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Review

Neurosteroids, stress and depression: Potential therapeutic opportunities

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ABSTRACT

Neurosteroids are potent and effective neuromodulators that are synthesized from cholesterol in the brain. These agents and their synthetic derivatives influence the function of multiple signaling pathways including receptors for γ-aminobutyric acid (GABA) and glutamate, the major inhibitory and excitatory neurotransmitters in the central nervous system (CNS). Increasing evidence indicates that dysregulation of neurosteroid production plays a role in the pathophysiology of stress and stress-related psychiatric disorders, including mood and anxiety disorders. In this paper, we review the mechanisms of neurosteroid action in brain with an emphasis on those neurosteroids that potently modulate the function of $GABA_A$ receptors. We then discuss evidence indicating a role for GABA and neurosteroids in stress and depression, and focus on potential strategies that can be used to manipulate CNS neurosteroid synthesis and function for therapeutic purposes.

Contents

Abbreviations: 5α-DHP, 5α-dihydroprogesterone; 3α-HSD, 3α-hydroxysteroid dehydrogenase; 3α5β-PC, 3α,5β-20-oxo-pregnane-3-carboxylic acid; 17-PA, 3α5α-17-phenylandrost-16-en-3-ol; ANT, adenine nucleotide transporter; ACTH, adrenocorticotrophic hormone; alloP, allopregnanolone; BDZ, benzodiazepine; CNS, central nervous system; CSF, cerebrospinal fluid; CRH, corticotrophin releasing hormone; DHEAS, dehydroepiandrosterone sulfate; DBI, diazepam binding inhibitor; ECT, electroconvulsive therapy; fMRI, functional magnetic resonance imaging; GABA, γ-aminobutyric acid; $GABA_A$Rs, $GABA_A$ receptors; HPA, hypothalamic-pituitary-adrenal; IPSCs, inhibitory postsynaptic currents; LTP, long-term potentiation; NMDARs, N-methyl-D-aspartate glutamate receptors; CYP11A1, P450 side-chain cleavage enzyme; PVN, paraventricular nucleus; PXRs, pregnane xenobiotic receptors; PREGS, pregnenolone sulfate; rTMS, repetitive transcranial magnetic stimulation; SSRIs, selective serotonin reuptake inhibitors; logP, solubility in octanol vs. water; StAR, steroidogenic acute regulatory protein; TSPO, translocator protein 18 kDa; TM, transmembrane regions; VDAC, voltage-dependent anion channel.

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1. Introduction

Psychiatric disorders are very common with at least 30% of adults suffering from one of these illnesses at some point in their lives (Zorumski and Rubin, 2011). These mental disorders are among the leading causes of disability in western societies, and comprise approximately 40% of illnesses that result in an inability to work productively (Iglehart, 2004). Psychiatric disorders are also major contributors to mortality. While heart and lung disease, stroke, diabetes and cancer are well known causes of morbidity and mortality, it is less appreciated that these end-state illnesses often reflect longstanding consequences of alcoholism, nicotine dependence, drug abuse, and unhealthy lifestyles including obesity (Mokdad et al., 2004). Depression and schizophrenia also contribute significantly to mortality and are "risk factors" for cardiovascular disorders, diabetes and metabolic syndrome (Newcomer and Hennekens, 2007). Furthermore, the presence of co-morbid depression worsens the outcomes of primary medical illnesses and vice versa (Moussavi et al., 2007; Prince et al., 2007). Deaths from motor vehicle accidents and violence are also often associated with psychiatric disorders, particularly alcohol abuse. Suicide claims the lives of over 30,000 individuals per year in the United States, and is almost always the result of a major psychiatric illness.

Modern neuroscience and genetics are providing important insights into brain mechanisms underlying these devastating disorders. Advances are being made in understanding the fundamental biology of a spectrum of neuropsychiatric disorders including dementias such as Alzheimer's disease, major mood disorders, schizophrenia, anxiety disorders, alcoholism, and drug dependence. This work underscores the importance of abnormalities in the activity of specific brain networks and neurocircuits that underlie the pathophysiology and clinical symptoms of these brain disorders. Functional neuroimaging in particular is helping to define defects in neural circuitry associated with altered emotion, motivation and cognition, and collectively these findings provide new opportunities for therapeutic intervention (Ressler and Mayberg, 2007; Zorumski and Rubin, 2011; Buckholtz and Meyer-Lindenberg, 2012).

At the same time, however, there has been far less progress in identifying new pharmacological treatments for psychiatric disorders. Current medications represent only marginal advances over those introduced more than 50 years ago. Despite the fact that the current psychiatric drugs are only moderately effective with the vast majority of patients only partially responding to antidepressants or antipsychotics, the pharmaceutical industry is now largely abandoning efforts to develop new psychiatric medications (Insel and Sahakian, 2012). Many factors contribute to this unfortunate state of affairs. Among these are gaps in understanding psychiatric illnesses at a molecular level and the tendency of biopharmaceutical companies to pursue well trodden paths with more immediate payoffs based on existing chemical structures and proven mechanisms of action and demonstrated efficacy. There is thus a critical need to identify viable new drug targets in order to discover more effective agents.

One consideration in neuropsychiatric drug development is whether efforts are better directed toward agents that have highly specific mechanisms of action or whether the development of agents with broader actions altering a number of systems is preferred. Roth et al. (2004) have referred to this as a "magic bullet vs. magic shotgun" approach to therapeutics. Because we have little molecular insight into the pathophysiology of common neuropsychiatric disorders, we would argue that agents that affect multiple major targets may have the highest efficacy, particularly agents that modulate key neurotransmitter and signaling systems. In this light, we propose that neurosteroids represent viable targets for drug development in neuropsychiatry. Here, we will focus on the possible role that neurosteroids play in stress-related conditions and depression, and how these agents might be developed for therapeutic purposes. Our emphasis is on steroid derivatives that alter the function of the γ-aminobutyric acid (GABA) transmitter system, but we also consider other potential targets where appropriate.

Fig. 1. The list outlines potential therapeutic targets for neuroactive steroids. With the exception of Memory Dysfunction, these are targets for steroids that enhance the function of $GABA_A$Rs. Memory Dysfunction would be a more likely target for steroids that either enhance the function of NMDARs or that inhibit $GABA_A$Rs.

2. Neurosteroids and neuroactive steroids

The term "neurosteroid" was coined by Etienne Baulieu in the early 1980's and refers to a class of endogenous steroids synthesized in the brain and nervous system from cholesterol that are potent and effective modulators of the two major neurotransmitter systems that govern CNS activity – glutamate, the major excitatory neurotransmitter, and GABA, the major inhibitory neurotransmitter (Baulieu, 1981, 1997). Neurosteroids are a subset of the broader class of "neuroactive steroids" that includes endogenous agents made in the body outside the nervous system as well as synthetic derivatives that have CNS actions similar to neurosteroids (Paul and Purdy, 1992).

Because they modulate transmitter systems involved in arousal, cognition, emotion and motivation, neurosteroids (or neuroactive steroids with improved drug-like properties) have the potential to become novel treatments for multiple neuropsychiatric disorders (Paul and Purdy, 1992; Zorumski et al., 2000; Frye et al., 2012). Furthermore, current evidence indicates that endogenous production of neurosteroids in the brain is altered in behavioral states of "stress" and in several neuropsychiatric disorders, including depression (Girdler and Klatzkin, 2007; Schule et al., 2011). Thus, these steroids may mediate fundamental mechanisms that underlie behavioral symptoms that cut across current diagnostic categories. Potential clinical targets for neurosteroids include mood and anxiety disorders, schizophrenia, alcoholism, sleep disorders, chronic pain, epilepsy, traumatic brain injury and neurodegenerative disorders (Zorumski et al., 2000; Gunn et al., 2011). The effects of neurosteroids in most of these disorders are thought to involve direct actions in the brain, whereas the ability of neurosteroids to modulate chronic pain likely involves the spinal cord as well as brain (Kawano et al., 2011a,b; Sasso et al., 2012). Neuroactive steroids also have potential for development as rapidly acting intravenous anesthetics (Selye, 1941; Phillipps, 1974; Morgan and Whitwam, 1985) (Fig. 1).