Viau and Meaney, 1996; Viau, 2002; Williamson and Viau, 2008). Because these brain regions provide afferent input to the PVN, or the peri-PVN, it has been postulated that androgens act through androgen receptors to regulate PVN neuropeptide expression and secretion through a transsynaptic mechanism. In support of this, retrograde tracing studies show that AR-ir are found in neurons of the BnST, MPOA and anteroventral periventricular n. that project to the PVN (Suzuki et al., 2001a; Williamson and Viau, 2007). However, these areas may not be the only brain site(s) mediating androgen's inhibitory effect on HPA reactivity. Androgen treatment has been reported to attenuate the serotonergic activation of the HPA axis perhaps through modulation of hippocampus or lateral septum (Goel et al., 2011). Moreover, stereotaxic application of DHT to a region just above the PVN (to prevent mechanical disruption of the PVN) was as effective as peripherally administered DHT in inhibiting HPA function (Lund et al., 2006). Such results raise the possibility that androgens can work at multiple brain sites to regulate the gain of the HPA axis.

5.5 Steroid metabolism and pre-receptor regulation of HPA axis function

It is now well established that testosterone, the principle circulating androgen in males, can be intracellularly converted to estradiol in brain tissue by the aromatase enzyme (Roselli et al., 1985; Roselli et al., 1997), or to DHT by the 5α-reductase enzyme (5αR; (Lephart, 1993)). Although both testosterone and DHT bind the AR with high affinity, DHT has classically been used in studies of androgen action as it is considered to be a more potent

and selective agonist for ARs and is not a substrate for aromatization to estradiol. However, whether the actions of androgen require such pre-receptor selection of ligand to allow receptor specific actions remains to be determined. 5α reduction of testosterone to DHT is thought to be a necessary step for the inhibitory effects of androgens on HPA function since inhibition of 5α-reductase with finasteride treatment can increase the HPA reactivity to stress in intact males in a fashion similar to gonadectomy. Furthermore, central administration of finasteride can block the effects of testosterone treatment on HPA axis reactivity ((Handa et al., 2013), submitted), suggesting testosterone's effect is mediated centrally by DHT.

Under most conditions, DHT is intracellularly reduced to 5α androstane-3α,17β-diol (3α-diol) or 5α-androstane-3β,17β-diol (3β-diol) (Jin and Penning, 2006; Rizner et al., 2003; Steckelbroeck et al., 2004). Animal studies show that oxidative 3α -hydroxysteroid dehydrogenase (3α-HSD) activity can convert 3α-diol back to DHT and this represents an alternative pathway for DHT synthesis (Ishizaki et al., 2013; Shaw et al., 2006). However, unlike 3α-diol, the synthesis of DHT from 3β-diol is thought to be minimal because 3β-diol is either irreversibly hydroxylated at C-6 and/or C-7 positions or is oxidized to (epi) androsterone (Becker et al., 1973; Gemzik et al., 1992; Ofner et al., 1983), although a recent report indicates that this retro conversion may occur in prostate cancer cells (Ishizaki et al., 2013). Interestingly, 3β-diol exhibits very weak affinity for the AR (T. Lund and R. Handa, unpublished), yet selectively binds and transactivates ERβ (Kuiper et al., 1997). Importantly, it has been suggested that 3β-diol is the endogenous ligand for ERβ in the male since studies in prostate gland show that it inhibits growth in a way that counteracts the growth promoting actions of its precursor, DHT (Weihua et al., 2002).

The conversion of DHT to 3β-diol involves any one of several enzymes, 3α-HSD, 3β-hydroxysteroid dehydrogenase (3β-HSD), 17β-hydroxysteroid dehydrogenase (17β-HSD), 20α-hydroxysteroid dehydrogenase (20α-HSD) (Gangloff et al., 2003; Jin and Penning, 2001; Steckelbroeck et al., 2004; Torn et al., 2003; Weihua et al., 2002). Of interest, the expression of the mRNAs for many of the enzymes in this pathway, including 5αR and cyp7b1 (the enzyme responsible for the metabolism of 3β-diol), have been demonstrated in the PVN (Lund et al., 2006). This raises the unique possibility that biological effects, including effects on HPA axis activity, once attributed to DHT binding to the AR may in part be mediated through conversion to 3β-diol and binding to ERβ. Hence, the local regulation of ligand selection prior to receptor binding and activation become important control points for determining which receptor pathways will be activated.

Similar to the actions of DHT, 3β-diol is a potent inhibitor of HPA axis reactivity (Lund et al., 2004b; Lund et al., 2006). Treatment of gonadectomized mice or rats with 3β-diol can reduce plasma CORT and ACTH responses to stress (Lund et al., 2004a). This effect is not present in ERβ null mice (M Oyola, S. Mani, unpublished observation). This effect of 3β-diol on HPA activity can also be seen after central administration to areas adjacent to the PVN (Lund et al., 2006). In further support of an ER-mediated mechanism, Lund et al (2006) showed that the effects of 3β-diol and DHT are not blocked by the AR antagonist flutamide, but rather, are blocked with tamoxifen, an ER antagonist. Thus, these studies provide an interesting twist to the emerging story concerning the regulatory mechanisms

whereby gonadal steroids influence HPA axis gain. Adjusting the ligand identity prior to receptor binding can work to direct activity through different receptor pathways and thereby fine tune hormone signaling events.

Additionally, 3α- and 3β-diol may have biological actions other than through activation of steroid hormone receptors. In particular, and similar to other 3α-tetrahydrosteroids, such as 3α-hydroxypregnane neurosteroids, 3α diol may be an allosteric mediator of the ionotropic $GABA_A$ receptor (Belelli and Lambert, 2005; Lambert et al., 2001). These effects of 3α tetrahydrosteroids are not shared by the 3β-diastereomers, such as the 3β-hydroxypregnanes, which may be direct noncompetitive blockers of GABA(A) receptors (Wang et al., 2002). Whether these latter effects hold true for 3β-diol, and are relevant for its actions in regulating HPA axis activity, remains to be determined.

6. Molecular Mechanism for Gonadal Steroids in Controlling the HPA Axis

The subfamily of nuclear receptors that contain the steroid hormone receptors are characterized by their ability to regulate transcription by interacting with select DNA response elements. The classically described DNA element is the inverted repeat, a nucleotide sequence that is the reversed complement of another downstream sequence, in which both sequences are separated by a variable number of nucleotides. Alternatively, steroid hormone receptors can act via composite elements, which consist of a hormone response element half-site and a half-site for a monomer of another transcription factor (Malkoski et al., 1997). This type of element has been implicated in the negative glucocorticoid regulation of the CRF promoter (Malkoski and Dorin, 1999). Finally, an ‘alternative’ pathway involves a third type of element, a tethering element, by which one transcription factor regulates, through protein:protein interactions, the activity of another transcription factor that is bound to its DNA-binding site. A good example of this mechanism is seen when ER associates with an AP-1 or SP-1 bound transcription (Kushner et al., 2000; Paech et al., 1997; Safe and Kim, 2008) to alter its specificity. All three of these interactions can be implicated in the estrogen regulation of neuroendocrine neuropeptides (for review see: Handa et al., 2011) that are involved in the control of HPA axis reactivity.

6.1 CRF regulation by estrogen receptors

The molecular mechanisms for the regulation of CRF by estradiol was initially described by Vamvakopoulos and Chrousos (1993) who showed that the human CRF promoter is devoid of classical EREs but ERE half-sites are present. Moreover, earlier studies by Seasholtz et al, (1988) demonstrated that CRF expression is dependent upon a cAMP response element (CRE) in the proximal promoter. The cAMP regulatory element binding protein (CREB) and steroid receptor coactivators (SRC) were found to interact with CREB binding protein (CBP) (McKenna et al., 1999) to regulate transcription through a CRE. Based on these discoveries, ER regulation of gene expression was shown to involve the formation of an ER: SRC: CBP complex (Kushner et al., 2000) and this mechanism remains a possibility for the estrogenic regulation of the CRF promoter as well.

By using a CRF promoter:reporter gene construct, it was shown that the CRF promoter could be activated through estradiol binding to ERβ (Miller et al., 2004). Importantly, the

anti-estrogen, tamoxifen could also activate the promoter through the wild type ERβ, raising the possibility that CRF promoter regulation involves an alternate pathway (Miller et al., 2004). Both ERα and ERβ occupancy the region of the CRE within the CRF promoter increase very quickly following E2 treatment and this corresponded with SRC-1 and CBP occupancy (Lalmansingh and Uht, 2008). Estradiol and DPN have also been shown to increase CRF promoter reporter gene activity in hypothalamic cells whereas the ERα agonist, PPT did not (Ogura et al., 2008). Evidence for regulation of the CRF promoter by other ligands that bind ERβ has also been demonstrated (Huang et al., 2008). 3β-diol also increases CRF promoter activity in a fashion equivalent to that of estradiol suggesting an ERβ mechanism. These effects could be blocked by tamoxifen treatment thus confirming ER involvement. Together, these data demonstrate that the regulation of the CRF promoter can be activated by ERβ and that this may involve an alternate pathway of gene regulation. One caveat to this mechanism is the finding that many CRF expressing neurons in the PVN do not contain ERα or ERβ, thus the significance of these findings is partly tempered by the somewhat restricted overlap between the receptors in question and the neuropeptide targets (Laflamme et al., 1998; Suzuki and Handa, 2005).

6.2 Vasopressin regulation by gonadal steroid receptors

The differential regulation of the vasopressin promoter by ERα and ERβ were originally examined by Shapiro et al, (2000) who showed ERα and ERβ activation through an upstream ERE. ERβ also possesses constitutive activity upon the AVP promoter which is not shared by ERα, although the degree to which this occurs is still arguable (Pak et al., 2007; Shapiro et al., 2000). Treatment with 3β-diol potentiates ERβ mediated AVP promoter activity (Pak et al., 2007), and 3β-diol induced activity may be greater than that of estradiol. In contrast to 3β-Diol, DHT has been shown to suppress the AVP promoter through an androgen receptor dependent mechanism. Thus, the gonadal steroid regulation of the AVP promoter is dependent upon the type of steroid receptor present in the neuron (e.g. AR, ERα, ERβ) as well as the identity of the ligand involved (i.e. DHT, 3β diol, E2), further emphasizing pre-receptor regulatory mechanisms as important factors to consider when examining receptor mediated control of neuronal function.

6.3 Oxytocin regulation by estrogen receptors

Increasing evidence shows that oxytocin is anxiolytic and inhibits the activity of the HPA axis both in females and males (Neumann et al., 2000b; Windle et al., 1997; Windle et al., 2004) when acting at the level of the PVN. Oxytocin treatment also reduces activation of parvocellular PVN neurons in a similar pattern to that shown for ERβ agonists (Lund et al., 2006). For example, ICV administration of oxytocin, decreased anxiety related behaviors, the CORT and ACTH response to stress, and the induction of c-Fos expression in neurons of the PVN (Ochedalski et al., 2007; Windle et al., 2004; Windle et al., 2006). Oxytocin knockout mice show enhanced CORT secretion (Mantella et al., 2004) and increased CRH expression in the PVN (Mantella et al., 2004; Nomura et al., 2003) and central blockade of OTR with des Gly-NH(2) d(CH(2))(5) [Tyr(Me)(2),Thr(4)] OVT, enhances HPA reactivity (Neumann et al., 2000a; Neumann et al., 2000b). Together these studies provide evidence that oxytocin is involved in the central regulation of the HPA axis and thus, oxytocin neurons may be a target for estrogen action.

It has long been known that the oxytocin promoter is under estrogen regulation (Burbach et al., 1994; Richard and Zingg, 1990) (for review see (Burbach et al., 2001)). The primary site of estrogen regulation appears to lie in a complex composite response element that exists between nucleotides −72 to −148 in the rat OT promoter (Adan et al., 1993; Richard and Zingg, 1990). This composite response element is consistent across many species and it contains a variant of an ERE but with no spacing (Burbach et al., 1998). Both the human and rat oxytocin promoters can be stimulated through this site by ERs, thyroid hormone receptors (THRs) and retinoic acid receptors (RARs; (Adan et al., 1993; Burbach et al., 1998; Richard and Zingg, 1990; Richard and Zingg, 1991)). Koohi et al (2005) showed that E2 and ER antagonists bound ERα and activated the bovine OT promoter but not through direct DNA binding, suggesting an alternate pathway. Furthermore, ERα and ERβ are differentially recruited to the OT promoter in a ligand dependent fashion. Using chromatin immunoprecipitation, Sharma et al, (2012) showed that both 3β-diol and E2 increased ERβ occupancy of the composite response element, but with differing time courses that corresponded with their relative efficacy in increasing oxytocin transcript expression. Promoter occupancy by ERα was not apparent after 3β-diol and E2 treatment. This pattern of receptor occupancy of the oxytocin promoter is consistent with the ability of ERβ to increase oxytocin expression in the rat PVN (Hiroi et al., 2013) and activate a human oxytocin promoter / reporter gene construct (Hiroi et al., 2013). The effect of ERβ on the oxytocin promoter is mediated through the composite response element at approximately −160 since targeted mutation of the response element eliminated the response. Moreover, 3β-diol is slightly more effective than estradiol in increasing oxytocin promoter activity through ERβ even though it has a relative binding affinity that is much less than estradiol. Thus, the pattern of promoter activation by estradiol and 3β-diol is consistent with the neuroanatomical findings showing that ERβ is expressed highly in oxytocin neurons of the PVN (Hrabovszky et al., 2004; Suzuki and Handa, 2005). Although ERα may also drive the OT promoter, the absence of its expression in OT neurons (Hrabovszky et al., 2004; Suzuki and Handa, 2005), indicates that this may be a little–utilized pathway, at least for the rodent PVN. Together, these findings support the contention that ERβ may be involved in regulating PVN function and this may underlie the effects of ERβ agonists on HPA reactivity.

The actions of OT are mediated by the OT-receptor (OTR), a member of the G-protein-coupled receptor super-family. OTRs are closely related to the AVP receptors and together are classified as V1a, V1b, V2 or OTR. The V1b receptor and OTR are found extensively in brain and modulate behaviors and HPA axis functions (Vaccari et al., 1998). Of importance, estradiol treatment has been shown to upregulate oxytocin receptors in some brain areas (Champagne et al., 2001), but not the PVN (Patisaul et al., 2003). This effect of estradiol is mediated by ERα (Young et al., 1998), and therefore, because ERα is expressed by few PVN neurons (Suzuki and Handa, 2005), it appears that estradiol may not act to alter OT sensitivity at the level of the PVN.

7. Gonadal Steroid Regulation of Stress-Related Behaviors

7.1 Effects of estrogens on anxiety and depressive like behaviors

Studies examining anxiety and depressive like behaviors in ERα and ERβ knockout (βERKO) mice have generally concluded that ERβ is involved in dampening anxiety and stress related behaviors. The initial clue that ERβ might be involved in regulating anxiety-like behaviors came from studies by Krezel et al, (2001) who demonstrated elevated anxiety in female ERβ null mutant mice in the open field arena and the elevated plus maze. Correspondingly ERβ null mice show increased expression of 5-HT1a receptors, and, as one of the principal 5-HT receptors, the 5-HT1a receptor is a demonstrated regulator of GABA function (Levkovitz and Segal, 1997). Alterations in behaviors in the elevated plus maze were also shown in the βERKO mouse by Imwalle et al, (2005), who also demonstrated corresponding reductions in 5-HT content within the BnST, preoptic area and hippocampus. These findings are supported by those of Donner and Handa (2009) who showed that implants of an ERβ agonist into the dorsal raphe, the main nuclear group synthesizing serotonin in the midbrain, resulted in an upregulation of tryptophan hydroxylase 2 (TPH-2) mRNA, a brain specific variant of TPH, the rate-limiting enzyme in 5-HT synthesis. A recent study has also demonstrated that ERβ agonists can also increase TPH-1 mRNA (Clark et al., 2012). Thus the serotonergic system of the brain is a principal target of ERβ and this may be one mechanism where estradiol can exert actions to modify anxiety and depressive-like behaviors.

Depressive-like behaviors, such as the amount of time struggling, or time to immobility in the forced swim test (Porsolt et al., 1977) are also modulated by estradiol, but the effects of estradiol are lost in βERKO mice further supporting the concept that estradiol's antidepressant actions are mediated through ERβ (Rocha et al., 2005). Similarly, ERβ agonist treatment, whether administered peripherally or by implants directly into the raphe nuclei, has been shown to reduce depressive like behaviors in the forced swim test (Clark et al., 2012; Donner and Handa, 2009) in a fashion similar to treatment following estradiol (Estrada-Camarena et al., 2006; Kandi and Hayslett, 2011). Neuroanatomical evidence also supports a role for ERβ in regulating 5-HT synthesis. More than 90% of ERβ expressing neurons in the dorsal raphe and periaqueductal gray co-express TPH in the mouse (Nomura et al., 2005), Guinea pig (Lu et al., 1999) and the primate (Gundlah et al., 2001). By contrast, few ERα expressing neurons colocalize with markers of 5-HT synthesis (Lu et al., 1999) in guinea pig although others (Nomura et al., 2005; Sheng et al., 2004) report some expression of ERα in 5-HT neurons of the rostral dorsal raphe nucleus of mice. These findings suggest that estradiol acts predominantly through ERβ to modulate serotonin neurotransmission in the dorsal raphe to regulate behaviors, and this may also be reflected by changes in HPA activity.

Studies utilizing subtype specific ER agonists have generally supported the initial observations using knockout animals. In the open field test, ovariectomized females show more anxiolytic behaviors in the open field test and elevated plus maze following treatment with the ERβ agonists, DPN and WAY200070 (Lund et al., 2005; Walf and Frye, 2005; Weiser et al., 2009). That these effects of ERβ agonists on behavior are not found in βERKO

mice, further support the role of ERβ dependent pathways in regulating anxiety and depressive like behaviors (Oyola et al., 2012). Furthermore, the Flinders Sensitive Line (FSL) of rat, a strain selectively bred for showing depressive-like behaviors, exhibit decreased immobility in the forced swim test and increased social interactions following DPN treatment, both anti-depressive signals (Overstreet et al., 2006). The ERβ agonist, WAY200070 has also been shown to have anti-depressant actions in the tail suspension test in male mice (Hughes et al., 2008). Thus, similarities seen in multiple tests of anxiety and depressive-like behaviors and across multiple ERβ agonists consistently implicate ERβ as being a positive modulator for mood.

By contrast to ERβ agonists, treatment with the ERα agonist, PPT has been shown to be anxiogenic in the elevated plus maze and open field apparatus and enhanced depressive-like behaviors in the forced swim test (Lund et al., 2005; Walf and Frye, 2006; Weiser et al., 2009). This was consistent with its actions in enhancing the neuroendocrine response to restraint stress (Lund et al., 2006). Correspondingly, animals with elevated levels of ERα seem to respond to estradiol with anxiogenic types of responses (Spiteri et al., 2012). Taken together, these opposing actions of ERα and ERβ agonists on anxiety and depressive like behaviors in rodent models may help explain previous reports of both anxiogenic and anxiolytic effects following estradiol (Leret et al., 1994; Palermo-Neto and Dorce, 1990). A more thorough description of effects of estradiol on a variety of behaviors and mechanisms of regulation can be found in Gasbarri et al., 2012, and Luine and Frankfurt, 2012.

7.2. Effects of androgens on anxiety and depressive like behaviors

Although the effects of estradiol on mood have been well studied in rodent models, the role of androgens in stress-related behaviors is less well understood. Gonadectomy of male rats, to remove the source of circulating androgens, causes increased anxiety-and depressive –like behaviors that are reversed by systemic testosterone treatment (Adler et al., 1999; Frye and Seliga, 2001; Slob et al., 1981). Treatment with the non-aromatizable androgen, dihydrotestosterone, can also reduce anxiety and depressive like behaviors (Edinger and Frye, 2005; Frye and Wawrzycki, 2003). Further evidence that this effect is mediated by the androgen receptor comes from studies of mice with the testicular feminizing mutation (Tfm). In these animals, a mutation in the AR gene renders the AR protein nonfunctional and they display increased anxiety in the elevated plus maze and open field arena that cannot be reversed by androgen treatment (Rizk et al., 2005; Zuloaga et al., 2008). Similar responses are seen in men following chemical castration for prostate cancer treatment (Almeida et al., 2004) or during the decline in androgen levels that is associated with aging (Amore, 2005). Taken together, these data suggest that androgens are predominantly anxiolytic in nature.

The molecular mechanisms underlying androgen’s effect on mood are not well described in the literature but may involve CRF. A dysregulation of CRF signaling has been suggested in the development of depression and anxiety (Arborelius et al., 1999; Heuser et al., 1998; Reul and Holsboer, 2002). The receptors for CRF, designated CRFR1 and CRFR2 have integral roles in regulating stress sensitivity and alterations in receptor expression can be linked to behavioral disorders (for review see Bale and Vale, (2004)). Specifically, CRFR2 has been

implicated in regulating anxiety type behaviors and it is also expressed in stress responsive regions of the rodent brain, many of which also express androgen receptor (Van Pett et al., 2000). Moreover, the CRFR2 upstream promoter contains EREs and AREs suggesting the possibility of an interaction (Catalano et al., 2003). Examination of androgen receptor dependent increases in CRFR2 mRNA and binding in the male rat forebrain showed that DHT treatment increased CRFR2 mRNA in specific brain regions. The effect of DHT on both receptor binding and mRNA levels was found in the lateral septum. Androgen treatment could also increase CRFR2 expression in primary hippocampal cell cultures, and this could be blocked with the AR antagonist flutamide (Weiser et al., 2008). These data suggest the possibility that androgen regulation of CRFR2 expression may be a potential mechanism whereby ARs modulate stress and stress-related behaviors. Lastly, because the HPA and HPG axis interact considerably, androgen regulation of other behaviors such as aggression, may also influence HPA function (Cunningham et al., 2012).

8. Summary and Conclusions

It is becoming apparent that the ability of the hypothalamus to oversee normal physiology and make rapid adjustments in response to shifts in the environment is swayed by the reproductive status of the animal. Hence, the hypothalamus monitors reproductive state through neurons that express receptors for gonadal steroid hormones. The identification and function of these androgen and estrogen receptor containing neurons and the neuroanatomical and molecular pathways that they utilize to influence neuroendocrine stress reactivity and autonomic function and behaviors are an emergent area of research. Sex differences in homeostatic mechanisms and autonomic responses are the result of developmental programming events as well as differing adult levels of gonadal steroid hormones. These can profoundly impact, not only normal physiology, but also the development of stress-related neuropathology. The body of work tying the changes in gonadal steroid hormones across the lifetime to the efficacy of mounting a stress response to environmental challenges, whether actual or perceived, is still incomplete in animals and in humans. Nonetheless, it is clear that genetic sex and gonadal steroid hormone levels should be taken into account when considering normal homeostatic responses as well as therapeutic approaches to combat stress-related illnesses.

Abbreviations

3β-diol	5alpha-androstane-3beta, 17beta-diol
3α-diol	5alpha-androstane-3alpha, 17beta-diol
5-HT	serotonin
5αR	5-alpha-reductase
ACTH	adrenocortcotropin releasing hormone
AR	androgen receptor
AVP	arginine vasopressin

BnST	bed nucleus of the stria terminalis
BSA	bovine serum albumin
CBP	CREB binding protein
CORT	corticosterone
CRE	cyclic adenosine monophosphate response element
CREB	CRE binding protein
CRF	corticotropin releasing factor
DES	diethylstilbesterol
DEX	dexamethasone
DHT	dihydrotestosterone
DPN	diarylproprionitrile
ER	estrogen receptor
ERE	estrogen response element
FSH	follicle stimulating hormone
FSL	flinders sensitive line
GABA	gamma-aminobutyric acid
GAS	general adaptation syndrome
GH	growth hormone
GLP-1	glucagon-like peptide 1
GnRH	gonadotropin releasing hormone
GPER	G-protein coupled estrogen receptor
GR	glucocorticoid receptor
HPA	hypothalamo-pituitary-adrenal
HPG	hypothalamo-pituitary-gonadal
HRE	hormone respone element
HSD	hydroxysteroid dehydrogenase
ICV	intracerebroventricular
ir	immunoreactive
ISH	in situ hybridization

LH	luteinizing hormone
LHRH	luteinizing hormone releasing hormone
MPOA	medial preoptic area
MR	mineralocorticoid receptor
NTS	nucleus of the solitary tract
PPT	propylpyrazoletriol
PR	progesterone receptor
PVN	paraventricular nucleus
RAR	retinoic acid receptors
SCN	suprachiasmatic nucleus
SRC	steroid receptor coactivators
T	testosterone
Tfm	testicular feminizing mutation
THR	thyroid hormone receptors
TPH	tryptophan hydroxylase
TRH	thyrotropin releasing hormone
TSH	thyroid stimulating hormone

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Highlights

- The HPA axis is a complex neuroendocrine loop that integrates stressor-related information.
- Sex differences in the HPA axis arise through effects of gonadal steroid hormones.
- Estrogen can alter HPA function though divergent actions mediated by ERalpha and ERbeta.
- Androgens inhibit HPA function through actions at the androgen receptor or ERbeta.

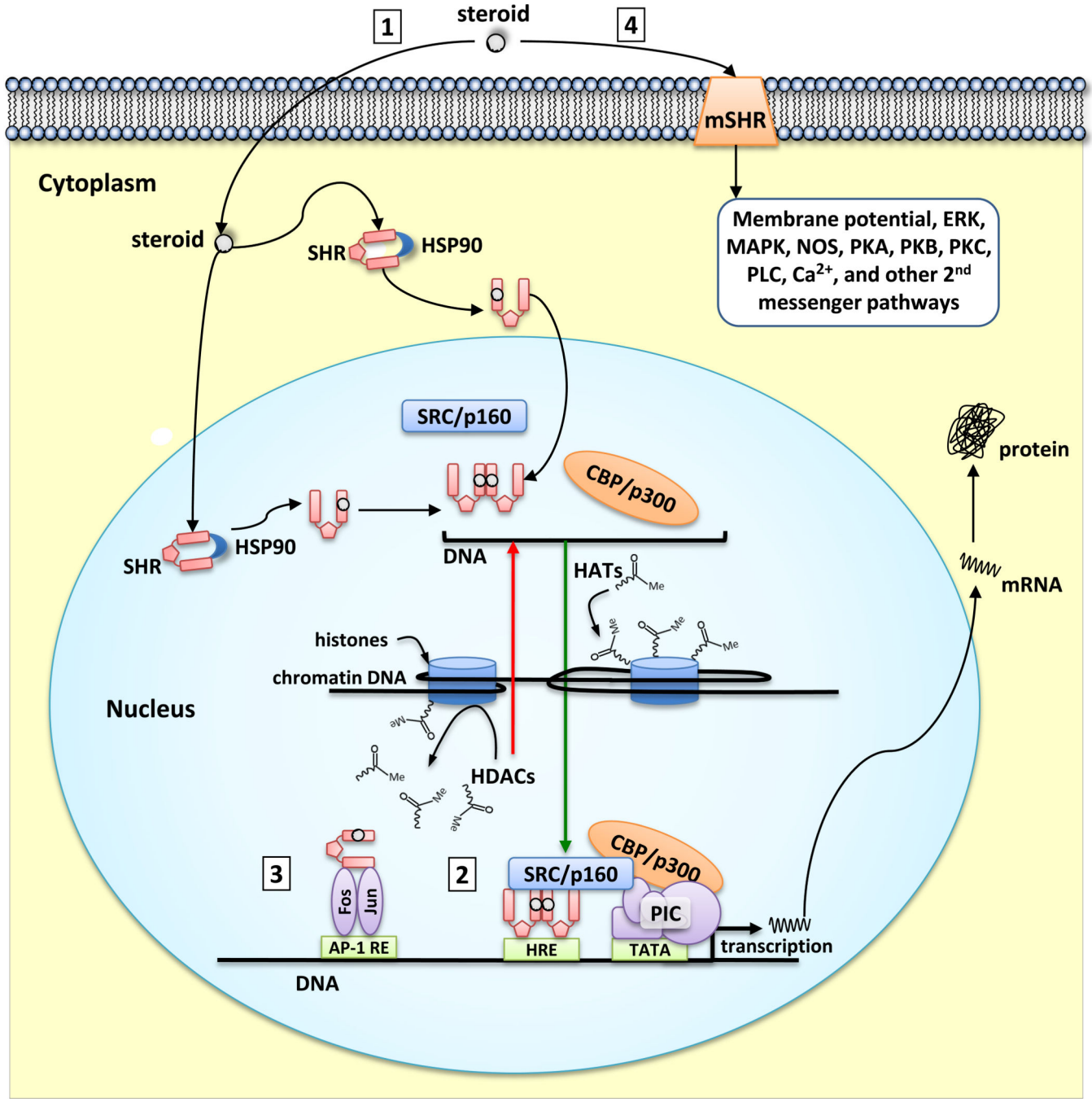

Figure 1.

Diagrammatic representation of the various Intracellular actions of steroid hormone receptors. (1) Steroids can freely diffuse through the plasma membrane lipid bilayer and bind to a steroid hormone receptor (SHR) associated with heat shock protein (HSP90) in the cytoplasm or nucleus. Steroid binding leads to the release of HSP90 and translocation of the SHR to chromatin DNA. (2) SHR homo- or heterodimers recruit coregulatory proteins such as the p160 and p300 family of coactivators. These coactivators have intrinsic histone acetyl transferase (HAT) activity and can acetylate histones associated with inactive chromatin to

uncoil DNA and expose regulatory regions and transcription initiation sites of target genes. The SHR dimer then binds to a regulatory region (e.g., hormone response element, HRE) and in association with these coregulatory protein factors (e.g., SRC, CBP) can stimulate transcription through activation of the pre-initiation complex (PIC). Transcription can subsequently be inhibited by the activity of histone deacetylases (HDACs), which act to remove acetyl groups from histones and promote chromatin recoiling. (3) Steroid-bound receptor can also act as a coactivator or corepressor and affect gene expression by tethering to other DNA bound transcription factors (e.g. fos and jun at an AP-1 response element). (4) Steroids have effects attributable to actions at a membrane-associated steroid hormone receptor (mSHR). These receptors can be classic SHRs tethered to the membrane, G-protein coupled receptors, or ion channels. These effects are diverse and include alterations in membrane potential and second messenger pathways. AP-1 RE, activator protein 1 response element; Ca^{2+}, calcium; CBP, cyclic adenosine monophosphate response element binding protein (CREB) binding protein; ERK, extracellular regulated kinase; HAT, histone acetyl transferase; HDAC, histone deacetylase; HRE, hormone response element; HSP90, heat shock protein 90; MAPK, mitogen-activated protein kinase; mSHR, membrane-associated steroid hormone receptor; NOS, nitric oxide synthase; PIC, pre-initiation complex; PKA, protein kinase A; PKB, protein kinase B; PKC, protein kinase C; PLC, phospholipase C; SHR, steroid hormone receptor; SRC, steroid receptor coactivator; TATA, core promoter sequence.

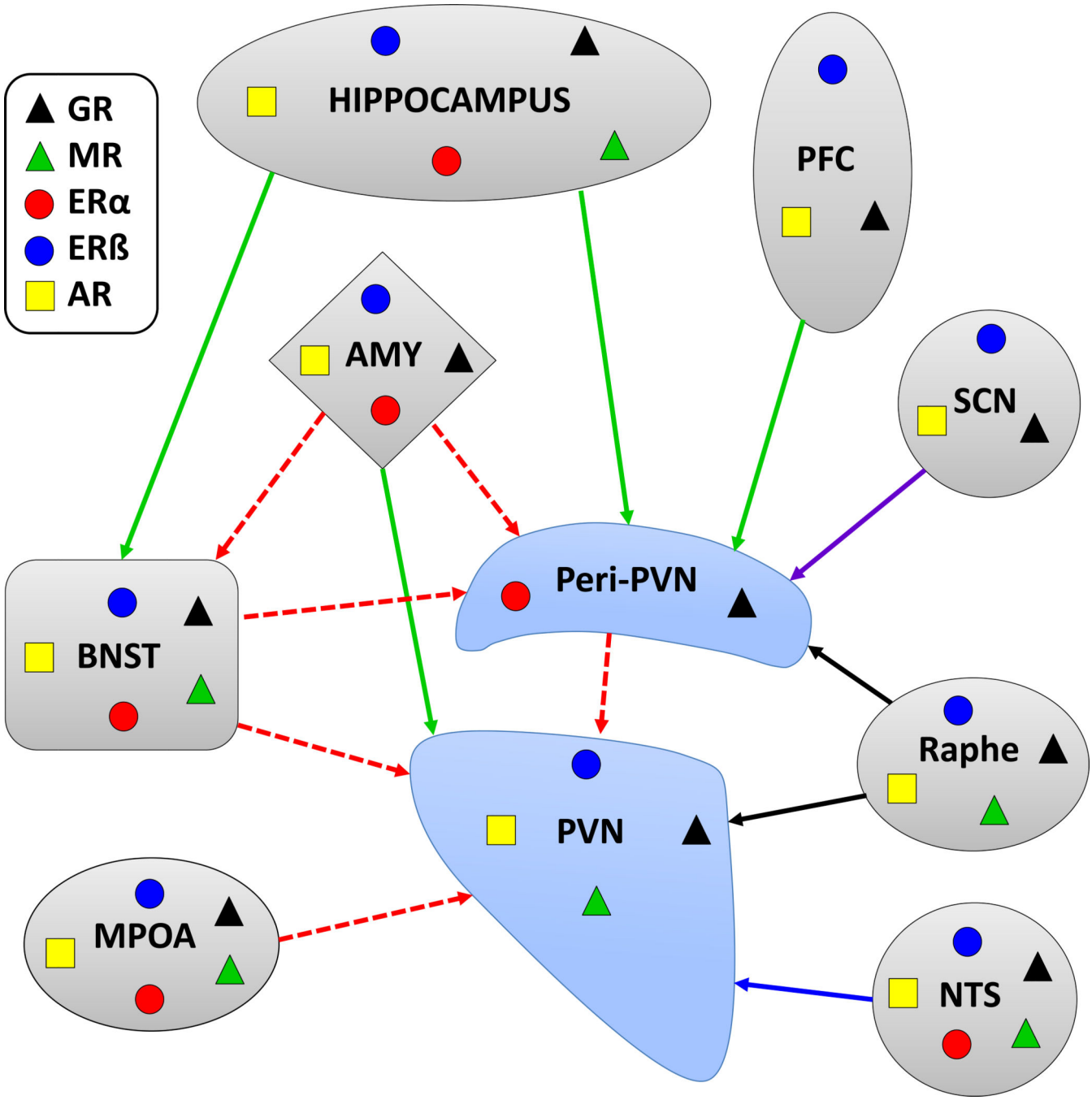

Figure 2.

Distribution of gonadal and adrenal steroid hormone receptors in relationship to inputs to HPA circuitry. Gonadal and adrenal steroid hormone receptors have considerable overlap in expression within brain regions that have direct inputs to the paraventricular nucleus (PVN) and peri-PVN. The brain regions involved and the overall influence on the output of the PVN depends upon stressor modality (psychogenic, limbic; homeostatic, brain stem) and gonadal steroid hormone levels derived from systemic and/or local *de novo* sources. Green solid arrows indicate excitatory glutamate connections. Red dashed arrows indicate

inhibitory gamma-aminobutyric acid (GABA) connections. Black arrow indicates serotonergic connections. Blue arrow indicates mixed norepinephrine and glucagon-like peptide 1 connections. Purple arrow indicates mixed GABA and arginine vasopressin connections. AMY, amygdala; AR, androgen receptor; BNST, bed nucleus of the stria terminalis; ERα, estrogen receptor alpha; ERβ, estrogen receptor beta; GR, glucocorticoid receptor; MPOA, medial preoptic area; MR, mineralocorticoid receptor; NTS, nucleus of the solitary tract; PFC, prefrontal cortex; PVN, paraventricular nucleus; Raphe, dorsal raphe nucleus; SCN, suprachiasmatic nucleus.