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1,2,3,4-Tetrahydroisoquinoline produces an antidepressant-like effect in the forced swim test and chronic mild stress model of depression in the rat: Neurochemical correlates

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ABSTRACT

1,2,3,4-Tetrahydroisoquinoline (TIQ) is an exo- and endogenous amine naturally present in mammalian brain which displays antidepressant-like effect in various animal models: the forced swim test (FST) and chronic mild stress (CMS) paradigm in rats. To elucidate this action we compared the effects of TIQ with imipramine, a classic antidepressant drug and one of the most clinically effective. Applied behavioral tests showed that TIQ produced an antidepressant-like effect with a potency comparable to that of imipramine. TIQ (25–50 mg/kg i.p.), similarly to imipramine (10–30 mg/kg i.p.), reduced the immobility time in FST and completely reversed the decrease in sucrose intake caused by CMS in the rat. In addition, in order to avoid the possible psychostimulating effect of TIQ we examined the influence of its administration on locomotor activity in rats. TIQ, like imipramine, produced a reduction in horizontal locomotor activity. This suggested that TIQ did not have psychostimulant properties and that prolonged swimming in the FST was a result of an increased motivation to escape from the stressful situation. The biochemical analyses have shown that TIQ activates monoaminergic systems as a reversible monoamine oxidase (MAO) inhibitor and free radical scavenger. Beyond the activation of noradrenaline and serotonin systems, TIQ also moderately affects the dopamine system. On the basis of the presented behavioral and biochemical studies we suggest that TIQ is a potential new antidepressant which may be effective for the depression therapy in a clinical setting.

1. Introduction

The biological etiology of depression is not yet fully understood. It is known that the emotional disorders in this disease are largely due to neurohormonal substrate. Nonetheless, one of the main theories postulates a deficiency in monoaminergic neurotransmitters, and more specifically, deficiencies in noradrenaline and serotonin (Richelson, 1994). Most of the currently used antidepressant drugs are associated with monoaminergic transmission as inhibitors of monoamine reuptake or their metabolism and catabolism in the brain (Kasamo et al., 1996; Reneric and Lucki, 1998). The main catabolic enzyme for brain monoamines is monoamine oxidase (MAO) and MAO inhibitors among other drugs with different mechanisms of action are used in clinical practice for treatment of depression (Kumagae et al., 1991; Haefely et al., 1992; Alvarez et al., 1999).

1,2,3,4-Tetrahydroisoquinoline (TIQ; see Fig. 1) naturally occurs in plants, a variety of food products and in the mammalian brain (Kohno et al., 1986; Makino et al., 1988; Niwa et al., 1989; Yamakawa et al., 1999). TIQ in low micromolar concentrations is a reversible MAO A/B inhibitor (Maruyama et al., 1993; Lorenc-Koci et al., 2000; Antkiewicz-Michaluk et al., 2001; Patsenka and Antkiewicz-Michaluk, 2004). Several short-acting and reversible MAO A/B inhibitors are under evaluation or in use as antidepressants, e.g. brofaromine, moclobemide (Miura et al., 1996; Youdim and Bakhle, 2006; Kitamura et al., 2008). TIQ, despite its structural similarity to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), does not appear to be a toxic compound because without the methyl group on the nitrogen, in contrast to MPTP, it is not a direct substrate for MAO in the formation of neurotoxic isoquinoline ion. In fact, TIQ expresses significant neuroprotective activity as demonstrated by recent extensive *in vitro* and *in vivo* experiments (Lorenc-Koci et al.,

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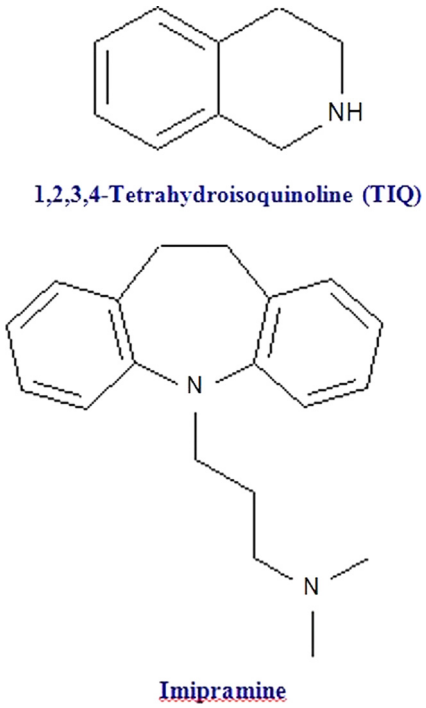

Fig. 1. Chemical structure of 1,2,3,4-tetrahydroisoquinoline and imipramine.

2005; Antkiewicz-Michaluk et al., 2006), as a free radical scavenger. Moreover, in mouse embryonic primary cultures it strongly reduced glutamate-evoked excitotoxicity and cell death (Antkiewicz-Michaluk et al., 2006). In the unilaterally malonate-lesioned rats, TIQ prevented the loss of dopamine neurons (Lorenc-Koci et al., 2005).

In that light the question arises as to whether TIQ may have an antidepressant effect. Its easy penetration into the brain through the blood–brain barrier and the neuroprotective properties might be relevant from the clinical point of view. What is more, TIQ has not yet been investigated in the context of its potential antidepressant properties. It should be also taken into account that antidepressants currently in use only have therapeutic effect with long-term administration, and often cause adverse side effects. Thus there is a justified need to search for new effective and faster acting antidepressants.

In the present study we tested the antidepressant-like effect of TIQ in comparison with the traditional antidepressant imipramine (Fig. 1). To examine its antidepressant properties we used two behavioral tests: the forced swim test (FST) and the chronic mild stress (CMS) model of depression in rats. The FST is a test with high predictivity of antidepressant efficacy in human depression. Recently, a behavior sampling technique was developed that scores individual response categories, including immobility, swimming and climbing (Detke et al., 1995). Additionally, the locomotor activity test was used to check the motor function of rats after administration of the drugs being investigated.

The CMS model is a chronic procedure, based on the evaluation of anhedonia which is a core symptom of the human depressive disorder. What is more, it was reported that conventional antidepressants, such as tricyclics (for example imipramine) and MAOIs were effective in these both tests (Porsolt et al., 1978; Willner, 1997).

In addition to behavioral tests, we also carried out a neurochemical *ex vivo* study in the rat's brain structures to determine the level of monoamines and their metabolites, as well as the rate of monoamine metabolism, and indicators of neuronal activity.

2. Materials and methods

2.1. Animals

Behavioral tests were carried out on male Wistar rats, of initial body weight 220–240 g (about 7 weeks old). The animals were kept under standard laboratory conditions with free access to standard laboratory food and tap water, at room temperature of 22 °C with an artificial day–night cycle (12/12 h, light on at 7 a.m.). Each experimental group consisted of 6–8 rats.

All the procedures were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were granted an approval from the Bioethics Commission as compliant with Polish Law. All the experimental procedures were approved by the Local Bioethics Commission of the Institute of Pharmacology, Polish Academy of Sciences in Cracow.

2.2. Drugs

TIQ (1,2,3,4-tetrahydroisoquinoline hydrochloride, Sigma-Aldrich, USA) and IMI (imipramine hydrochloride, Sigma-Aldrich, USA) were obtained commercially. All the compounds were dissolved in sterile 0.9% NaCl solution and injected in a volume of 4 ml/kg. The chemical structures of the TIQ and IMI are shown in Fig. 1.

2.3. Behavioral experiments

2.3.1. Forced swim test (FST) procedure

The studies were carried out on rats and were based on the method of Porsolt et al. (1978). All the animals were individually tested in the FST on two consecutive days with one session per day. On the first day, the rats were individually placed in non-transparent plastic cylinders (diameter: 23 cm, height: 50 cm) containing 30 cm of water, maintained at 25–26 °C. They were let to swim for 15 min before being removed (pre-test session). After that the animals were dried and returned to their home cages. The procedure was repeated for 5 min 24 h later, and the time of the escape-oriented behavior of the rats was recorded (test session). The rats were administrated imipramine (IMI) at a dose of 30 mg/kg intraperitoneally (i.p.) 1 hr before the forced swimming test (FST). TIQ was administrated in three different doses: 10, 25 or 50 mg/kg also 1 hr before the behavioral test (FST). Control rats were treated with an appropriate solvent. The observed behavioral parameters, in the order of priority, were as follows: time spent floating in water (immobility), swimming and struggling (climbing). According to Detke et al. (1995), the immobility is described as behavior of the rat when it makes only the movements necessary to keep its head above the water. In this case, animals can make certain, slight swimming movements in order to remain afloat. Climbing is defined as vigorous movements of four limbs, with the front paws breaking against the wall of the cylinder. During swimming rats make coordinated and sustained movements (more than necessary) with all four limbs, usually traveling around the interior of the cylinder, but without breaking the surface of the water with forelimbs. Water was changed between subjects. Immediately after the end of behavioral tests, the rats were killed by decapitation and the brain was rapidly removed and dissected on different brain structures (substantia nigra, dorsal striatum, nucleus accumbens, brain stem) on an ice-cold glass plate. The experiments were carried out between 9 a.m. and 3 p.m.