Acute exposure to caffeine decreases the anticonvulsant action of ethosuximide, but not that of clonazepam, phenobarbital and valproate against pentetrazole-induced seizures in mice

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Abstract:
This study examines the effect of acute administration of caffeine sodium benzoate (CAF) on the anticonvulsant action of four conventional antiepileptic drugs (AEDs: clonazepam – CZP, ethosuximide – ETS, phenobarbital – PB and valproate – VPA) against pentetrazole (PTZ)-induced clonic seizures in mice. The results indicate that CAF at a dose of 92.4 mg/kg significantly reduced the threshold for PTZ-induced clonic seizures in mice from 69.5 to 51.7 mg/kg (p < 0.05), being ineffective at lower doses of 69.3 and 46.2 mg/kg. Moreover, CAF at doses of 69.3 and 92.4 mg/kg attenuated the protective action of ETS against PTZ-induced seizures, by increasing its median effective dose (ED₅₀) from 127.7 to 182.3 (p < 0.05), and 198.3 mg/kg (p < 0.01), respectively. In this case, no pharmacokinetic changes in total brain ETS concentrations after systemic ip administration of CAF (at 92.4 mg/kg) were observed, indicating a pharmacodynamic nature of interaction between ETS and CAF in the PTZ-test in mice. In contrast, CAF (at a dose of 92.4 mg/kg reducing the threshold for PTZ-induced seizures) combined with other AEDs (CZP, PB and VPA) did not affect their anticonvulsant action in the PTZ test in mice. Moreover, CAF (92.4 mg/kg) did not alter significantly total brain concentrations of the remaining AEDs (CZP, PB and VPA). The evaluation of potential acute adverse effects produced by AEDs in combination with CAF revealed that neither CAF (up to 92.4 mg/kg) administered alone nor combined with the studied drugs (at doses corresponding to their ED₅₀ values in the PTZ-test) affected motor performance of animals in the chimney test.
In conclusion, the acute exposure to CAF may diminish the antiseizure protection offered by ETS in epileptic patients. Therefore, patients treated with ETS should avoid CAF.

Key words:
caffeine, ethosuximide, antiepileptic drugs, pentetrazole, pharmacodynamic interaction