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Original article

Antidepressant-like effect of 1,2,3,4-tetrahydroisoquinoline and its methyl derivative in animal models of depression

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ABSTRACT

Background: Most of the currently used antidepressant drugs are monoamine-based compounds, acting by the inhibition of re-uptake or metabolism of noradrenaline (NA) and/or serotonin (5-HT), because these neurotransmitters play a key role in the pathophysiology of depression. The aim of this study was to investigate the potential antidepressant-like activity of an endogenous amine, 1,2,3,4-tetrahydroisoquinoline (TIQ) and its close derivative, 1-methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ).
Methods: The experiments were carried out on male C57BL6J mice. The antidepressant-like activity of TIQs was evaluated in the behavioral tests: the forced swim test (FST) and tail suspension test (TST) and neurochemical analysis. TIQ and 1MeTIQ were administrated in three differences doses of 10, 25 or 50 mg/kg. Imipramine (IMI; 15 or 30 mg/kg) was used as a reference drug. In the neurochemical *ex vivo* study, the levels of NA, 5-HT and their metabolites, the rate of monoamine metabolism and their neuronal activity in different mouse brain structures were determined by HPLC with electrochemical detection.
Results: The results of this study have demonstrated that TIQ and 1MeTIQ produced antidepressant-like effect in the FST and TST because they significantly decreased the immobility time comparably to IMI. Biochemical data have demonstrated that administration of TIQs led to the activation of NA and 5-HT systems.
Conclusions: The results reported in this paper indicate that TIQ and 1MeTIQ possess a distinct antidepressant activity. In the light of these findings, we suggest that both tested compounds may be effective for the depression therapy in a clinical setting with better tolerance of side effects.
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Introduction

Depression is one of the most common diseases worldwide associated with a high rate of suicides. Despite intensive research the etiology and pathogenesis of depression remains unclear. Preclinical and clinical studies suggest that monoamine neurotransmitters such as dopamine (DA), noradrenaline (NA) and serotonin (5-HT) in the central nervous system play a key role in the pathophysiology of depression [1–3]. These studies have focused largely on the levels of monoamines and their receptors, and have led to several theories of depression, including the monoamine depletion and receptor sensitivity hypothesis theories [4–6]. Despite the advances in the treatment of depression with selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) [7,8], there continue to be many unmet clinical needs with respect to both efficacy and side effects [9]. Recent advances in molecular and cellular neurobiology have provided new insights into the long-term adaptations that underlie the therapeutic action of antidepressant medications [10–13]. Effective drugs for depression are MAO inhibitors and/or 5-HT and NA reuptake inhibitors [7–9]. Although there has been a lot of efforts in the development of a new drugs in the last years the situation still is unsatisfying. The results and strategies discussed provide a framework for future studies, at the basic to further characterize the pathophysiology and treatment in depression. Finally, a more complete understanding of depression will be dependent on critical future studies, the suitable animal models to identify the additional intracellular pathways involved in the mechanism of this complex psychiatric disorder, and can greatly push our knowledge forward. To address these needs, antidepressants with novel mechanisms of action and without side effects are in great demand.

1,2,3,4-Tetrahyroisoquinoline (TIQ) and its methyl derivative, 1-methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ) are members of

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tetrahydroisoquinoline family (TIQs). They are the most numerous alkaloids widespread in plants, a variety of food products as well as in the human, primate and rodent brain [14–18]. In most cases, TIQs can be formed as condensation products of biogenic amines (i.e., phenylethylamines and catecholamines) with aldehydes or α-keto acids by the so-called Pictet-Spengler reaction [14,17,19], although some of them for example 1MeTIQ may be also synthesized enzymatically in the brain [20–23]. TIQ and 1MeTIQ easily penetrate into the brain through the blood brain barrier with the high affinity for the brain tissue [24,25]. Exogenous TIQs was actively transported from the blood into the brain by organic cation transporter system. What is interesting, the concentration of TIQs in the brain was several-fold higher than in plasma both after acute and chronic administration. A half-life of TIQ in the rat brain was $t_{1/2}$ = 3 h 58 min while the respective value in the plasma was $t_{1/2}$ = 2 h 38 min [24]. What is important to mention is that both of these substances express a significant neuroprotective activity as demonstrated by recent extensive *in vitro* and *in vivo* experiments [26–29]. They have structural similarities to DA and can interact with agonistic conformation of DA receptors as partial agonists what makes their behavioral profile different from the typical neuroleptics [29–31]. Additionally, it has been found that TIQ and 1MeTIQ in low micro molar concentrations inhibit enzymatic activity of both isoforms of monoamine oxidase A (MAO A) and B (MAO B). Consequently, they inhibit the main catabolic pathway of DA, MAO-dependent oxidative deamination of DA, the route by which free oxygen radicals are generated and increase monoamine neurotransmitter levels in the brain [30,32–34]. Simultaneously, they shift DA catabolism towards COMT-dependent *O*-methylation what has essential neuroprotective significance [30,35]. What is more, as demonstrated in preclinical investigations in the 1970s, MAO inhibitors showed antidepressant-like properties [36]. Several short-acting and reversible MAO A and MAO B inhibitors are now under evaluation or in use as antidepressants, e.g. brofaromine, moclobemide [37].

The aim of the present study was to investigate the antidepressant-like effect of TIQ and its neuroprotective methyl derivative, 1MeTIQ in comparison with the classical tricyclic antidepressant, imipramine. The forced swim test (FST) and tail suspension test (TST) were used to examine their antidepressant-like activity in mice. The FST and TST are the screening tests with sensitivity to a short-term drug administration and high predictivity of antidepressant efficacy in human depression. Additionally, the locomotor activity test was used to check the motor function of mice after administration of the investigated compounds.

In addition to behavioral experiments, we also carried out a neurochemical *ex vivo* study in different mouse brain structures to determine the level of monoamines and their metabolites as well as the rate of monoamine (NA and 5-HT) metabolism and indicators of neuronal activity.

Materials and methods

Animals

The behavioral experiments were carried out on male C57BL6J mice (25 ± 2 g) (Charles River Laboratories, Sulzfeld, Germany). The animals were housed 5–8 per cage (57 × 35 × 20 cm) in a colony room maintained at 21 ± 1 °C and with a 40–50% humidity under an artificial day-night cycle (12/12 h, the light on at 7 a.m.). The animals had free access to standard laboratory food and tap water before the experiment. All the procedures were conducted during the light phase.

All the experimental protocols were approved by the Local Bioethics Commission for Animal Experiments at the Institute of Pharmacology, Polish Academy of Sciences in Krakow. All efforts were made to minimize animal suffering and the number of animals used.

Chemicals

TIQ (1,2,3,4-tetrahydroisoquinoline hydrochloride, Sigma-Aldrich, USA) and IMI (imipramine hydrochloride, Sigma-Aldrich, USA) were obtained commercially. 1MeTIQ (1-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride) was synthesized at the Medicinal Chemistry Department Institute of Pharmacology Polish Academy of Sciences. Purity of the compound was verified by measurement of the melting point, and homogeneity was assessed on a chromatographic column. All the investigated compounds were dissolved in a sterile 0.9% NaCl solution and injected intraperitoneally (*ip*). The chemical structures of the TIQ, 1MeTIQ and IMI are shown in Fig. 1.

Behavioral experiments

Behavior despair study

For the forced swim test (FST) animals were divided into nine groups (n = 6-7 animals/per group): Control (0.9% saline), IMI 30 mg/kg, and three doses of TIQ (10, 25, 50 mg/kg) or 1MeTIQ (10, 25, 50 mg/kg).

For the tail suspension test (TST), animals were divided into six groups (n = 8 animals/per group): Control (0.9% saline), IMI 15 mg/kg, and two doses of TIQ (10, 25 mg/kg) or 1 MeTIQ (10, 25 mg/kg).

All investigated compounds were administrated once 60 min before a behavioral test.

Forced swim test (FST)

The procedure was carried out on mice according to the method of Porsolt [38]. Briefly, each mouse was placed individually in an open cylindrical container (diameter: 10 cm, height: 25 cm) filled with water up to 9 cm at 22 ± 1 °C. The immobility time was

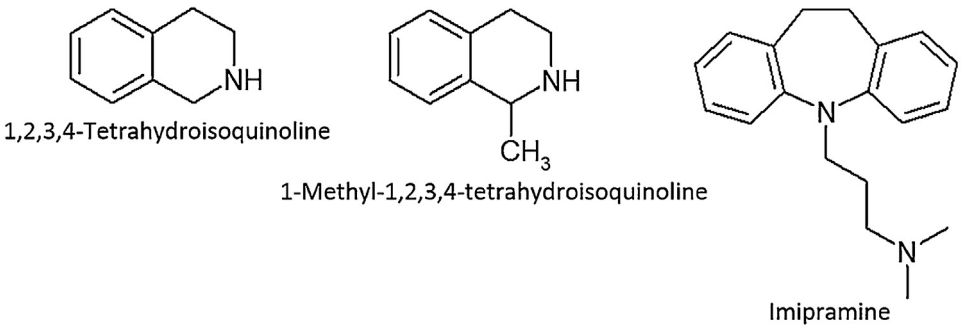

Fig. 1. The chemical structure of TIQ, 1MeTIQ and IMI.

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