

Benzodiazepine-induced hippocampal CA1 neuron alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor plasticity linked to severity of withdrawal anxiety: differential role of voltage-gated calcium channels and N-methyl-D-aspartic acid receptors.

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Withdrawal from 1-week oral administration of the benzodiazepine, flurazepam (FZP) is associated with increased alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor (AMPA) miniature excitatory postsynaptic currents (mEPSCs) but reduction of N-methyl-D-aspartic acid (NMDA) receptor (NMDAR)-evoked (e)EPSCs in hippocampal CA1 neurons. A positive correlation was observed between increased AMPAR-mediated mEPSC amplitude and anxiety-like behavior in 1-day FZP-withdrawn rats. These effects were disrupted by systemic AMPAR antagonist administration (GYKI-52466, 0.5 mg/kg, intraperitoneal) at withdrawal onset, strengthening the hypothesis that CA1 neuron AMPAR-mediated hyperexcitability is a central component of a functional anatomic circuit associated with the expression of withdrawal anxiety. Abolition of AMPAR current upregulation in 2-day FZP withdrawn rats by GYKI-52466 injection also reversed the reduction in NMDAR-mediated eEPSC amplitude in CA1 neurons from the same rats, suggesting that downregulation of NMDAR function may serve a protective, negative-feedback role to prevent AMPAR-mediated neuronal overexcitation. NMDAR antagonist administration (MK-801, 0.25 mg/kg intraperitoneally) had no effect on modifying increased glutamatergic strength or on withdrawal anxiety, whereas injection of an L-type voltage-gated calcium channel antagonist, nimodipine (10 mg/kg, intraperitoneally) averted AMPAR current enhancement and anxiety-like behavior, suggesting that these manifestations may be initiated by a voltage-gated calcium channel-dependent signal transduction pathway. An evidence-based model of likely cellular mechanisms in the hippocampus contributing to benzodiazepine withdrawal anxiety was proposed implicating regulation of multiple CA1 neuron ion channels.

PMID: 17762513 [PubMed - indexed for MEDLINE]