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Caffeine potentiates the release of GABA mediated by NMDA receptor activation: Involvement of adenosine A1 receptors

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Caffeine, a widely consumed psychoactive substance, acts in several targets in the nervous system. We investigated its role in retinal explants of chick embryo analyzing the role of purinergic receptors in [3H]-GABA release induced by D-aspartate (D-asp). D-asp increases GABA-release 4.5-fold when compared to basal levels from 13-day-old chick embryo retinal explants. Caffeine 500μM elevated D-asp-induced GABA release in 60%. The release was inhibited in the presence of NNC-711, a GABA transporter-1 (GAT-1) blocker or by MK-801, an N-methyl-d-aspartate receptor (NMDAR) antagonist. Caffeine did not modify [3H]-GABA uptake carried out for 5, 10, 30 and 60 min and did not increase the release of D-asp or glutamate at basal or stimulated conditions. Caffeine effect was mimicked by the adenosine A1 receptor antagonist DPCPX and by the adenylyl cyclase activator forskolin. It was also blocked by the protein kinase A (PKA) inhibitor H-89, tyrosine kinase inhibitor genistein or by the src family kinase (SFK) inhibitor PP1. Forskolin-stimulated cyclic adenosine monophosphate (cAMP) levels were reduced in the presence of the A1 receptor agonist CHA. Western blot analysis revealed that caffeine increased phosphoGluN2B expression levels in approximately 60% when compared to total GluN2B levels in embryonic E13 retina. The GluN2B subunit-containing NMDAR antagonist ifenprodil inhibited caffeine effect. Our results suggest that caffeine potentiates D-asp-induced GABA release, which is mediated by GAT-1, via. inhibition of adenosine A1 receptor and activation of the PKA pathway. Regulation of NMDAR by phosphorylation of GluN2B subunit by a SFK may also be involved in the effect promoted by caffeine.

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Postnatal development and reproductive performance of f1 progeny exposed in utero to an aqueous formulation of *Tinospora cordifolia*

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The present study investigated the development effect of aqueous extract of Tinospora cordifolia commonly known as Guduchi and Giloy. It is an herbaceous vine of the family Menispermaceae. The reproductive toxicity of Tinospora cordifolia was evaluated in rats administered oral doses of 250, 500 or 1000 mg/kg. Twenty rats per sex per dose group were selected in both Parent and F1 generation. In the fertility and early embryonic development to implantation study, male and female rats were treated 2 weeks of pre-mating, 2 weeks of mating and 6 weeks of post-mating in which 3 weeks of Gestation (GD) and 3 weeks of lactation until necropsy. However, in F1 the pups were treated post natal until necropsy including developmental stages of maturation, pre mating, mating and post mating. In the pre- and postnatal development study, pregnant rats were treated from GD 3 weeks through lactation day 3 weeks. Selected F1 pups from this study were evaluated in sensory and behavioral tests and were subsequently mated. No treatment-related effects were observed fetal development, parturition or lactation in the Parent (P) generation. Similarly, no adverse effects of Tinospora cordifolia treatment were observed on pre- and postnatal growth, development, reproductive performance and embryo-development in the F1 offspring. Based on the results of this study, the No-Observed-Adverse-Effect-Level (NOAEL) for development and reproductive toxicity in rats was considered to be 1000 mg/kg/day, the highest dose tested.

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