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Neurosteroids as endogenous regulators of seizure susceptibility and use in the treatment of epilepsy

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SUMMARY

Neurosteroids such as allopregnanolone are positive allosteric modulators of GABA_A receptors with powerful antiseizure activity in diverse animal models. Neurosteroids may be endogenous regulators of seizure susceptibility, for example, in catamenial epilepsy. Clinical trials with the synthetic neurosteroid analog ganaxolone in the treatment of refractory partial seizures and infantile spasms have been encouraging. Neurosteroids and analogs such as ganaxolone show promise in the treatment of diverse forms of epilepsy. For an expanded treatment of this topic see *Jasper's basic mechanisms of the epilepsies*, 4th ed. (Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV, eds) published by Oxford University Press (available on the National Library of Medicine Bookshelf [NCBI] at www.ncbi.nlm.nih.gov/books).

Keywords

Allopregnanolone; clinical trials; GABA_A receptor; Ganaxolone; Infantile spasms; Partial seizures

Neurosteroids are endogenous steroid hormone metabolites that lack conventional hormonal activity and instead rapidly alter neuronal excitability through direct interaction with neurotransmitter-gated ion channels, most notably GABA_A receptors (Hosie et al., 2007). At low concentrations, neurosteroids such as allopregnanolone potentiate GABA receptor currents, whereas at higher concentrations, they directly activate the receptor. Natural and synthetic GABA_A receptor modulating neurosteroids confer seizure protection in diverse animal models, without the development of tolerance (Reddy, 2003). Ganaxolone, the synthetic 3 β -methyl analog of allopregnanolone, is the only neurosteroid-like agent that has been evaluated in human clinical trials for the treatment of epilepsy (Rogawski et al., 2010). Ganaxolone modulates GABA_A receptors in a comparable fashion to allopregnanolone and has protective activity against clonic seizures induced by diverse chemoconvulsants including pentylenetetrazol and limbic seizures in the 6 Hz model. In addition, a recent study in female amygdala kindled mice demonstrated suppression of behavioral and electrographic seizures with ED₅₀ of 6.6 mg/kg (Reddy and Rogawski, 2010). Over the past decade, ganaxolone has been studied in various clinical trials to assess its efficacy and safety in the treatment of epilepsy. A recent randomized, double-blind controlled study compared

ganaxolone (500 mg, t.i.d.) to placebo in 147 adults with partial onset seizures who were refractory to conventional antiepileptic drugs. The mean weekly seizure frequency, the primary endpoint, and the percent change from baseline in weekly seizure frequency were significantly improved in the ganaxolone group.

A randomized, placebo-controlled study of 56 infants and toddlers with refractory infantile spasms showed clear trends toward benefit in terms of reduction in seizure clusters, responder rate, resolution of hypsarrhythmia, and investigator's global assessment, although the study did not reach significance with respect to its predefined outcome.

More than 900 subjects have received ganaxolone in human clinical trials; common treatment-related adverse events are dizziness and fatigue but discontinuation rates have generally been similar to that of placebo. Overall, ganaxolone appears to be an efficacious, well-tolerated and safe treatment for partial seizures that is probably also effective for infantile spasms.

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