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Original research article

Influence of caffeine on the protective activity of gabapentin and topiramate in a mouse model of generalized tonic-clonic seizures

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ABSTRACT

Background: Caffeine may interact with classical antiepileptic drugs (AEDs), reducing their anticonvulsant effects in basic seizure models. The aim of the present study was to ascertain whether intraperitoneal caffeine (acute or chronic for 15 days) could attenuate the anticonvulsant effect of some newer AEDs: gabapentin (GBP) and topiramate (TPM) against electroconvulsions in mice.
Methods: Maximal electroshock (MES)-induced mouse seizure model was used for the estimation of the anticonvulsant activity of TPM whilst the protective activity of GBP was evaluated in the threshold test for maximal (tonic) convulsions. Adverse effects were evaluated by measurement of long-term memory (the step-through passive avoidance task) and motor coordination (chimney test). Plasma AED concentrations were also measured to determinate any pharmacokinetic contribution to the observed effects.
Results: Caffeine (both acute and chronic at 23.1 and 46.2 mg/kg) significantly reduced the protective effects of TPM against MES. As regards GBP, caffeine (acutely at 46.2 mg/kg and chronically at 23.1 or 46.2 mg/kg) significantly diminished the GBP-induced increases in the electroconvulsive threshold. In addition, caffeine did not affect the free plasma concentrations of TPM or GBP. Acute and chronic caffeine (23.1 and 46.2 mg/kg) enhanced the impairment of motor coordination in mice pretreated with GBP whilst an opposite effect was observed in TPM injected mice and pretreated with chronic caffeine at 46.2 mg/kg.
Conclusion: The results indicate that newer AEDs, GBP or TPM behave in the exactly same way as classical antiepileptics in mice challenged with caffeine. This hazardous effect of caffeine is not subject to tolerance.
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Introduction

Caffeine (1,3,7-trimethylxanthine) belongs to the group of purine alkaloids and is found in beverages such as coffee, tea, and many soft drinks as well as in chocolate products and desiccated coconut. This methylxantine (MTX) is probably the most consumed psychoactive substance in the world. It is estimated that in developed countries 90% of people ingest caffeine on a daily basis [1–4]. The daily consumption of this MTX is about 200 mg per person, which produces pharmacologically active blood concentrations [1]. Caffeine, apart from its questionable impact on the improvement of cognitive function, has a number of adverse effects through stimulation of the sympathetic nervous system, leading to elevated blood pressure, enhanced lipolysis with an increase in the concentration of free fatty acids in plasma and psychomotor agitation. In addition to behavioral effects – irritability, increased tension, anxiety, caffeine can cause cardiac arrhythmias, panic attack, insomnia or hypertension [5–9]. Long-term use of caffeine leads to the development of dependence and tolerance to its central effects and the cessation of its use produces a discrete withdrawal syndrome – headache, irritability, drowsiness [1,10].The most dangerous complication of caffeine overdose is seizure activity. This MTX has been shown not only proconvulsant in animal models of seizures [11–13] but also to increase seizure frequency in patients with epilepsy [14,15].

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The inhibitory role of adenosine in the control of seizure activity has been well characterized [16,17]. There are four main adenosine receptors: A1, A2A, A2B, and A3. All these types are coupled to G-proteins and adenosine is their endogenous ligand [18,19]. Caffeine has been documented to produce seizures *per se* [11,12,18] and induce epileptic discharges [20]. This effect of caffeine is correlated with its affinity to A_1 adenosine receptors.

Interestingly, caffeine may interact with antiepileptic drugs (AEDs) and reduce their anticonvulsant effects in basic seizure models. The experimental data indicate that this MTX administered acutely (11.55–92.4 mg/kg, which is an equivalent to 12.5–100 mg/kg of aminophylline) impairs the protective activity of conventional AEDs: carbamazepine, phenobarbital, phenytoin and valproate against maximal electroshock (MES)-induced seizures in mice [17]. However, caffeine remained ineffective upon the protective activity of some newer antiepileptics, lamotrigine, oxcarbazepine, and tiagabine against electroconvulsions in mice [21]. The aim of the present study was undertaken to ascertain whether caffeine could attenuate the anticonvulsant effects of other newer AEDs: gabapentin (GBP) and topiramate (TPM). Electroconvulsive mouse seizure model was used for the estimation of the anticonvulsant activity of studied drugs and adverse effects were ascertained by measurement of long-term memory (the step-through passive avoidance task) and motor coordination (chimney test). Plasma AED concentrations were also measured to determinate any pharmacokinetic contribution to the observed effects.

Materials and methods

Animals

The experiments were conducted on male Swiss mice, weighing 22–27 g. Experimental groups, consisting of 8–10 animals, were chosen randomly. The animals were housed in colony cages, under standard laboratory conditions, with free access to food (chow pellets, Bacutil, Motycz, Poland) and tap water.

All mice were maintained at an ambient temperature of $20 \pm 1^{\circ}$ and on the natural light-dark cycle. Animals from appropriate groups were tested on the same day, in order to provide optimally objective results of the experiment. All procedures undertaken in this study were approved by a Local Ethical Committee.

Drugs

The following AEDs were used in this study: topiramate (TPM; Cilag AG, Schaffhausen, Switzerland) and gabapentin (GBP, Parke-Davis Pharmaceutical Research, Plymouth, UK). AEDs were suspended in a 1% solution of Tween 80 (Sigma, St. Louis, MO, USA). Caffeine (Coffeinum Natrium benzoicum, Pliva, Kraków, Poland) was available as a commercial solution, made up with sterile saline to the desired volume and given *ip* in doses referring to the pure MTX. All doses of AEDs, which were also administered *ip*, refer to their free forms. The injection volume was 5 ml/kg.

Experimental schedule

Caffeine or vehicle was injected twice a day (at 7.00 a.m. and 7 p.m.) as follows:

- Group 1 – a control group for the estimation of the electroconvulsive threshold. Saline was given for 15 days
- Group 2 – saline for 14 days and then on day 15th caffeine was given prior to the estimation of the electroconvulsive threshold
- Group 3 – caffeine for 15 days prior to the threshold evaluation
- Group 4 – a control group for the calculation of ED_{50} values for the tested AEDs. Saline was administered for 15 days twice daily, followed by the injection of an AED on day 15th
- Group 5 – saline for 14 days twice daily and then, on the 15th day, caffeine in a single dose (acute caffeine) + an AED
- Group 6 – caffeine for 14 days, twice a day (chronic caffeine), the last injection of caffeine + an AED being given on day 15th.

On day 15th, mice from groups 4–6, as indicated above, received TPM or GBP, given 60 min before tests. Caffeine was administered 30 min before tests. Doses of caffeine were 23.1 and 46.2 mg/kg. Caffeine doses used in this study were estimated on the basis of the previous research [22]. Treatment times to provide maximum anticonvulsant effects were also based on the results of previous studies [23,24].

MES

MES was produced with the use of auricular electrodes and alternating current (50 Hz and fixed current intensity of 25 mA), delivered by a Hugo Sachs generator (rodent Shocker, type 221, Freiburg, Germany). The stimulus duration was 0.2 s. The end point was the tonic extension of the hind limbs. The protective efficacy of TPM was determined as its ability to protect 50% of mice against the MES-induced tonic hind limb extension and expressed as its median effective dose (ED_{50}) value.

Determination of the convulsive threshold

GBP influence on the threshold for electroconvulsions was estimated, because this AED is not fully effective against MES-induced tonic seizures in mice. Electroconvulsions were induced by an alternating current (60 Hz) delivered via ear-clip electrodes, by the Hugo Sachs generator. The experimental groups were challenged with electroshocks of various intensities and duration of 0.2 s. The electroshock intensity applied in the control group oscillated between 6 and 8 mA, and in the GBP group – between 12 and 16 mA. Tonic hind limb extension was taken as the criterion for the occurrence of seizure activity. The convulsive threshold as a CS_{50} value (current strength 50%) was determined. Each CS_{50} value represents the current strength (in mA) necessary to induce tonic hind limb extension in 50% of the animals challenged with electroconvulsions.

Chimney test

The effects of TPM and GBP alone or in combination with caffeine on motor performance of mice were quantified with the chimney test of Boissier et al. [25]. In this test, animals had to climb backwards up a plastic tube with rough inner surface (25-cm length, 3-cm inner diameter). Motor impairment was characterized by the inability of the animals to perform the test within 60 s. The neurotoxic effects of AEDs were expressed as their TD_{50} values, representing the doses at which the AEDs impaired motor coordination in 50% of the animals tested.

Passive avoidance task

According to Venault et al. [26], the step-through passive avoidance task may be considered as a measure of long-term memory acquisition. The test was performed during two consecutive days. The animals were placed separately in an illuminated box (10 cm × 13 cm × 15 cm), connected to a larger (25 cm × 20 cm × 15 cm) dark compartment equipped with an electric grid floor. The entry into the dark compartment was

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