Neuroactive steroids: focus on human brain

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Abstract—Studies in experimental animals have revealed important roles of neuroactive steroids in the control of central nervous system functions during physiological and pathological conditions, suggesting that they may represent good candidates for the development of neuroprotective strategies for neurodegenerative and psychiatric disorders. Even if the characterization of the roles played by neuroactive steroids in humans is still at the beginning, several data are already available showing that they may be synthesized within the human CNS. Among the different enzymes, a prominent role is dedicated to aromatase that synthesizes estradiol whose neuroprotective effects have been described in experimental animals. Neuroactive steroid levels are modified by neurodegenerative conditions (i.e. Alzheimer’s and Parkinson’s diseases, multiple sclerosis) or in other mental diseases (i.e. schizophrenia), and may have an important role in physiological conditions, as the reorganization of grey and white matter during human puberty and adolescence or as a consequence of emotional responses. The interaction of some neuroactive steroids (i.e., allopregnanolone and isopregnanolone) with GABA-A receptor is particularly important in mood disorders. The presumptive role of estradiol and progesterone in neuroprotection is here discussed by comparing contradictory data that have been collected in humans. In conclusion, the state of the art of our knowledge of the role of neuroactive steroids in the normal and pathological human brain suggests several lines of future therapeutic developments in the treatments of neurological, neurodegenerative and affective disorders.

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Key words: neurodegenerative disorders, mood disorders, GABA-A receptor, neurosteroids.

Abbreviations: T, testosterone; TSPO, translocator protein 18 kDa.
Steroids that regulate physiological functions of the CNS are known as neuroactive steroids (Melcangi and Panzica, 2006; Melcangi et al., 2008). These molecules are synthesized either in the steroidogenic peripheral glands (i.e., hormonal steroids) or directly in the CNS (i.e., neurosteroids). Indeed, molecules involved in the conversion of cholesterol into pregnenolone, the first step of steroidogenesis, are expressed in the CNS. These molecules include translocator protein 18 kDa (TSPO; also known as peripheral benzodiazepine receptor) and steroidogenic acute regulatory protein, which are involved in the transport of cholesterol to the mitochondria and cytochrome P450 side chain cleavage, the enzyme that converts cholesterol into pregnenolone. In addition, enzymes involved in steroid metabolism, such as 3-hydroxysteroid dehydrogenase, cytochrome P450c17, 5-reductase (5-R), 3-hydroxysteroid oxidoreductase, 17-hydroxysteroid dehydrogenase and aromatase are also expressed by different neuronal and glial populations (Pelletier, 2010).

In animal models neuroactive steroids have been shown to affect the development function of the CNS. For instance, testosterone (T), which is locally metabolized by neural tissue to 17-estradiol and dihydrotestosterone by the enzymes aromatase and 5-R, respectively, acting on specific moments during fetal or early postnatal development, induce the generation of sexual dimorphisms in the CNS. The organizational effects of T and its metabolites generate male-specific traits in specific regions of the brain and the spinal cord, resulting in sex differences in the morphology, size and number of neurons and glial cells, the density of neuronal and glial processes in the neuropil and the number of synapses (Panzica et al., 1995; Cooke et al., 1998; Segovia et al., 1999; Simerly, 2002; Morris et al., 2004). Organizational effects of neuroactive steroids on synaptic connectivity and neuronal differentiation have been reported not only in limbic and hypothalamic areas controlling reproductive behaviors (Nishizuka and Arai, 1981a,b; Matsumoto and Arai, 1986; Matsumoto, 1991) and the release of pituitary hormones (Garcia-Segura et al., 1994a; Mong et al., 2001), but also in other brain regions such as the cerebellum (Sakamoto et al., 2003; Tsutsui et al., 2004), the cerebral cortex (Muñoz-Cueto et al., 1990, 1991) and the hippocampal formation (Gould et al., 1991; Juraska, 1991; Bender et al., 2010). In addition, neuroactive steroids regulate the development of glial cells. Indeed, morphology, immunoreactivity, enzymatic activity and gene expression of astroglia are sexually dimorphic in several brain areas and can be modified by postnatal actions of neuroactive steroids (Garcia-Segura and Melcangi, 2006). These effects may also be highly relevant for the sexual differentiation of neuronal connectivity (Garcia-Segura et al., 2008).

Neuroactive steroids have also different effects in the adult CNS, acting on brain regions involved in the control of sex behavior and neuroendocrine regulation, modulating the release of neurotransmitter and the expression and function of neurotransmitter receptors and inducing plastic functional remodeling of synapses (Olmos et al., 1989; Parducz et al., 2002; Csakvari et al., 2007) and associated glial processes (Garcia-Segura et al., 1994a,b). In addition, neuroactive steroids influence cognitive brain regions, regulating the number of dendritic spines and synapses and the induction of long term potentiation (LTP) in the CA1 region of the rat hippocampus (Woolley et al., 1990, 1996; Woolley and McEwen, 1992; Murphy and Segal, 1996; Córdoba Montoya and Carrer, 1997; Leranth et al., 2000, 2003; Leranth and Shanabrough, 2001; Yankova et al., 2001; Bender et al., 2010), as well as adult neurogenesis in the dentate gyrus (Galea and McEwen, 1999; Tanapat et al., 1999, 2005; Ormerod and Galea, 2001; Ormerod et al., 2003; Galea et al., 2006).
As extensively demonstrated, neuroactive steroids exert also important neuroprotective effects. For instance, T, estradiol and progesterone are neuroprotective in different experimental models of neuronal injury including hippocampal excitotoxicity, substantia nigra degeneration and experimental forebrain ischemia and are also protective against affective disorders (Garcia-Segura et al., 2001; Wise, 2003; Wise et al., 2005).

Altogether, studies in experimental animals have revealed an important role of neuroactive steroids in the control of CNS function during physiological and pathological conditions, suggesting that they may represent good candidates for the development of neuroprotective strategies for neurodegenerative and psychiatric disorders. Therefore, it is now time to characterize the role of neuroactive steroids in humans. This special issue has been dedicated to approach this question, analyzing the present knowledge on the function of neuroactive steroids in the human brain.

The levels of neuroactive steroids as well as their synthesizing enzymes have been detected in the human brain (Steckelbroeck et al., 1999a,b; Stoffel-Wagner et al., 1999; Stoffel-Wagner, 2003). For instance, in this special issue a particular focus is on biosynthesis of estradiol by the enzyme aromatase (see review by Azcoitia et al., 2011). Due to the important neuroprotective effects exerted by estradiol it would be of great interest to learn more on how human brain aromatase is regulated, to design specific modulators to selectively increase estradiol synthesis within the human CNS. In addition it is important to determine the specific neuronal circuits that express aromatase in the human brain and whether this expression is modulated by physiological or pathological conditions (Santen et al., 2009). Indeed, recent studies have shown that neuroactive steroid levels are modified by the neurodegenerative conditions in the human brain (Weill-Engerer et al., 2002; Ahboucha et al., 2006; Marx et al., 2006; Luchetti et al., 2009, 2010), in agreement with previous findings in animals (di Michele et al., 2000; Meffre et al., 2007a,b; Caruso et al., 2008, 2010; Patte-Mensah and Mensah-Nyagan, 2008; Giatti et al., 2010; Pesaresi et al., 2010). In recent years, several data have been collected for Alzheimer’s disease, Parkinson’s disease and Multiple Sclerosis (see the review of Luchetti, Luchetti et al., 2011). These data further support the possible therapeutic use of neuroactive steroids. On the other hand, changes in neuroactive steroid levels might be also considered as biomarkers. On this point of view, it is important to highlight that as reported in different experimental models, both in physiological and in pathological situations, changes in the levels of neuroactive steroids in plasma do not exactly reflect the changes that take place in the CNS (Kancheva et al., 2007; Caruso et al., 2008, 2010; Giatti et al., 2010; Pesaresi et al., 2010). Therefore, because plasma levels are usually utilized as diagnostic marker in clinical studies, one possibility could be to analyze neuroactive steroid levels in cerebrospinal fluid, as reviewed in this special issue by Kancheva and collaborators (Kancheva et al., 2011).

As mentioned above, animal models have clearly suggested that neuroactive steroids are able to influence brain organization during early and late postnatal critical periods (McCarthy et al., 2009). Neuroimaging techniques have recently demonstrated that also in humans neuroactive steroids may have a profound influence on brain organization. In particular, Peper and collaborators in this special issue analyze the link between neuroactive steroids and structural reorganization of grey and white matter during human puberty and adolescence (Peper et al., 2011). In addition, van Wingen and collaborators (2011), discuss the influence
of neuroactive steroids on human brain structures, such as amygdala, medial prefrontal and orbitofrontal cortex, which are important for emotional responses. Indeed, as analyzed by Backstrom and colleagues, neuroactive steroids, acting on GABA-A receptor, may induce in some women negative mood symptoms (Backstrom et al., 2011). In particular, the effects of GABA-A receptor modulators are reported as biphasic. Thus, low concentrations show adverse anxiogenic effects while higher concentrations induce calming properties. This paradoxical effect, particularly that exerted by the progesterone metabolite allopregnanolone (also known as tetrahydroprogesterone), is discussed in this special issue in the context of premenstrual dysphoric disorder or premenstrual syndrome. As reviewed by Schule and collaborators, GABA-A receptor, play an important role in the pathophysiology of depression and anxiety (Schule et al., 2011). Interestingly, the activity of this receptor is regulated not only by allopregnanolone, a positive modulator, but also by its isomer, isopregnanolone (also known as 3, 5-tetrahydroprogesterone), which antagonizes the effect of allopregnanolone on the GABA-A receptor in vitro and in vivo (Wang et al., 2002; Lundgren et al., 2003; Bäckström et al., 2005), although it does not bind directly to the GABA-A receptor (Bitran et al., 1991). The equilibrium in the levels of these two neuroactive steroids is modified during depression. Interes

estingly, the treatments with antidepressants or with ligands of TSPO, acting on neurosteroidogenesis, are able to normalize the disequilibrium with therapeutic effects (see Schule et al. in this special issue).

The levels of neuroactive steroids are also altered in postmortem brain tissue from patients with schizophrenia. Marx and collaborators, address the importance of pregnenolone as a promising candidate for therapy (Marx et al., 2011). Indeed, clinical trials have demonstrated that pregnenolone is able to decrease negative symptoms and extrapyramidal side effects and to improve verbal memory, attention and working memory performance in schizophrenic patients. Furthermore, as pointed out by Ritsner, not only pregnenolone, but also dehydroepiandrosterone is promising for the treatment of schizophrenia (Ritsner, 2011). Thus, the plasma levels of dehydroepiandrosterone are decreased in schizophrenic patients and better performance on executive tasks is associated with increased plasma levels of this neuroactive steroid.

As mentioned above neuroactive steroids exert important protective effects in experimental models. In human studies, very interesting results have been obtained with progesterone treatment for traumatic brain injury. In particular, as reviewed by Stein, clinical trials have indicated a reduction in the mortality and an improvement of functional outcomes (Stein, 2011).

Peri and collaborators, report that overexpression of a gene named seladin-1 (for Selective Alzheimer’s Disease indicator-1) in neuroblastoma cells increases the amount of membrane cholesterol and induces resistance against beta-amyloid aggregates (Peri et al., 2011). This is very interesting because this gene has been proposed to be a mediator of the neuroprotective effects of estrogens. Indeed as reviewed in this paper, estradiol and selective estrogen receptor modulators, such as raloxifene and tamoxifen, exert in human fetal neuroepithelial cells protective effects against beta-amyloid toxicity and oxidative stress. Interestingly, these treatments also increase the expression of seladin-1 and amount of cell cholesterol while silencing of this gene abolished the protective effects of estrogens (Peri et al., 2011).
The effects of estradiol in the human brain have been highly debated since the publication of the findings of the Women’s Health Initiative study, showing an increase in the risk of stroke and no benefits for cognition in women that took hormonal therapy several years after menopause. These findings contradicted data obtained in animal studies by many laboratories. Thus, neural effects of hormone therapy in postmenopausal women are currently being analyzed with different approaches. Examples of these new analyses are provided by Bayer & Hausmann, who have taken in consideration whether hormone therapy may affect important parameters of brain organization, such as functional cerebral asymmetries and interhemispheric interactions, in postmenopausal women (Bayer and Hausmann, 2011). Data here reviewed indicate that these parameters are still susceptible to the effect of estrogen therapy. Henderson & Popat present a detailed analysis on the influence of endogenous estrogen levels and of hormone therapy treatments on episodic memory and executive functions in women, based on published studies (Henderson and Popat, 2011). Their conclusion is that there is not a consistent association between endogenous estrogens concentration and episodic memory or executive functions and no significant impact of hormonal therapy on episodic memory or executive functions. However, as mentioned before, changes in the levels of neuroactive steroids in plasma do not exactly reflect the changes that take place in the CNS (Kancheva et al., 2007; Caruso et al., 2008, 2010; Giatti et al., 2010; Pesaesi et al., 2010). Therefore, it cannot be excluded that local aromatase expression and activity in the brain (see Azcoitia et al. in this special issue) and, therefore, local estradiol levels may be more relevant than plasma estrogen levels for cognition. However, there is no data available at present to assess this possibility. On the other hand, targeting synaptic estrogen receptors, as proposed by Morrison and colleagues (Bailey et al., 2011), may provide a better alternative than estrogen therapy to prevent cognitive decline in postmenopausal women.

In conclusion, the papers contained in this special issue present an updated overview of the function of neuroactive steroids in the human brain under physiological and pathological conditions and present several clues for future therapeutic developments in the treatments of neurological, neurodegenerative and affective disorders.

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