CellPress

Review

Clinical Potential of Neurosteroids for CNS Disorders

Doodipala Samba Reddy[1,*] and William A. Estes[1]

Neurosteroids are key endogenous molecules in the brain that affect many neural functions. We describe here recent advances in US National Institutes of Health (NIH)-sponsored and other clinical studies of neurosteroids for CNS disorders. The neuronal GABA-A receptor chloride channel is one of the prime molecular targets of neurosteroids. Allopregnanolone-like neurosteroids are potent allosteric agonists as well as direct activators of both synaptic and extrasynaptic GABA-A receptors. Hence, neurosteroids can maximally enhance synaptic phasic and extrasynaptic tonic inhibition. The resulting chloride current conductance generates a form of shunting inhibition that controls network excitability, seizures, and behavior. Such mechanisms of neurosteroids are providing innovative therapies for epilepsy, status epilepticus (SE), traumatic brain injury (TBI), fragile X syndrome (FXS), and chemical neurotoxicity. The neurosteroid field has entered a new era, and many compounds have reached advanced clinical trials. Synthetic analogs have several advantages over natural neurosteroids for clinical use because of their superior bioavailability and safety trends.

Trends

Dysfunction of extrasynaptic GABA-A receptors may cause profound impact in many CNS conditions.

Extrasynaptic GABA-A receptors are emerging as novel targets for epilepsy, pain, insomnia, and mood disorders. Neurosteroids activate extrasynaptic GABA-A receptor function and thus are attractive therapeutic agents.

Clinical trials are currently assessing neurosteroids for the treatment of diverse CNS disorders, such as epilepsy, SE, FXS, TBI, and Alzheimer's disease.

Neurosteroids can effectively control refractory SE because they affect both synaptic and extrasynaptic GABA-A receptors. New analogs are being identified based on neurosteroid pharmacophore map.

Neurosteroids

Neurosteroids (see Glossary) are endogenous steroids synthesized within the central nervous system (CNS) that have rapid effects on neuronal excitability. A variety of neurosteroids are present in the brain, including pregnane, androstane, and estrogen classes. The three prototype neurosteroids that are the most widely studied are allopregnanolone (AP, 5α-pregnan-3α-ol-20-one), allotetrahydrodeoxycorticosterone (THDOC, 5α-pregnan-3α,21-diol-20-one), and androstanediol (5α-androstan-3α-ol-20-diol) (Figure 1). Neurosteroids are synthesized in the brain from cholesterol or steroid hormone precursors via progressive A-ring reductions [1]. All necessary enzymes for the biosynthesis of neurosteroids are present in the brain. Neurosteroid synthesis occurs in glia and neurons in many brain regions, including the hippocampus and neocortex [1,2]. The biosynthesis of neurosteroids is controlled by the translocator protein **TSPO**. Neurosteroids are highly lipophilic, and therefore can easily cross the blood–brain barrier.

It has been known since the 1940s, from the pioneering work of Hans Selye, that steroid hormones progesterone and deoxycorticosterone can exert anesthetic and anticonvulsant actions [3–6]. In the early 1980s the synthetic neurosteroid, alphaxolone, was found to enhance synaptic inhibition via an action on GABA-A receptors in the brain [7]. A major advance occurred when neurosteroids were found to enhance GABA-A receptor function [8]. Consequently, neurosteroids have been shown to possess robust activity in animal models, and may have advantages over benzodiazepines, including lack of **tolerance** development with extended use

[1]Department of Neuroscience and Experimental Therapeutics, College of Medicine, Texas A&M University Health Science Center, Bryan, TX 77807, USA

*Correspondence: reddy@medicine.tamhsc.edu (D.S. Reddy).

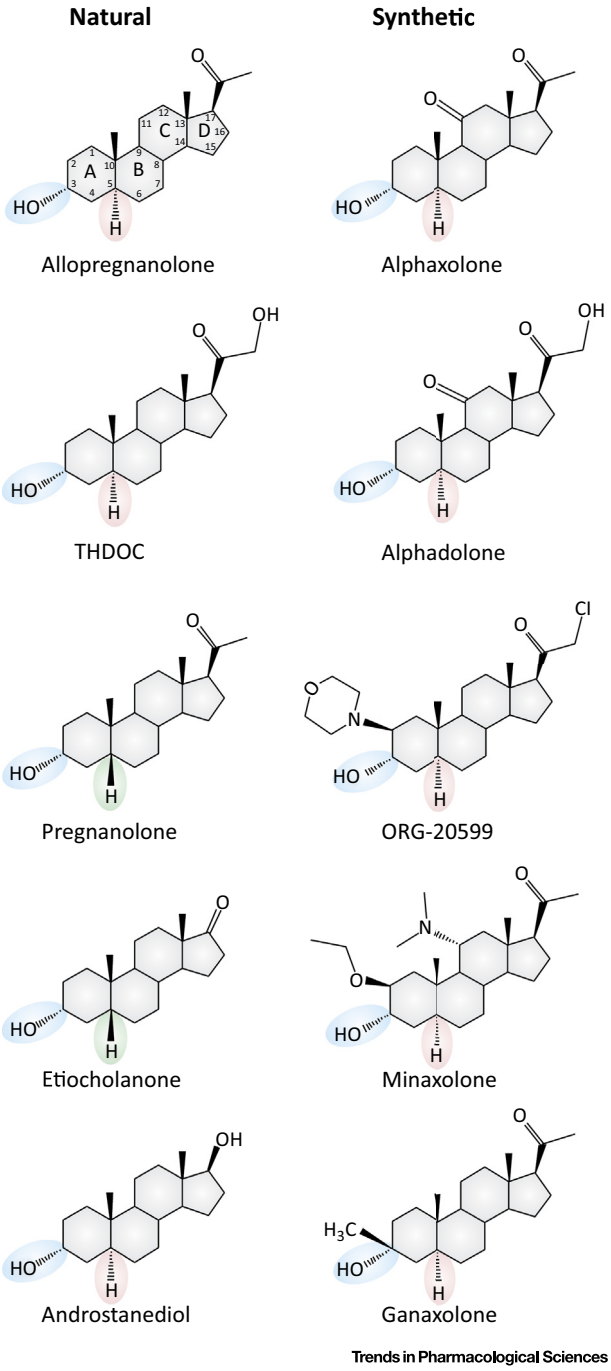

Figure 1. Chemical Structures of Natural and Synthetic Neurosteroids. The key stereospecific features of C3-OH and C5-H groups are highlighted for both naturally-occurring neurosteroids and their synthetic analogs.

Glossary

Allosteric agonist: an agonist that potentiates the response of an agonist by binding to a different site on the receptor by changing the affinity of the receptor for the agonist. The effect is saturable (ceiling) because potentiation reaches a limiting value when the allosteric site is fully occupied.

Catamenial epilepsy: a form of pharmacoresistant epilepsy in women in which seizures are clustered around specific points in the menstrual cycle, most often around the perimenstrual (C1) or periovulatory (C2) period.

DS2: 4-chloro-*N*-[2-(2-thienyl)imidazo [1,2-a]pyridin-3-yl]benzamide, a highly-selective experimental ligand of extrasynaptic δGABA-A receptors.

Neurosteroid: steroids that are synthesized locally within the brain and that rapidly alter neuronal excitability. Neuroactive steroids encompass both naturally occurring neurosteroids and their synthetic analogs that rapidly modulate neuronal excitability in the CNS.

ORG-20599: a water-soluble synthetic neurosteroid with allosteric GABA-A receptor activity: 2β,3α,5α-21-chloro-3-hydroxy-2-(4-morpholinyl) pregnan-20-one methanesulfonate.

Phasic inhibition: the post-synaptic inhibitory current conductance that occurs with synaptic release of GABA followed by transient activation of synaptic GABA-A receptors.

Status epilepticus (SE): a neurological emergency characterized by continuous seizure activity or multiple seizures without regaining consciousness for more than 30 minutes. It may be manifested in two types, generalized convulsive and nonconvulsive.

THIP: 4,5,6,7-tetrahydroisoxazolo-[4,5,c]-pyridin-3-ol, also called gaboxadol, is a δGABA-A receptor-preferring agonist. It has sedative and hypnotic activity, but its clinical development for insomnia was halted due to serious side-effects.

Tolerance: decreased response to repeated or chronic administration of the same drug.

Tonic inhibition: the extra-synaptic inhibitory current conductance that occurs with ambient or extracellular GABA, which persistently activates extra- and peri-synaptic GABA-A receptors.