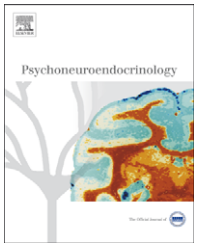
Psychoneuroendocrinology (2007) **32**, 1062–1078

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen



Neuroactive steroids modulate HPA axis activity and cerebral brain-derived neurotrophic factor (BDNF) protein levels in adult male rats

Gaëlle Naert[a,b,c], Tangui Maurice[a,b,c], Lucia Tapia-Arancibia[a,b,c], Laurent Givalois[a,b,c,*]

[a]*Université Montpellier 2, F-34095 Montpellier, France*
[b]*Inserm U710, F-34095 Montpellier, France*
[c]*EPHE, F-75007 Paris, France*

Received 28 March 2007; received in revised form 4 September 2007; accepted 4 September 2007

KEYWORDS
Depression;
Neuroactive steroids;
HPA axis;
BDNF;
Forced swimming test;
Rat

Summary
Depression is characterized by hypothalamo-pituitary-adrenocortical (HPA) axis hyperactivity. In this major mood disorder, neurosteroids and neurotrophins, particularly brain-derived neurotrophic factor (BDNF), seem to be implicated and have some antidepressant effects. BDNF is highly involved in regulation of the HPA axis, whereas neurosteroids effects have never been clearly established. In this systematic *in vivo* study, we showed that the principal neuroactive steroids, namely dehydroepiandrosterone (DHEA), pregnenolone (PREG) and their sulfate esters (DHEA-S and PREG-S), along with allopregnanolone (ALLO), stimulated HPA axis activity, while also modulating central BDNF contents. In detail, DHEA, DHEA-S, PREG, PREG-S and ALLO induced corticotropin-releasing hormone (CRH) and/or arginine vasopressin (AVP) synthesis and release at the hypothalamic level, thus enhancing plasma adrenocorticotropin hormone (ACTH) and corticosterone (CORT) concentrations. This stimulation of the HPA axis occurred concomitantly with BDNF modifications at the hippocampus, amygdala and hypothalamus levels. We showed that these neurosteroids induced rapid effects, probably via neurotransmitter receptors and delayed effects perhaps after metabolization in other neuroactive steroids. We highlighted that they had peripheral effects directly at the adrenal level by inducing CORT release, certainly after estrogenic metabolization. In addition, we showed that, at the dose used, only DHEA, DHEA-S and PREG-S had antidepressant effects. In conclusion, these results highly suggest that part of the HPA axis and antidepressant effects of neuroactive steroids

*Corresponding author. U710 Inserm, EPHE, Université Montpellier 2, cc 105, place Eugène Bataillon, F-34095 Montpellier, France. Tel.: +33 467 14 36 99; fax: +33 467 14 33 86.
E-mail address: lgivalois@univ-montp2.fr (L. Givalois).

0306-4530/$ - see front matter
doi:10.1016/j.psyneuen.2007.09.002

could be mediated by BDNF, particularly at the amygdala level. They also suggest that neurosteroids effects on central BDNF could partially explain the trophic properties of these molecules.

1. Introduction

Depression is a major mood disorder that can affect anybody at some point in life. There is still a lack of knowledge concerning the etiology, pathophysiology and neurochemical changes involved. Depression relies on psychological, neuroendocrine and somatic symptoms. Indeed, in severely depressed patients, emotional arousal, cognitive abnormality and vulnerability to psychotic episodes are linked to a hyperactive hypothalamo-pituitary-adrenocortical (HPA) axis and high level of circulating glucocorticoids, which returns to normal after antidepressant treatment (Holsboer and Barden, 1996; Mason and Pariante, 2006). The susceptibility pathways underlying these disturbed brain functions are influenced by genetic factors, early-life priming experiences and later-life events. Glucocorticoids are an important determinant in this so-called three hit model. The action of glucocorticoids is protective, but can become unsafe if exposure of susceptibility pathways to the stress hormone is excessive and sustained or inadequate (DeKloet et al., 2007). HPA axis abnormalities in patients with major depression are remarkably similar to those present in animals experiencing chronic stress (Pariante, 2003). Furthermore, it is well known that stress modifies neurotrophin expression, especially brain-derived neurotrophic factor (BDNF) expression. BDNF is a member of the nerve growth factor (NGF) family and has been shown to play an important role in normal peripheral and central nervous system (CNS) development (Tapia-Arancibia et al., 2004). In contrast, in the mature CNS, it has been suggested that these molecules are important mediators that can translate neuronal activity into biochemical and structural plasticity (McAllister et al., 1999). Several reports show that BDNF expression is modified by stress (for review see, Tapia-Arancibia et al., 2004). It has been reported that single (2-h or 8-h immobilization stress) or repeated immobilization stress (2 h/day for 7 days) decreases BDNF mRNA throughout the hippocampus (Smith et al., 1995a; Ueyama et al., 1997) and increases BDNF mRNA in the hypothalamic paraventricular nucleus (PVN) (Smith et al., 1995b). In these studies, time-course effects of stress application were not investigated in spite of early events occurring after stress stimulus appear to be extremely important. Thus, we have reported that single stress rapidly increases BDNF mRNA and protein levels in the hippocampus, hypothalamus and pituitary, i.e. the principal structures of the HPA axis (Givalois et al., 2001; Rage et al., 2002; Marmigere et al., 2003a; Givalois et al., 2004a). Recently, we have shown that central administration of exogenous BDNF induces substantial modifications in HPA axis activity (Givalois et al., 2004a; Naert et al., 2006). This confirms the involvement of BDNF in HPA axis activity. Moreover, several recent studies support the hypothesis of BDNF involvement in depression (Ridder et al., 2005; Castren et al., 2007). In depressed patients, the serum BDNF level is decreased (Karege et al., 2002). Further indirect evidence has been obtained in studies showing an increase in hippocampus BDNF expression in post-mortem brains of subjects treated with antidepressants at the time of death vs. untreated subjects (Chen et al., 2001). BDNF expression is upregulated by antidepressant treatment (Dias et al., 2003) and notably by electroconvulsive therapy (Altar et al., 2003), and in rats, BDNF induces direct antidepressant-like effects (Siuciak et al., 1997; Shirayama et al., 2002).

In other respects, neuroactive steroids have been shown to be involved in mood disorders. E.E. Baulieu introduced the term "neurosteroid" in 1981 to designate steroids, which are synthesized *de novo* in the brain via the classic mevalonate pathway to cholesterol and independently of plasma levels (Baulieu, 1981). Steroids are known to have genomic actions, but they can also have non-genomic effects by interacting with several types of neurotransmitter receptors and neuromodulatory proteins (Rupprecht, 2003). These steroids can be considered as "neuroactive" on the basis of this feature. The main neurosteroids are dehydroepiandrosterone (DHEA), pregnenolone (PREG) and their respective sulfate esters, progesterone and allopregnanolone (ALLO). The relationship between depression and neurosteroids is intriguing, and much work needs to be done to gain further insight into this phenomenon. A blunted circadian variation in DHEA concentrations is observed in patients suffering from major depression (Osran et al., 1993). Some interactions between the serotoninergic system and neurosteroids have also been described, thus supporting the hypothetical involvement of neurosteroids in depression (Griffin and Mellon, 1999). In particular, neuroactive steroids, including DHEA, 5α-dihydroprogesterone, ALLO or ganaxalone, modulate the activity of dorsal raphe serotoninergic neurons, alone or in combination with selective serotonin reuptake inhibitors (Robichaud and Debonnel, 2004). It is interesting to note that, like neurotrophins, neurosteroid levels are increased by a single stress (Paul and Purdy, 1992; Urani et al., 2001), and in aged rats neurosteroids (like neurotrophins) are decreased in the CNS (Kroboth et al., 1999), and neuroactive steroids (like neurotrophins) have antidepressant properties (Prasad et al., 1997; Urani et al., 2001; Van Broekhoven and Verkes, 2003).

The current *in vivo* study investigates the effects of systemic/pharmacological administered neuroactive steroids (DHEA, DHEA-S, PREG, PREG-S and ALLO) on temporal variations, in the same rats, of hypothalamus corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) contents and plasma ACTH and corticosterone (CORT) concentrations. We therefore selected one active dose of each neuroactive steroid according to previously reported central effects. Moreover, in an effort to clarify the influence of neuroactive steroids in HPA axis regulation,