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The endocrine nervous system: Source and target for neuroactive steroids

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ABSTRACT

For a long time the endocrine brain was considered to be the hypothalamus and to its special relationships with the hypophysis. The discovery of the wide distribution of steroid hormone receptors, as well as that of the possibility of metabolizing or synthesizing steroids by neural cells (neuroactive steroids), suggest, on the contrary, that interactions among steroids and nervous system are key points of the regulatory processes in the central and peripheral nervous system in normal conditions as well as in pathological conditions. In this brief overview we illustrate a few examples of these relationships with major emphasis on papers collected in this special issue.

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Several studies performed during the last century have illustrated the role of the brain as part of the endocrine system. The pioneering studies of Ernst and Bertha Scharer demonstrated the presence of so called neurosecretory neurons in the hypothalamus of all vertebrates (for a review see [Scharer, 1987](#)). In mammals, these neurons are clustered in two main groups denominated supraoptic and paraventricular nucleus. The magnocellular elements of these two nuclei produce two small peptides: oxytocin and vasopressin (vasotocin and mesotocin in other vertebrates) ([Dierickx, 1980](#)). These peptides are synthesized within the cell bodies, transported along the axons to the neurohypophysis and finally released into the blood ([Brownstein et al., 1980](#)).

For many years, the hypothalamo-neurohypophyseal system was considered a singularity. This view was reinforced by the discovery of other (parvocellular) secretory neurons sending their axons to the median eminence, releasing their peptides into the hypothalamo-hypophyseal circulatory system, and controlling the activities of hypophyseal cells. Only several years after these earlier studies did researchers

understand that the hypothalamic parvocellular hypophysiotropic neurons were the first examples of a large and variable population of neurons (today collectively called peptidergic neurons) distributed in the whole central, autonomic, and peripheral nervous system. Further studies elucidated that these peptides (named today neuropeptides) play several roles in neuronal communication (for a recent review, see [Guillemin, 2005](#)).

This early view of the endocrine brain was therefore indicative of a role for hypothalamus and adjacent regions as an endocrine gland chiefly dedicated to the control of the hypophysis. According to this hypothesis, the hypothalamic cells should be controlled by the hormones produced by the peripheral target glands (feedback control).

Two of the main axes regulated in this way are the hypothalamo-hypophyseal-gonadal and the hypothalamo-hypophyseal-adrenal axis ([De Kloet and Voorhuis, 1992](#)). In both cases the peripheral glands produce steroid hormones (corticosteroids, androgens, estrogens, progestins ([Fink et al., 1991](#))). For this reason several pioneering studies

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investigated the presence and distribution of steroid hormone receptors within the central nervous system by binding autoradiography (Kim et al., 1978; Morrell et al., 1975; Stumpf et al., 1975) and considered the brain as one of the main targets for the action of steroid hormones (McEwen et al., 1979). Also in this case, the first idea of a limited expression of steroid hormone receptors chiefly within the hypothalamus was erroneous, as demonstrated by the presence of these receptors in several brain regions, such as the amygdala, the hippocampus, the cerebral cortex, the midbrain, the cerebellum, the medulla, or the spinal cord, in variable quantities according to the location and the age (Jordan et al., 1997; Merchenthaler et al., 2004; Mitra et al., 2003; Murphy et al., 1999; Ozawa, 2005).

Steroid hormone receptors act, when linked to the specific hormone, at the level of the genome, inducing or repressing transcription within different nuclei. This is now called the classical action of steroid hormones and involves a direct genomic action of steroid hormones on neural circuits, both inducing neural differentiation during the development and regulating their activity in adult animal. For instance, the actions of estrogen are mediated by two distinct estrogen receptor (ER) systems, ER alpha (ER α) and ER beta (ER β) (Enmark and Gustafsson, 1999). In the brain, ER α plays a critical role in regulating reproductive neuroendocrine function and behavior (Rissman et al., 1997).

Several important aspects of animal physiology originated from the interaction among steroid hormones and the nervous system. One main feature is the role played by estrogens in the control of the GnRH system. Rather surprisingly, estrogens cannot act directly on GnRH cells, but they regulate the activity of hypothalamic/preoptic neurons that project on the GnRH-expressing neurons. This circuit was at first hypothesized on the basis of the lack of coexistence among ER α and GnRH neurons (Shivers et al., 1983), but only recently have papers elucidated part of these circuits. In particular, the dominant populations of ER α -expressing neuronal afferents to GnRH neurons are located in a periventricular continuum referred to as the rostral periventricular area of the third ventricle (RP3V). The RP3V neurons are positively regulated by estrogens and express glutamate, GABA, kisspeptin, and neurotensin (see Herbison, 2008). There is growing evidence that among these neurotransmitters and neuropeptides, kisspeptin may play a central role (Dungan et al., 2006). In different mammalian models, kisspeptin neurons are located both in the anteroventral periventricular nucleus (AVPV, rodents) and in the arcuate nucleus (sheep) and play a role in the positive feedback regulation of GnRH secretion (see Smith, 2008).

Among the numerous steroid-dependent neural pathways that have been investigated, the vocal communication controlling pathways have been the subject of many studies in recent years. Non-mammalian model systems have provided interesting examples of how motor and sensory systems, respectively, produce and encode communication signals. These same models, mainly developed for a few species of fish, amphibians, and birds, have proven to be equally important for demonstrating how steroids and other hormones shape the neural mechanisms of vocal communication (see Bass, 2008).

A definitive role for ER β in any neurobiological function is still under discussion (Pettersson and Gustafsson, 2001). A number of splice variants of ER β mRNA have been reported in brain tissue, and their amounts vary depending upon brain region. Examination of neuropeptide promoter regulation by ER β splice variants demonstrates that ER β functions as a constitutively active transcription factor, and recent studies implicate ER β as an important modulator of some non-reproductive neurobiological systems (see Weiser et al., 2008).

In addition to ERs, recent studies, mainly based on the use of genetic males affected by the testicular feminization syndrome (Tfm), led to the identification of a parallel role for non-aromatized gonadal steroids acting through the androgen receptor (AR) in the differentiation of neuronal systems such as the olfactory pathway of rodents (see Bodo, 2008).

One of the recently discovered roles of gonadal hormones is the regulation of neurogenesis within the central nervous system, not only during development but also in adult life (McEwen, 1994). A major target of this action is the hippocampus, where gonadal hormones may modulate neurogenesis in the dentate gyrus differentially in male and female adult rodents (see Galea, 2008); however, newly proliferated neurons have also been documented in other brain regions, including the amygdala and hypothalamus (see Fowler et al., 2008).

Because of their important roles, any event that may alter the steroid balance in the organism has a potential dangerous effect on brain functions and development. This has been recently illustrated by studies showing alterations in development of brain circuits and related behaviors in a variety of animal models as a consequence of early exposure to chemicals that can bind to steroid hormone receptors and that are present in the environment (endocrine disrupting chemicals, EDCs) (Panzica et al., 2005). Major models for testing the actions of these compounds are the rodent hippocampus and preoptic sexually dimorphic nuclei, or several hypothalamic systems in birds including the parvocellular vasotocin system (see Ogiue-Ikeda et al., 2008; Ottinger et al., 2008; Patisaul and Polston, 2008). In addition to alterations in brain circuits, exposure to EDCs during embryonic development may impact several behaviors. These behavioral alterations have the advantage of revealing both direct and indirect effects of exposure to an EDC and in some cases provide a valuable clue to functional deficits at different physiological levels (Ottinger et al., 2008; Panzica et al., 2007).

In the last 15 to 20 years, a novel concept has arisen, based on the pioneering studies of E.E. Baulieu and co-workers. These studies demonstrated that within the central and peripheral nervous system are localized enzymes involved in the synthesis of steroids starting from the cholesterol (Akwa et al., 1991). These nervous system born steroids are today collectively named neurosteroids (Baulieu and Robel, 1990) and together with peripherally born steroids (e.g., corticosteroids, gonadal steroids) are now classified as neuroactive steroids (Melcangi and Panzica, 2006; Rupprecht and Holsboer, 1999).

Several studies described in this special issue suggest important roles for neuroactive steroids (in particular for progesterone and its derivatives) in health and human diseases. Progesterone is an important agent affecting many central nervous system functions, can play an important role

in promoting and enhancing repair after traumatic brain injury and stroke, and may be a safe and effective treatment for traumatic brain injury and other neural disorders in humans (Stein, 2008). Allopregnanolone, a metabolite of progesterone, is a neurogenic agent for rodent hippocampal neural progenitors and for human neural progenitor cells derived from the cerebral cortex. Its neurogenic potential changes with age, indicating that allopregnanolone may maintain the regenerative ability of the brain and modify progression of Alzheimer's disease (AD) related pathology (Wang et al., 2008). Similarly, administration of allopregnanolone in the neonatal period in mice that are a model for Niemann–Pick disease resulted in a doubling of lifespan, substantial delay in onset of neurological symptoms, survival of cerebellar Purkinje and granule cell neurons, and reduction in cholesterol and ganglioside accumulation, probably through GABA_A receptors (Mellon et al., 2008).

Among neuroactive steroids, estrogens have a central role. They may be generated both peripherally from the ovary and at the level of the nervous system by the action of the enzyme aromatase. Novel therapeutic approaches are based on the use of estradiol analogues (such as the 17 α -estradiol) that are equally neuroprotective, but more than 200-fold less active as a hormone. Studies of structure–activity relationships and mitochondrial function have led to a mechanistic model in which these steroidal phenols intercalate into cell membranes, where they block lipid peroxidation reactions and are in turn recycled. The neuroprotective and mitoprotective potencies of a series of estrogen analogs are significantly correlated, suggesting that these compounds prevent neuronal cell death in large measure by maintaining functionally intact mitochondria (see Simpkins and Dykens, 2008).

Estradiol is a critical survival, neurotrophic, and neuroprotective factor for dopaminergic neurons of the substantia nigra pars compacta (SNpc) (Kuppers et al., 2000), the cells that degenerate in Parkinson's disease (PD). The contributions of brain aromatase and extragonadally generated estradiol as vulnerability factors for PD pathology in female brain have been elucidated by the observation that genital aromatase deficiency from early embryonic life significantly impairs the functional integrity of SNpc tyrosine hydroxylase-positive neurons and dopamine transporter innervation of the caudate-putamen in adulthood (see Morale et al., 2008). Finally, testosterone may also have a role in neurodegenerative diseases; in fact, testosterone depletion leads to functional impairments and increased risk of disease in androgen-responsive tissues throughout the body, including brain. In particular, androgens may regulate the accumulation of β -amyloid protein (A β), which is a key initiating factor in AD pathogenesis. Emerging data suggest that the regulatory actions of androgens on both A β and the development of AD support consideration of androgen therapy for the prevention and treatment of AD (see Rosario and Pike, 2008).

The action of neuroactive steroids is not limited to the central nervous system. There are interactions between peripheral nerve injury and neurosteroid biosynthesis in the central nervous system. In particular, the sciatic nerve ligature may alter the neurosteroidogenesis in the spinal cord and brainstem areas, including the parabrachial, raphe magnus, and dorsal raphe nuclei which control nociception

(see Patte-Mensah and Mensah-Nyagan, 2008). In addition, peripheral nerves are able to synthesize and metabolize neuroactive steroids by themselves and are a target for these molecules, because they express classical and non-classical steroid receptors. Neuroactive steroids modulate the expression of key transcription factors for Schwann cell function, regulate Schwann cell proliferation, and promote the expression of myelin proteins involved in the maintenance of myelin structure. These actions may result in the protection and regeneration of peripheral nerves affected by different forms of pathological alterations (see Roglio et al., 2008).

The rise of interest in neuroactive steroids also stimulated a series of studies indicating that not all of the registered effects of neuroactive steroids can be explained by the classical mechanism (e.g., the stimulation of a steroid receptor acting as a transcription factor (Schmidt et al., 2000; Wehling, 1997)). Thus, the presence of membrane-bound receptors (Schumacher et al., 1990) and/or of interactions among steroids and membrane receptors for other molecules were suggested as interfering in the functionality of these last receptors (Gee, 1988).

Several important physiological activities are likely to be modulated by these kinds of interactions. In vitro experiments demonstrate that estradiol stimulates progesterone synthesis in astrocytes, considered to be the most active steroidogenic cells in the CNS. To stimulate neurosteroidogenesis, estradiol acts through membrane ER and type 1a metabotropic glutamate receptors to activate the PLC-IP₃ pathway. This neuroprogesterone also facilitated proceptive behavior (see Micevych et al., 2008). Action of estradiol on membrane receptors is also important during development of brain regions not as sexually specialized as the cerebellum. In particular, estrogens have a pathologic role in medulloblastoma, common pediatric brain tumors that arise from cerebellar granule cell-like precursors (see Belcher, 2008).

A putative membrane receptor of progesterone (25-Dx), distinct from the classical intracellular PR isoforms, with a single membrane-spanning domain, has been cloned. In spinal cord, 25-Dx is localized in cell membranes of dorsal horn neurons and ependymal cells lining the central canal. In brain, 25-Dx is particularly abundant in the hypothalamic area, circumventricular organs, ependymal cells of the ventricular walls, and the meninges. 25-Dx expression is up-regulated in neurons and induced in astrocytes after traumatic brain injuries. Thus 25-Dx may be involved in the neuroprotective effect of progesterone in the injured brain and spinal cord (see Guennoun et al., 2008).

Sulfated steroids may regulate synaptic transmission by altering the function of postsynaptic neurotransmitter receptors (Gibbs et al., 2006). However, these agents may also regulate glutamatergic synaptic transmission at the presynaptic level. In developing neurons, pregnenolone sulfate increases the probability of glutamate release acting on NMDA receptors with a mechanism involving the activation of σ 1-like receptors. These presynaptic actions of sulfated steroids could play important roles in physiological processes ranging from synapse maturation to learning and memory (see Valenzuela et al., 2008). The action of metabolites of progesterone (such as the allopregnanolone) on the GABA_A receptor is

important in regulating brain excitability and sensitivity to stimuli, thus indicating a possible role of these compounds in the regulation of behavior and pointing out their possible role in psychiatric and neurological disorders (see *Serra et al., 2008*).

As reported by Swaab and co-workers (see *Bao et al., 2008*), the hypothalamus–hypophyseal–adrenal axis is also deeply influenced by steroid hormones (mainly corticosteroids) at brain level. Glucocorticoids and gonadal hormones (estrogens) may cooperate in inducing alterations of brain circuits that are involved in stress control, as well as in depression.

Mice carrying mutations of glucocorticoid (GR) receptor show alterations in the hypothalamic–pituitary–adrenal (HPA) system that are comparable to those observed in depressed patients; therefore, they may have strong relevance as models for depression (see *Chourbaji and Gass, 2008*).

The balance of actions mediated by GR and mineralocorticoid (MR) receptors in certain regions of the brain, predominantly in the limbic system, appears critical for neuronal activity, stress responsiveness, and behavioral programming and adaptation. The balance (or imbalance) between MR/GR activation influences not only cell birth and death but also other forms of neuroplasticity, such as dendritic growth and synaptic plasticity occurring for example in stress conditions (see *Sousa et al., 2008*).

A major question that has arisen in recent times is the long lasting effects of pre- and perinatal alteration of glucocorticoids in the newborn on the adult, as well as their transgenerational effects. Glucocorticoids may cross the placenta, affect fetal HPA development and induce changes in HPA axis function that persist throughout life. For example, in rats, repeated restraint stress of the pregnant dam produces long lasting changes in the HPA axis function and behaviors in the offspring (see *Darnaudéry and Maccari, 2008*).

Studies in animal models indicate that fetal exposure to excess glucocorticoids represents a critical mechanism inducing an increased risk for the development of chronic disease in later life, likely involving epigenetic mechanisms. Incoming human data are indicating attention deficit hyperactivity disorder (ADHD)-like symptoms in children exposed in utero to repeated courses of synthetic glucocorticoids (see *Kapoor et al., 2008*).

A major problem of current research in this field is that almost all available data are from rodents (rat). A comparative review of data on the expression of MR and GR in adult and neonatal life in rodents, monkeys, and primates (human) allow for identification of interspecies consistencies and differences in the relative levels of MR and GR expression across brain regions and ontogenetic stages. In addition, data have demonstrated within-species inter-individual variation in MR and GR expression. Therefore, if the expression levels of MR and GR at the time of early-life stress determine the effects of GR on the long-term expression levels and functioning of MR, then the long-term effects of early life stress on corticosteroid receptor expression and function will be species-, brain-region-, and receptor-type specific (see *Pryce, 2008*).

Altogether, the present observations provide new insights into the roles of neuroactive steroids as key physiological regulators of central and peripheral nervous functions. In addition, they are involved in such phenomena as neuropro-

tection and neurogenesis and therefore may also represent an interesting therapeutic strategy for neurodegenerative events. Further details on these important aspects are provided in the present special issue, collecting the invited lectures that were presented during the 4th International Meeting on Steroids and Nervous System (February 2008, Torino, Italy).

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Information about this series of conferences is available at the dedicated website <http://www.dafml.unito.it/anatomy/panzica/neurosteroids/index.html>.

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