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Short communication

Cytisine inhibits the anticonvulsant activity of phenytoin and lamotrigine in mice

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Abstract:
Background: Cytisine (CYT), the most commonly used drug for smoking cessation in Poland, was experimentally found to induce convulsions. There is a lack of studies on the influence of CYT on the anticonvulsant activity of antiepileptic drugs (AEDs).
Methods: The effects of CYT on the anticonvulsant activity of six AEDs were examined in maximal electroshock (MES)-induced seizures in mice.
Results: Single intraperitoneal (*ip*) administration of CYT in a subthreshold dose of 2 mg/kg antagonized the protective activity of *ip* phenytoin and lamotrigine against MES-induced seizures in mice. A dose of 1 mg/kg did not reverse the protective activity of phenytoin and lamotrigine. CYT in a dose of 2 mg/kg had no effect on the anticonvulsive activity of carbamazepine, oxcarbazepine, phenobarbital, and valproate magnesium.
Conclusion: CYT ability to antagonize the anticonvulsive activity of phenytoin and lamotrigine can be of serious concern for epileptic smokers, who might demonstrate therapeutic failure to these drugs resulting in possible breakthrough seizure attacks.

Key words:
cytisine, epilepsy, lamotrigine, maximal electroshock, nicotinic receptors, phenytoin, smoking cessation

Introduction

Cytisine (CYT) is a plant alkaloid used in medicine for hundreds years, including smoking cessation [4, 14, 16, 19]. Recent clinical trials conducted in Poland demonstrated that CYT was at least equally, if not more, effective for smoking cessation as the available pharmacological therapies [18, 21]. The evidence suggests that the antismoking effects of CYT are determined by its partial agonism at brain $\alpha 4\beta 2$ nicotinic acetylcholine receptors (nAChRs) [9]. CYT, binding to these receptors and causing a moderate and sustained release of mesolimbic dopamine, attenuates

the consequences of both nicotine exposure and its withdrawal [2, 10].

CYT seems to be well tolerated in healthy smokers [17, 18, 21]; however, despite its 40+ years on the market, the number of preclinical and clinical studies on its safety is very limited and existing data are not sufficient to support registration of the drug in most European countries and the US [15]. Given the life-saving potential of the drug across the globe there is an urgent need to undertake a rigorous evaluation of its safety.

The activation of brain nAChRs is involved in clonic-tonic convulsions induced by nicotine [3]. It was experimentally found that CYT could also induce convulsions [1, 12], but its effect on the course and clinical outcome of epilepsy in patients remains unknown. In addition, there is a lack of studies on the effects of CYT on the anticonvulsant activity of antiepileptic drugs in epileptic patients.

Therefore, we examined the influence of CYT on the anticonvulsive action of six antiepileptic drugs on maximal electroshock (MES)-induced seizures, which are thought to be an experimental model of human generalized tonic-clonic seizures in mice.

Materials and Methods

Animals

The experiments were performed on adult male Swiss mice weighing 20–25 g. The animals were kept in standard laboratory conditions on a natural light-dark cycle, with ambient temperature of 18–22°C, relative humidity of 52–58%, and unlimited access to chow pellets and water. All animals were acclimatized to their home cages for 1 week before testing. The experimental groups, consisting of 8 mice, were chosen by means of a randomized schedule. Each mouse was used only once. The tests were performed between 8:00 and 14:00 h. The control groups were always tested on the same day as the corresponding experimental groups. The experimental protocol and procedures were followed according to "Principles of Laboratory Animal Care" (NIH publication No. 86–23, revised 1985), approved by the Medical University of Lublin Ethics Committee for the use of experimental animals and confirmed with the European Communities Council Directive (86/609/EEC).

Drugs

The following drugs were used in this study: carbamazepine (CBZ, Sigma-Aldrich, St. Louis, MO, USA), cytisine (CYT, Tabex, Sopharma-Poland Sp. z o.o. Warszawa, Poland), lamotrigine (LTG, Lamitrin, GlaxoSmithKline Export Ltd., Brentford, Great Britain), oxcarbazepine (OXC, Trileptal; Novartis Pharma GmbH, Nürnberg, Germany), phenobarbital (PHB, Pharmaceutical Company "Unia", Warszawa, Poland), phenytoin (DPH, Warsaw Pharmaceutical Works Polfa S.A., Warszawa, Poland), valproate magnesium (VPA, ICN Polfa Rzeszów S.A., Rzeszów, Poland).

All the drugs were suspended in a 1% solution of Tween 80 (Sigma-Aldrich, St. Louis, MO, USA) in sterile saline (NaCl, 0.9%, Baxter Terpol, Sieradz, Poland) immediately before intraperitoneal (*ip*) administration at a volume of 10 ml/kg of body weight. Fresh drug solutions or suspensions were prepared *ex tempore* on each experimental day. Control animals were injected with equivalent amounts of sterile saline or 1% solution of Tween 80 in sterile saline using the same route.

Electroconvulsions

All the procedures were conducted after at least 30 min of acclimatization to the experimental conditions. Electroconvulsions were produced with a current delivered *via* ear-clip electrodes by a Rodent Shocker generator (constant-current stimulator Type 221, Hugo Sachs Elektronik, Freiburg, Germany). The criterion for convulsant activity was tonic hindlimb extension (i.e., the hind limbs of animals became extended at 180° to the plane of the body axis).

MES seizure threshold test

Animals were subjected to the current stimulation with constant duration (0.2 s) and different intensities (5–10 mA). Each time the number of convulsing out of total animals in an experimental group was registered and CS_{50} value (current $strength_{50}$), i.e., median current strength (in mA) necessary to induce tonic convulsions in 50% of animals, was calculated.

MES seizure test

Mice were challenged with set current intensity and stimulus duration (25 mA and 0.2 s, respectively) [7]. All animals in control groups produced seizures.