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Review

Multifunctional aspects of allopregnanolone in stress and related disorders

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ABSTRACT

Allopregnanolone (3α-hydroxy-5α-pregnan-20-one) is a major cholesterol-derived neurosteroid in the central nervous system and is synthesized from progesterone by steroidogenic enzymes, 5α-reductase (the rate-limiting enzyme) and 3α-hydroxysteroid dehydrogenase. The pathophysiological role of allopregnanolone in neuropsychiatric disorders has been highlighted in several investigations. The changes in neuroactive steroid levels are detected in stress and stress-related disorders including anxiety, panic and depression. The changes in allopregnanolone in response to acute stressor tend to restore the homeostasis by dampening the hyperactivated HPA axis. However, long standing stressors leading to development of neuropsychiatric disorders including depression and anxiety are associated with decrease in the allopregnanolone levels. $GABA_A$ receptor complex has been considered as the primary target of allopregnanolone and majority of its inhibitory actions are mediated through GABA potentiation or direct activation of GABA currents. The role of progesterone receptors in producing the late actions of allopregnanolone particularly in lordosis facilitation has also been described. Moreover, recent studies have also described the involvement of other multiple targets including brain-derived neurotrophic factor (BDNF), glutamate, dopamine, opioids, oxytocin, and calcium channels. The present review discusses the various aspects of allopregnanolone in stress and stress-related disorders including anxiety, depression and panic.

Contents

Abbreviations: HPA, Hypothalamus-pituitary- adrenal axis; BDNF, Brain-derived neurotrophic factor; TSST, Trier Social Stress test; SBBS, Steroidogenic stimulant; CRF, Corticotropin releasing factor; mPFC, median prefrontal cortex; PBR, Peripheral benzodiazepine receptors; TSPO, Translocator protein; PVN, Paraventricular nucleus; sEPSCs, Spontaneous excitatory postsynaptic current; NKCC1, Na^+-K^+-Cl^- co-transporter; 3α-HSD, 3α-hydroxysteroid dehydrogenase; AlloP, Allopregnanolone; NMDA, N-methyl-D-aspartate; NTS, Nucleus tractus solitaries; SON, Supraoptic nucleus; HVA, Homovanillic acid; PKA, Protein kinase A; MAPK, Msitogen-activated protein kinases; VMH, Ventromedial hypothalamus.

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1. Introduction

Stress has long been implicated in the etiology and pathophysiology of chronic physical and mental health conditions including anxiety, panic and depression. Stressful stimuli disturb the homeostasis and evoke a spectrum of adaptive physiologic responses, including the activation of autonomic function and the hypothalamic–pituitary–adrenal (HPA) axis (McEwen and Wingfield, 2003). Stress and anxiety are often used interchangeably; however, stress is an antecedent and is a causative factor for the development of anxiety. Furthermore, anxiety disorders generally precede the development of depression suggesting a continuum between these disorders with common pathophysiological features. Both of these disorders are the result of inappropriate adaptation to stressors; therefore, these have been termed as stress-related disorders with a causal role of HPA system dysregulation (Bali et al., 2013; Erhardt et al., 2006). The changes in neuroactive steroid levels are detected in stress and stress-related disorders including anxiety, panic and depression (Paul and Purdy, 1992) suggesting the pathophysiological role of neurosteroids in these neuropsychiatric disorders. Recently, Gunn et al. critically appraised the impact of brain-derived neurosteroids on the stress response to acute and chronic challenges with an aim to emphasize the therapeutic potential of neurosteroid for the treatment of stress-associated disorders (Gunn et al., 2011).

Neurosteroids (neuroactive steroids) are endogenous steroids that were earlier defined to function as endocrine messengers, however, now these are defined as local neuromodulators which act in a paracrine, or autocrine manner to “fine tune” inhibitory transmission in the central nervous system (Agís-Balboa et al., 2006). Within the brain, the steroid synthesizing enzymes are mainly expressed in corticolimbic glutamatergic neurons of the cortex, hippocampus, olfactory bulb, amygdala and thalamus. Agís-Balboa and collaborators, and other groups of scientists demonstrated that neither 5α-R type I nor 3α-HSD mRNAs are expressed in glial fibrillary acidic protein-positive glial cells (Agís-Balboa et al., 2006, 2007; Pinna et al., 2008). This is in contrast with previous studies which reported that these steroidogenic enzymes are widely expressed in the glia (Kiyokage et al., 2005; Melcangi et al., 1993a,b). Melcangi et al. demonstrated that neurons, astrocytes and oligodendrocytes possess significant 5α-reductase activity and among these cells, neurons exhibit significantly more 5α-reductase activity than oligodendrocytes followed by glial cells (Melcangi et al., 1990, 1993a,b). However, these scientists described that 3α-reductase is predominantly expressed in the astrocytes, with very low yield in neurons (Melcangi et al., 1993a, b). In subsequent years, Gottfried-Blackmore and co-workers demonstrated the mRNA expression of 5α-reductase type 1 in mouse microglia (Gottfried-Blackmore et al., 2008). Neurosteroids are synthesized de novo in the central and peripheral nervous system from cholesterol or steroidal precursors that are imported from the peripheral sources. Based on the structure, neurosteroids are mainly classified into pregnane neurosteroids including allopregnanolone and allotetrahydrodeoxycorticosterone and, androstane neurosteroids including androstanediol, etiocholanone and dehydroepiandrosterone. Progesterone (4-pregnene-3,20-dione) and deoxycorticosterone are the main precursors of allopregnanolone and allotetrahydrodeoxycorticosterone, respectively (Reddy, 2003). Neuroactive steroids such as allopregnanolone and allotetrahydrodeoxycorticosterone mainly exhibit inhibitory actions and produce sedation, anxiolytic, and anticonvulsant actions. On the other hand, sulfated neuroactive steroids such as pregnenolone sulfate and dehydroepiandrosterone sulfate produce excitatory actions to produce anxiogenic and proconvulsant actions. Furthermore, sulfated neurosteroids such as pregnenolone sulfate also serve as memory-enhancing agents (Mathis et al., 1996). Neurosteroids including allopregnanolone modulate neuronal excitability by genomic (classical intracellular steroid receptors) and non-genomic rapid actions (ion channels and membrane receptors) (Reddy, 2003; Rupprecht et al., 1993).

Allopregnanolone is the major cholesterol-derived neurosteroid in the brain and there have been evidences documenting that humans have the higher concentrations of allopregnanolone as compared to any other neurosteroid or its isomer (Parizek et al., 2005; Porcu et al., 2009). It is synthesized from cholesterol-derived progesterone in a two-step pathway requiring the enzymes 5α-reductase and 3α-hydroxysteroid dehydrogenase (Morrow, 2007). 5α-Reductase and 3α-hydroxysteroid dehydrogenase are highly expressed and co-localized in a region-specific manner in the primary GABAergic and glutamatergic neurons such as pyramidal neurons, granular cells, reticulothalamic neurons, nucleus accumbens, purkinje cells and medium spiny neurons of the striatum (Celotti et al., 1992; Melcangi et al., 1993a,b; Rupprecht, 1997; Kiyokage et al., 2005; Agís-Balboa et al., 2006, 2007; Magnaghi, 2007; Pinna et al., 2008). In periphery, allopregnanolone is mainly synthesized in the adrenal gland and gonads. However, the levels of these hormones are increased in the brain in response to stress even in adrenalectomized and gonadectomized animals suggesting that these neurosteroids are also synthesized in the brain (Paul and Purdy, 1992).

Numerous studies have documented the pathophysiological role of allopregnanolone in stress, anxiety, and depression (Nin et al., 2011; Purdy et al., 1991) (Table 1). It has been reported that the concentration of neurosteroids may reach 100 nM during the estrous cycle as well as during acute stress (Purdy et al., 1991). The changes in the endogenous allopregnanolone levels have been observed to be closely related to premenstrual and post-partum dysphoric disorders. Preclinical studies have also reported the influence of allopregnanolone in panic and lordosis behavior (González-Flores et al., 2010; Miryala et al., 2011). $GABA_A$ receptor complex has been considered as the primary target of allopregnanolone and majority of its inhibitory actions are mediated through GABA potentiation or direct activation of GABA currents (Shirayama et al., 2011; Singh and Kumar, 2008). Gunn and collaborators critically reviewed that the brain-derived neurosteroids influence the stress response to acute and chronic challenges, both prenatally and post-natally through adulthood by $GABA_A$ receptor interactions. There is a close relationship between early life stress experiences and development of highly debilitating psychiatric conditions including anxiety, depression and drug addiction. Neurosteroids play an important role in the early neuronal development and, it is suggested that impairment in brain signaling due to deficiency of these $GABA_A$ receptor modulating neurosteroids may be responsible for the development of early life adversity-associated psychiatric conditions in adulthood. Furthermore, neurosteroid-induced enhancement of GABAergic inhibition contributes in inhibiting anxious phenotype in adulthood in response to prenatal stress exposure and maternal separation in early lifehood (Gunn et al., 2011).

The role of progesterone receptors in ‘late actions’ of allopregnanolone particularly in lordosis facilitation has also been described (Miryala