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Dual effects of anandamide in the antiepileptic activity of diazepam in pentylenetetrazole-induced seizures in mice

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Abstract

The prototype endocannabinoid, anandamide activates both CB₁ and transient receptor potential vanilloid type 1 channels (TRPV1) receptor at different concentrations. At high concentrations, anandamide-mediated TRPV1 effects are opposite to its effects at low concentrations via CB₁ receptor. Thus, synaptic concentrations of anandamide govern the neuronal activity and consequently might affect the response of a drug. This study was undertaken to investigate the influence of high and low doses of anandamide on the anticonvulsant action of diazepam on the subcutaneous dose of pentylenetetrazole (PTZ) in Swiss mice weighing 20–25 g. Results revealed that intracerebroventricular administration of capsazepine (a TRPV1 antagonist: 1, 10, or 100 µg/mouse) and the low doses (10 µg/mouse) of anandamide, AM404 (anandamide transport inhibitor), or URB597 (fatty acid amide hydrolase inhibitor) augmented the anticonvulsant effect of diazepam. Conversely, higher dose of anandamide, AM404, URB597 (100 µg/mouse) as well as capsaicin (a TRPV1 agonist: 1, 10, or 100 µg/mouse) attenuated the protective effect of diazepam against PTZ-induced seizures. Thus, this study demonstrates that the effects of diazepam may be augmented by activating CB₁ receptors or dampened via TRPV1 receptors. The findings of the present study can be extrapolated to understand the use of TRPV1 blockers alone or in combination of benzodiazepines in the treatment of benzodiazepines-refractory status epilepticus, a condition associated with maladaptive trafficking of synaptic gamma-aminobutyric acid and glutamate receptors. However, potential clinical applications are needed to further support such preclinical studies.

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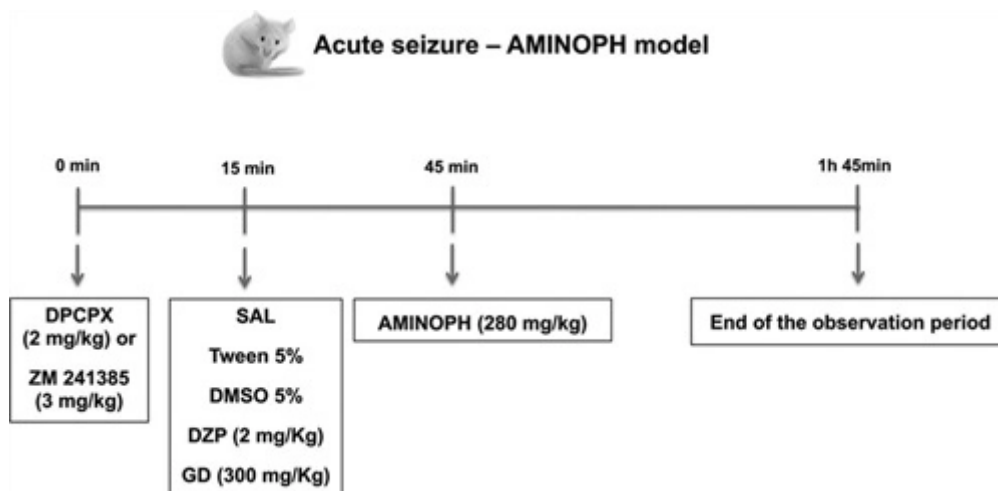
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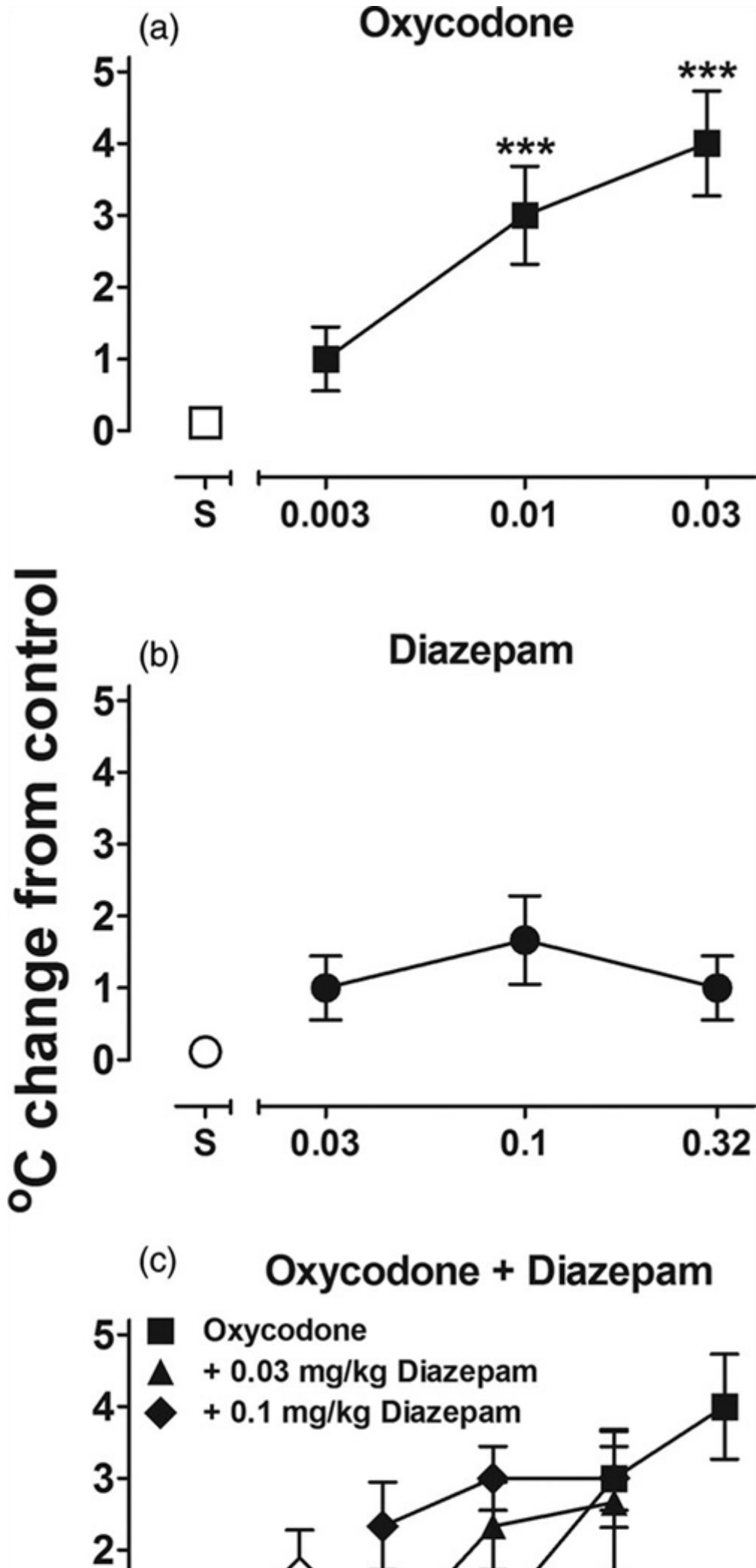
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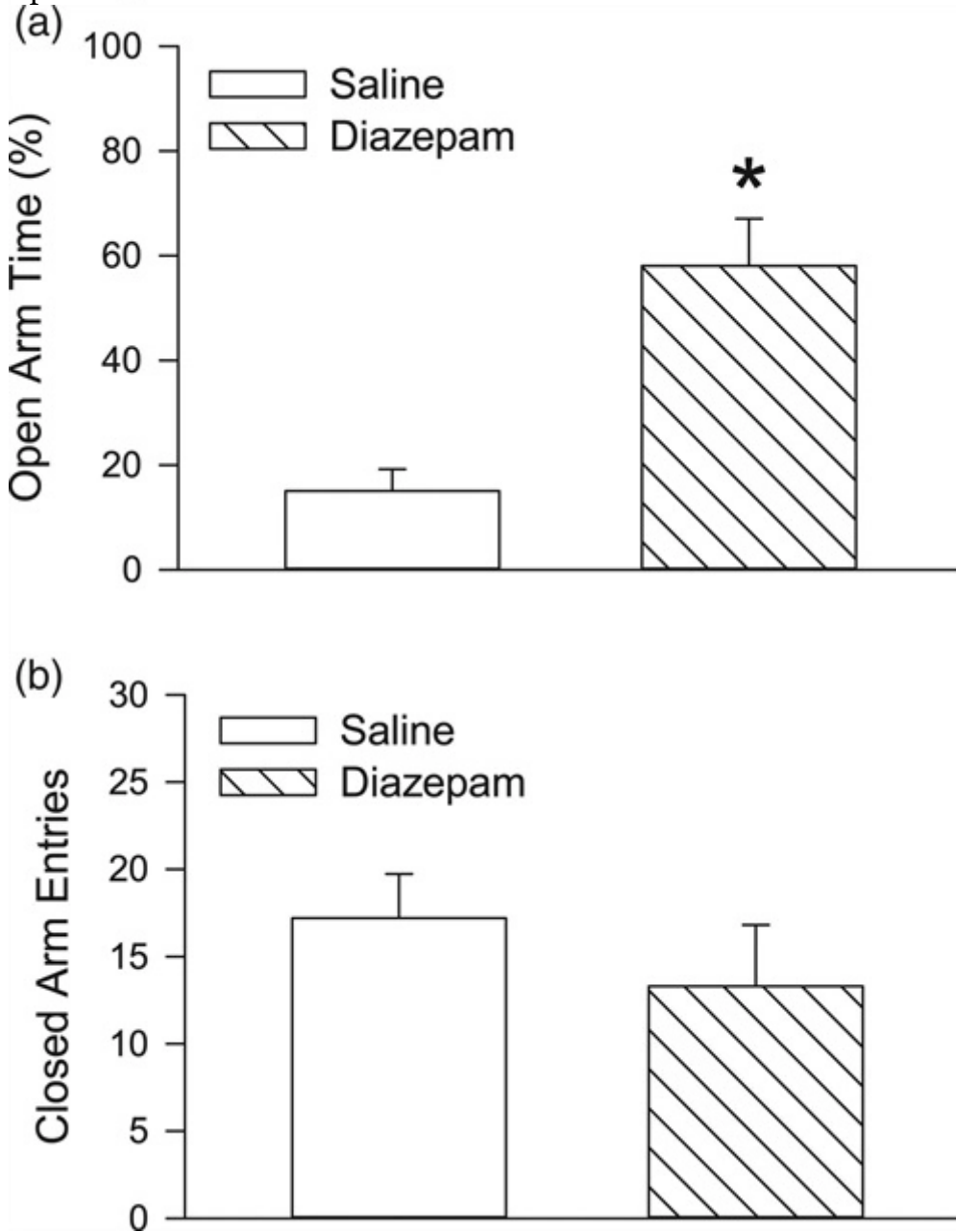
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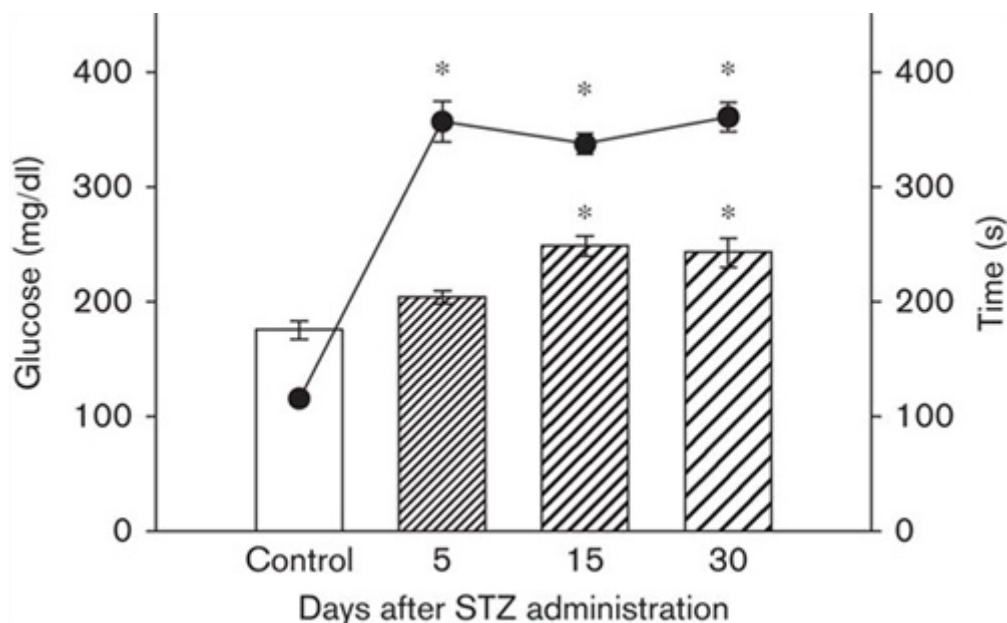
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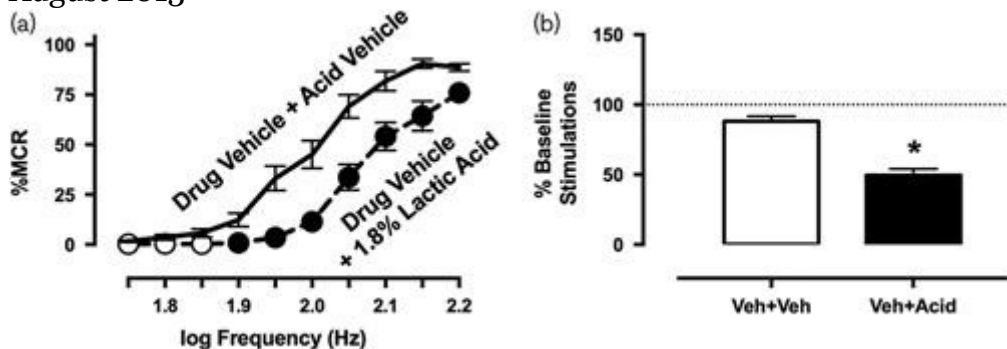
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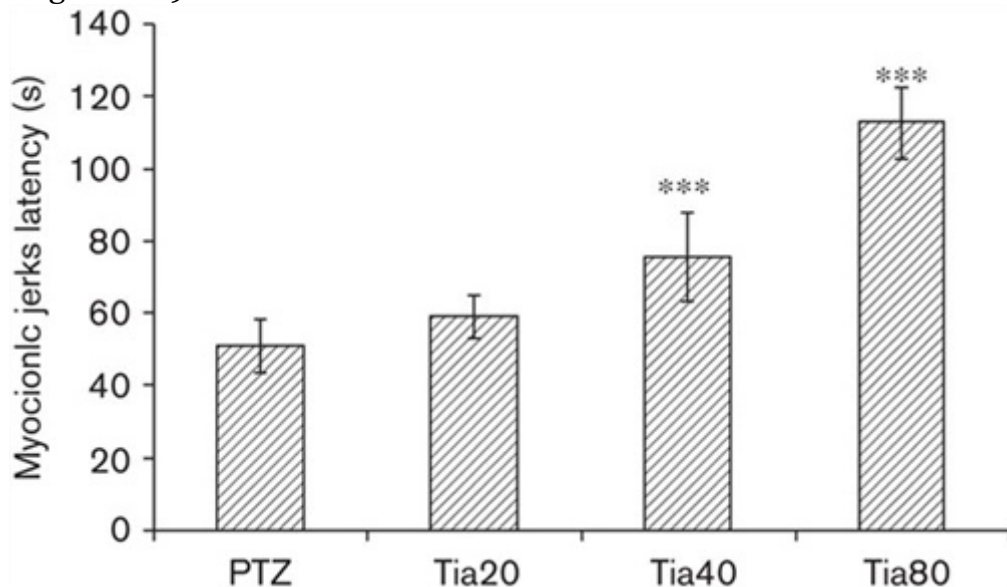
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