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Progress in Neuro-Psychopharmacology & Biological Psychiatry 29 (2005) 169–192

Progress In Neuro-Psychopharmacology & Biological Psychiatry

www.elsevier.com/locate/pnpbp

Review article

Steroids, neuroactive steroids and neurosteroids in psychopathology

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Accepted 19 November 2004
Available online 29 December 2004

Abstract

The term "neurosteroid" (NS) was introduced by Baulieu in 1981 to name a steroid hormone, dehydroepiandrosterone sulfate (DHEAS), that was found at high levels in the brain long after gonadectomy and adrenalectomy, and shown later to be synthetized by the brain. Later, androstenedione, pregnenolone and their sulfates and lipid derivatives as well as tetrahydrometabolites of progesterone (P) and deoxycorticosterone (DOC) were identified as neurosteroids. The term "neuroactive steroid" (NAS) refers to steroids which, independent of their origin, are capable of modifying neural activities. NASs bind and modulate different types of membrane receptors. The GABA and sigma receptor complexes have been the most extensively studied, while glycine-activated chloride channels, nicotinic acetylcholine receptors, voltage-activated calcium channels, although less explored, are also modulated by NASs. Within the glutamate receptor family, *N*-methyl-D-aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and kainate receptors have also been demonstrated to be a target for steroid modulation. Besides their membrane effects, once inside the neuron oxidation of Ring A reduced pregnanes, THP and THDOC, bind to the progesterone intracellular receptor and regulate gene expression through this path. The involvement of NASs on depression syndromes, anxiety disorders, stress responses to different stress stimuli, memory processes and related phenomena such as long-term potentiation are reviewed and critically evaluated. The importance of context for the interpretation of behavioral effects of hormones as well as for hormonal levels in body fluids is emphasized. Some suggestions for further research are given.

Keywords: Active neurosteroids; Anxiety; Depression; Evolution; Long-term potentiation; Memory; Neurosteroids; Steroids

Contents

Abbreviations: ACTH, adrenocorticotropic hormone; AD, antidepressant; ADHD, attention deficit hyperactivity disorder; ALDO, aldosterone; AMPA, α-amino-3 hydroxy-5-methyl-4-isoxazolepropronic acid; AS, androsterone sulfate; AVP, arginine vasopressin; CFS, chronic fatigue syndrome; CNS, central nervous system; CRH, corticotropic releasing hormone; CS, corticosterone; CSF, cerebrospinal fluid; DG, dentate gyrus; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; DHP, dihydroprogesterone; DOC, deoxycorticosterone; rECS, repeated electroconvulsive shock; EPSP, excitatory postsynaptic potential; ER, evoked response; GABA, gaba amino butiric acid; GC, glucocorticoid; GFAP, glial fibrillary acidic protein; GR, glucocorticoid receptor; HF, hippocampal formation; HPAA, hypothalamic pituitary adrenal axis; 3α HSD, 3α hydroxysteroid dehydrogenase; IPSP, inhibitory postsynaptic potential; LTD, long-term depression; LTP, long-term potentiation; MBP, myelin basic protein; MC, mineralocorticoid; MISS, membrane initiated steroid signalling; MR, mineralocorticoid receptor; NADPH, nicotinamide adenine dinucleotide phosphate; NAS, neuroactive steroid; NMDA, *N*-methyl-D-aspartate; NS, neurosteroid; 11β-OHD, 11β-hydroxysteroid dehydrogenase; OT, oxytocin; P, progesterone; PBR, peripheral benzodiazepine receptor; PKC, phosphokinase C; PMDD, premenstrual dysphoric disorder; PPD, postpartum depression; PS, pregnenolone sulfate; PS, population spike; PSD, partial sleep deprivation; REM, rapid eye movement; RF, reticular formatio; SSRI, selective serotonin reuptake inhibitor; TBSP, [35s] *t*-butylbicyclophorphorothionate; TCA, tricyclic antidepressant; THDOC, allo-tetrahydrodeoxycorticosterone; THP, allo-tetrahydroprogesterone.

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0278-5846/$ - see front matter © 2004 Published by Elsevier Inc.
doi:10.1016/j.pnpbp.2004.11.001

1. Introduction

In 1913, during the opening address of the Phipps Psychiatric Clinic, Cushing presented his concept of an interaction between emotions and endocrine secretions. He agreed with the notion that "psychic conditions profoundly influence the discharges from the glands of internal secretion." But, he added, "we are on a much less secure footing when we come to the reverse, namely, the effect on the psyche and nervous system of chronic states of glandular overactivity and under activity" (Cushing, 1913).

Cushing postulated that each glandular disorder would induce a typical psychopathology, "its peculiar symptom-complex and its more or less characteristic mental deviations." He concluded by pointing out a problem still very much alive in neuroendocrinology, "the present difficulty in determining which was the primary factor—the psychic instability or the disturbance of endocrine secretion" (Cushing, 1913). In 1932, Cushing noted that in patients with adrenal hyperactivity the presence of "sleeplessness, inability to concentrate, visual disturbances" and "fits of unnatural irritability alternated with periods of depression" (Cushing, 1932). These findings were repeatedly corroborated, and, although not the exclusive manifestation of Cushing's disorders (syndrome and disease), depression is the most frequent behavioral disturbance observed in patients with these disorders (Cohen, 1980; Dubrovsky, 1993; Gifford and Gunderson, 1970; Gold et al., 2002; Jeffcoate et al., 1979; Kelly et al., 1983; Kramlinger et al., 1981; Mitchell and Collins, 1984).

The incidence of depression in Cushing's disorders is significantly higher than in any other endocrine disorders (Cohen, 1980). Within this context, it is of great interest that the correction of hormonal imbalances in Cushing's alleviates the depression syndrome, even in cases where psychopharmacological treatment with tricyclic antidepressants were not effective (Kramlinger et al., 1981; Ravaris et al., 1988). These results led Cohen (1980) to suggest that, "the simplest explanation for these various observations is that where Cushing's syndrome develops it commonly causes depressive illness." In fact, inhibition of steroids secretion (Gold et al., 2002; Jeffcoate et al., 1979; Kramlinger et al., 1981; Price et al., 1996; Ravaris et al., 1988) or blocking of their effects (Belanoff et al., 2002; Price et al., 1996) have been proposed and are being used for the treatment of depression syndromes.

The spectrum of affective and cognitive symptoms in Cushing's disorders greatly overlaps with those described in the DSM IV (1994) to diagnose depressions: increase in fatigue and a loss of energy, dysphoric mood (i.e., depressed) and irritability, sleep disturbances and decreased libido, diminished ability to think and concentrate, increase and/or decrease in appetite, sense of hopelessness, social withdrawal and anxiety, are significantly present in patients with Cushing's disorders compared to control, healthy populations.

In normal subjects, approximately 20% of sleep is spent in stages 3 and 4, also known as the delta stage (Hobson, 1989). In patients with Cushing's disease, as well as in those with depression syndromes, there is an absence of, or marked reduction in, stages 3 and 4 (Krieger, 1978; Kupfer et al., 1973). Also, a shorter rapid eye movement (REM) sleep latency can be observed in both groups of patients (Kupfer et al., 1973).

However, patients with Cushing's disorders can also present with mania (Cleghorn, 1951; The Lancet, 1986), and Addison's patients can show depressions (Cleghorn, 1951; Drake, 1968). Also, in experimental animals, the induction of learned helplessness, a recognized model of depression, is enhanced by adrenalectomy (Edwards et al., 1980).

Neither in Cushing's nor in depression syndromes do the intensity of psychopathology correlate with cortisol levels (Starkman et al., 1986; The Lancet, 1986). This is not surprising as the adrenal glands produce a plethora of hormones. In 1985 Holzbauer et al. wrote: "the extent to which this gland contributes hormones not confined to so-called gluco and mineralocorticoid activities is much less considered and deserves attention. These include steroids commonly associated with the ovary, such as progesterone or pregnenolone, as well as other steroids devoid of gonadal or corticoid activity which may, nevertheless, have a biological role such as the ones related to their anesthetic action." Other adrenal hormones besides cortisol (Gold et al., 2002; Linkowsky et al., 1987), imbalances between counteracting steroids acting on the CNS (Erhart-Bornstein et al., 1998), neuroactive steroids (NAS) (Baulieu, 1998; Dubrovsky, 2000) and neurosteroids (NS) may contribute to steroid associated psychopathology (Brambilla et al., 2003;