Endogenous neurosteroids are required for normal synaptic transmission and plasticity in the dentate gyrus of the rat hippocampus.

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Exogenously applied some neurosteroids promote learning and memory by modulating synaptic functions in the hippocampus, yet little is known about the degree to which endogenously synthesized levels of neurosteroids in the brain contribute to this effect. Cytochrome P450scc is the enzyme that converts cholesterol to pregnenolone (PREG), which is required for the biosynthesis of all neurosteroids. We thus examined electrophysiologically the effects of aminoglutethimide (AG), an inhibitor of P450scc, on the synaptic transmission and plasticity in the dentate gyrus of rat hippocampal slices. An application of AG depressed basal excitatory synaptic transmission by approximately 23 % in 20 min. The AG-induced depression was nearly completely rescued by exogenously applied 500 nM PREG, and also was significantly rescued by 20 nM exogenous dehydroepiandrosterone, one of the neurosteroids synthesized from PREG. AG did not affect the presynaptic properties or GABAergic transmission, but significantly reduced AMPA receptor-mediated currents in postsynaptic granule cells. Moreover, AG reduced NMDA receptor-mediated currents, and thereby suppressed NMDA receptor-dependent long-term potentiation (LTP). These findings provide the first evidence that the neurosteroids locally synthesized in the brain potentiate basal excitatory synaptic transmission through the modulation of AMPA receptors, and facilitate synaptic plasticity by modulating NMDA receptors in the dentate gyrus.