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Neurosteroid regulation of central nervous system development

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Abstract

Neurosteroids are a relatively new class of neuroactive compounds brought to prominence in the past 2 decades. Despite knowing of their presence in the nervous system of various species for over 20 years and knowing of their functions as $GABA_A$ and *N*-methyl-D-aspartate (NMDA) ligands, new and unexpected functions of these compounds are continuously being identified. Absence or reduced concentrations of neurosteroids during development and in adults may be associated with neurodevelopmental, psychiatric, or behavioral disorders. Treatment with physiologic or pharmacologic concentrations of these compounds may also promote neurogenesis, neuronal survival, myelination, increased memory, and reduced neurotoxicity. This review highlights what is currently known about the neurodevelopmental functions and mechanisms of action of 4 distinct neurosteroids: pregnenolone, progesterone, allopregnanolone, and dehydroepiandrosterone (DHEA).

Keywords: Pregnenolone; Progesterone; Allopregnanolone; Dehydroepiandrosterone; Neurogenesis; Neurotoxicity; Neurodegeneration; Niemann Pick Type C

Contents

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1. Introduction

The first steroids identified in large concentrations in the rat brain were dehydroepiandrosterone (DHEA) and its sulfated ester (Corpechot et al., 1981). Shortly after this first publication, the immediate precursors of DHEA and its sulfate ester (DHEAS), pregnenolone and pregnenolone sulfate, were also identified in rat brains (Corpechot et al., 1983). The brain concentrations of all of these steroids were far greater than those found in the circulation. Furthermore, their concentrations in brain remained high after adrenalectomy and orchiectomy, suggesting that these steroids did not originate from steroidogenic tissue but rather that they originated through local brain synthesis. Hence, the concept of endogenous steroid synthesis in the brain, *neurosteroidogenesis*, was formed. Since that time, the function for these compounds began to be uncovered, and the mechanisms and receptors through which these compounds mediated their action also began to be studied (Costa & Paul, 1991; Mensah-Nyagan et al., 1999; Rupprecht & Holsboer, 1999a; Compagnone & Mellon, 2000; Baulieu et al., 2001; Puia et al., 2003; Rupprecht, 2003; Belelli & Lambert, 2005) and functions for these compounds in human diseases was also proposed (Rupprecht & Holsboer, 1999b; Morrow et al., 2001; Mellon & Griffin, 2002; Reddy, 2002; Rogawski & Reddy, 2002; Backstrom et al., 2003; Guarneri et al., 2003; Stoffel-Wagner, 2003; Barbaccia, 2004; Bernardi et al., 2004; Matsumoto et al., 2005; Belelli et al., 2006; Brinton & Wang, 2006; Campbell, 2006; Charalampopoulos et al., 2006; Uzunova et al., 2006). These references are merely a partial list of review articles written about neurosteroids and their functions, indicating the breadth of research on this topic. Among their multitude of functions, the various neurosteroids are modulatory ligands for a variety of neurotransmitter and nuclear steroid hormone receptors. As they are not unique or requisite ligands for many of these receptors, their functions as endogenous ligands for these receptors may be redundant with other endogenous ligands. Hence, loss of a particular neurosteroid may not result in devastating neurological consequences. However, as these compounds may be modulatory ligands for a variety of membrane and intracellular receptors, as well as for other as yet unidentified receptors, they may play a different type of modulatory role during development and in the adult. Furthermore, treatment of animal or human model systems with these compounds may reveal additional, and unexpected, functions for these compounds. This review highlights the novel functions and mechanisms of action of 4 neurosteroids, pregnenolone, progesterone, allopregnanolone, and DHEA, and their potential roles in the development and maintenance of the nervous system.

2. Pregnenolone and pregnenolone sulfate

2.1. General overview

Two of the original neurosteroids identified in brains of rats were pregnenolone and pregnenolone sulfate (Corpechot et al., 1983). In those studies, it was noted that concentrations of pregnenolone exceeded those of pregnenolone sulfate, and brain concentrations of both of these steroids were greater than that found in the circulation even after removal of steroidogenic organs. More recent data have suggested that the original identification of pregnenolone sulfate in rodent brains by radioimmunoassay or by gas chromatography/mass spectrometry was in error as a consequence of indirect methods of measure. Direct methods, such as high performance liquid chromatography-electrospray ionization tandem mass spectrometry, capillary column HPLC-nanoelectrospray ionization MS/MS, and ELISAs for the quantification of sulfated steroids, have failed to demonstrate the existence of pregnenolone sulfate in the rodent brain (Liere et al., 2000; Higashi et al., 2001, 2003a, 2003b; Liu et al., 2003; Liere et al., 2004). However, the presence of pregnenolone sulfate in human brain samples has been confirmed (Weill-Engerer et al., 2002).

2.2. Action at ligand-gated ion channel receptors

Studies identifying receptors that are activated by pregnenolone or pregnenolone sulfate have used pregnenolone sulfate. Pregnenolone sulfate acts at many different ligand-gated ion channel receptors. It is a negative modulator of $GABA_A$ receptors (Majewska et al., 1985; Majewska & Schwartz, 1987; Rabow et al., 1995), kainate and α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid (AMPA) receptors (Wu & Chen, 1997; Spivak et al., 2004; Mameli et al., 2005; Shirakawa et al., 2005), and it is a positive modulator of *N*-methyl-D-aspartate (NMDA) receptors (Wu et al., 1991; Bowlby, 1993; Irwin et al., 1994; Park-Chung et al., 1997; Horak et al., 2004). Hence, pregnenolone and pregnenolone sulfate are excitatory neurosteroids. At NMDA receptors, pregnenolone sulfate mediates its effects at a site distinct from the glycine modulatory site (Wu et al., 1991). Pregnenolone sulfate has been shown to augment responses from recombinant NMDA receptors in heterologous cells. The NR1 subunit can combine with NR2A, NR2B, NR2C, or NR2D subunits to form functional NMDA receptors.