The influence of chronic treatment with 1,2,3,4 tetrahydroisoquinoline on dopamine and serotonin metabolism, the level of glutathione and the activity of γ-glutamyl transpeptidase in the nigrostriatal dopaminergic system of Dark Agouti male rats

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Although for many years tetrahydroisoquinolines (TIQs) have attracted pharmacologists' and neurochemists' attention, their role in mammalian brain has not been well established so far. However, due to the structural similarity of some TIQs to the parkinsonism-inducing agent 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), they have been regarded as potential endogenous and/or exogenous neurotoxins which may be involved in the degeneration of nigrostriatal dopaminergic neurons. TIQs are widely distributed in the environment. Their occurrence in plants had been described earlier, long before they were found in human and animal organisms. 1,2,3,4-tetrahydroisoquinoline (TIQ), the simplest representative of a group of non-catecholic tetrahydroisoquinolines, was identified as an endogenous compound in the brain of parkinsonian patients and normal human subjects. It was also shown to be present in rodent and monkey brains. In general, TIQs are formed non-enzymatically through the so-called Pictet-Spengler condensation of 2-phenylethylamine or dopamine (DA) with aldehydes or α-keto acids, but some of them are also synthesized enzymatically. The preservation of an enzymatic system generating TIQ in mammalian brain in the course of evolution suggests that it may perform an important physiological function. In the brain, TIQ may also be of dietary origin, as it has been detected in diverse foods rich in 2-phenylethylamine. The metabolism of TIQ in the mammalian organism depends on enzymes belonging to the CYP2D subfamily. The 4-hydroxylation reaction catalyzed by a hepatic isoform of CYP2D2 in rats and the corresponding CYP2D6 in humans has been considered to be the main metabolic pathway of TIQ elimination from the body. Therefore it has been postulated that a defect in gene

encoding CYP2D2/CYP2D6 may lead to TIQ accumulation in the brain of rats and humans carrying this mutation. However, our recent studies have shown that due to the low efficacy of TIQ 4-hydroxylation in the liver of Wistar rats carrying a wild allele of CYP2D2, this reaction has no effect on TIQ accumulation in the brain. Nevertheless, transport is believed to play a very important role in the brain accumulation of this compound. In Wistar rats, TIQ is actively transported across the blood-brain barrier by an organic cation transporter system (OCT), and is quickly eliminated from it by P-glycoprotein. However, to date there have been no experimental data on TIQ accumulation in the brain of Dark Agouti rats carrying mutation in a gene encoding CYP2D2. Therefore we decided to examine the effect of chronic TIQ administration (20 mg/kg, twice daily for successive 14 days) on its accumulation in both the plasma and the brain of those rats, as well as on dopamine and serotonin metabolism, the level of glutathione and the activity of γ-glutamyl transpeptidase (γ-GT) in the striatum and substantia nigra.

The obtained results show that TIQ administered chronically in a dose of 20 mg/kg evokes accumulation of this compound in the brain of Dark Agouti rats comparable to that previously reported for a dose of 50 mg/kg applied to Wistar rats. TIQ has been found to attenuate the total catabolism of dopamine in both the striatum and substantia nigra. It also reduces the level of the intraneuronal metabolite DOPAC and elevates that of the extraneuronal 3-MT. In addition, TIQ evokes an increase in glutathione level and inhibits γ-GT enzymatic activity in the striatum. Our results obtained with Dark Agouti rats strongly suggest that in the brain TIQ seems to act as a neuromodulator rather than as a parkinsonism-inducing neurotoxin.