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Regulation of activity-dependent synaptic plasticity and synaptic expression of glutamate receptors by the neurosteroid pregnenolone sulfate: implications for learning and memory

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Abstract:
Neurosteroids and synthetic analogs may be the basis for the development of adjunctive treatments for multiple CNS disorders ranging from super-refractory status epilepticus to neurodevelopmental disorders such as schizophrenia. Clinical trials suggest that the endogenous neurosteroids pregnenolone (PREG) with its immediate metabolite pregnenolone sulfate (PregS) show promise in the treatment of cognitive disorders (Marx et al., 2014, Psychopharm. 231 (17):3647). For example, therapeutic approaches aimed at restoring steroidogenesis in patients with PCDH-19 female limited epilepsy have recently been reported (Trivisano et al., Epilepsia,1-5, 2017). 110xC19 steroids and PregS might serve as clinically useful biomarkers of disease control in 21-hydroxylase deficiency (Turcu et al., 2017 J. Clin. Endocrinol Metab. 2016-3989). We recently reported that low nanomolar concentration of PregS, induced a delayed onset increase of the neuronal response to NMDA and trafficking of NMDAR to the cell surface through an intracellular calcium ([Ca2+]i) dependent mechanism (Kostakis et al., 2013, Mol. Pharm. 84:261). Moreover we have shown that low picomolar PregS increases [Ca2+]i and CREB phosphorylation and the frequency of spontaneous excitatory postsynaptic currents (Smith et al., 2014, Mol. Pharm. 86:390)
Here we report that picomolar PregS stimulates synaptic expression of GluA1-containing AMPA receptor puncta on proximal spines of hippocampal neurons in culture in a synaptic GluN2B- and L-Type voltage gated Ca^{++} channel-dependent manner. cAMP-dependent PKA and casein kinase 2 are mechanistically involved in this process. Recent reports show that repeated injections of the neurosteroid PregS, in rats have resulted in enhanced memory, spatial orientation and object discrimination (Plescia et al., 2014, Behav. Brain Res. 258 :193). To ask

whether PREG and/or PregS might modulate spatial memory, we examined the effect of escalating doses of PregS and Preg (0.1, 1.0 and 10.0 mg/kg s.c.) on place cell dynamics. PregS but not PREG induced a dose dependent increase in spatial information content during repeated foraging-based exploration of a familiar environment. These findings suggest that spatial specificity of place cell firing is increased by PregS but not PREG.
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