Proof-of-concept trial with the neurosteroid pregnenolone targeting cognitive and negative symptoms in schizophrenia (Article)

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Abstract

The neurosteroid pregnenolone and its sulfated derivative enhance learning and memory in rodents. Pregnenolone sulfate also positively modulates NMDA receptors and could thus ameliorate hypothesized NMDA receptor hypofunction in schizophrenia. Furthermore, clozapine increases pregnenolone in rodent hippocampus, possibly contributing to its superior efficacy. We therefore investigated adjunctive pregnenolone for cognitive and negative symptoms in patients with schizophrenia or schizoaffective disorder receiving stable doses of second-generation antipsychotics in a pilot randomized, placebo-controlled, double-blind trial. Following a 2-week single-blind placebo lead-in, patients were randomized to pregnenolone (fixed escalating doses to 500 mg/day) or placebo, for 8 weeks. Primary end points were changes in BACS and MCCB composite and total SANS scores. Of 21 patients randomized, 18 completed at least 4 weeks of treatment (n = 9/group). Pregnenolone was well tolerated. Patients receiving pregnenolone demonstrated significantly greater improvements in SANS scores (mean change = 10.38) compared with patients receiving placebo (mean change = 2.33), p = 0.048. Mean composite changes in BACS and MCCB scores were not significantly different in patients randomized to pregnenolone compared with placebo. However, serum pregnenolone increases predicted BACS composite scores at 8 weeks in the pregnenolone group (r_s = 0.81, p = 0.022). Increases in allopregnanolone, a GABAergic pregnenolone metabolite, also predicted BACS composite scores (r_s = 0.74, p = 0.046). In addition, baseline pregnenolone (r_s = -0.76, p = 0.037), pregnenolone sulfate (r_s = -0.83, p = 0.015), and allopregnanolone levels (r_s = -0.83, p = 0.015) were inversely correlated with improvements in MCCB composite scores, further supporting a possible role for neurosteroids in cognition. Mean BACS and MCCB composite scores were correlated (r_s = 0.74, p = 0.0001). Pregnenolone may be a promising therapeutic agent for negative symptoms and merits further investigation for cognitive symptoms in schizophrenia.