Review Neuroscience. 2011 Sep 15;191:78-90. doi: 10.1016/j.neuroscience.2011.06.076. Epub 2011 Jul 1.

Pregnenolone as a Novel Therapeutic Candidate in Schizophrenia: Emerging Preclinical and Clinical Evidence

C E Marx [1], D W Bradford, R M Hamer, J C Naylor, T B Allen, J A Lieberman, J L Strauss, J D Kilts

Affiliations

Affiliation

1 Duke University Medical Center, Durham, NC, USA. marx0001@mc.duke.edu

PMID: 21756978 DOI: 10.1016/j.neuroscience.2011.06.076

Abstract

Emerging preclinical and clinical evidence suggests that pregnenolone may be a promising novel therapeutic candidate in schizophrenia. Pregnenolone is a neurosteroid with pleiotropic actions in rodents that include the enhancement of learning and memory, neuritic outgrowth, and myelination. Further, pregnenolone administration results in elevations in downstream neurosteroids such as allopregnanolone, a molecule with neuroprotective effects that also increases neurogenesis, decreases apoptosis and inflammation, modulates the hypothalamic-pituitary-adrenal axis, and markedly increases GABA(A) receptor responses. In addition, pregnenolone administration elevates pregnenolone sulfate, a neurosteroid that positively modulates NMDA receptors. There are thus multiple mechanistic possibilities for pregnenolone as a potential therapeutic agent in schizophrenia, including the amelioration of NMDA receptor hypofunction (via metabolism to pregnenolone sulfate) and the mitigation of GABA dysregulation (via metabolism to allopregnanolone). Additional evidence consistent with a therapeutic role for pregnenolone in schizophrenia includes neurosteroid changes following administration of certain antipsychotics in rodent models. For example, clozapine elevates pregnenolone levels in rat hippocampus, and these increases may potentially contribute to its superior antipsychotic efficacy [Marx et al. (2006a) Pharmacol Biochem Behav 84:598-608]. Further, pregnenolone levels appear to be altered in postmortem brain tissue from patients with schizophrenia compared to control subjects [Marx et al. (2006c) Neuropsychopharmacology 31:1249-1263], suggesting that neurosteroid changes may play a role in the neurobiology of this disorder and/or its treatment. Although clinical trial data utilizing pregnenolone as a therapeutic agent in schizophrenia are currently limited, initial findings are encouraging. Treatment with adjunctive pregnenolone significantly decreased negative symptoms in patients with schizophrenia or schizoaffective disorder in a pilot proof-of-concept randomized controlled trial, and elevations in pregnenolone and allopregnanolone post-treatment with this intervention were correlated with cognitive improvements [Marx et al. (2009) Neuropsychopharmacology 34:1885-1903]. Another pilot randomized controlled trial recently presented at a scientific meeting demonstrated significant improvements in negative symptoms, verbal memory, and attention following treatment with adjunctive pregnenolone, in addition to enduring effects in a small subset of patients receiving pregnenolone longer-term [Savitz (2010) Society of Biological Psychiatry Annual Meeting New Orleans, LA]. A third pilot clinical trial reported significantly decreased positive symptoms and extrapyramidal side effects following adjunctive pregnenolone, in addition to increased attention and working memory performance [Ritsner et al. (2010) J Clin Psychiatry 71:1351-1362]. Future efforts in larger cohorts will be required to investigate pregnenolone as a possible therapeutic candidate in schizophrenia, but early efforts are

promising and merit further investigation. This article is part of a Special Issue entitled: Neuroactive Steroids: Focus on Human Brain.

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