ANTIDOPAMINERGIC EFFECTS OF PUTATIVE ENDOGENOUS MPTP-LIKE AGENTS:
1,2,3,4-TETRAHYDROISOQUINOLINE AND 1-METHYL-6,7-DIHYDROXY-1,2,3,4-TETRAHYDROISOQUINOLINE

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INTRODUCTION

Tetrahydroisoquinolines, such as 1,2,3,4-tetrahydroisoquinoline (TIQ) and its derivative 1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (salsolinol), aroused considerable interest as molecular species that may be implicated in etiology of Parkinson's disease (Nagatsu and Yoshida, 1988; Gerlach and Riederer, 1996; Nagatsu, 1997). The suspicions that tetrahydroisoquinolines may be neurotoxic resulted from their ability to form isoquinolinium ions, analogous to MPP⁺ (Maruyama et al., 1997; Naoi et al., 1994).

In clinical studies we have found that the concentration of salsolinol in the CSF of patients with advanced parkinsonism was significantly augmented and this increase is related to the state of dementia rather than to advancement of parkinsonism (Antkiewicz-Michaluk et al., 1997). In the animal experiments we have shown that TIQ must be given repeatedly for at least three weeks to induce neurotoxic parkinsonian-like effects (Antkiewicz-Michaluk et al., 1998; Lorenc-Koci et al., 1999).

In this experiment we tested how single and chronic administration of two tetrahydroisoquinolines, TIQ and salsolinol, affect dopamine metabolism in the neurons of extrapyramidal and mesolimbic dopaminergic systems. Also we investigated behavioral and biochemical effects of single doses of TIQ and salsolinol, with special regard to their interference with dopaminergic system.

We report here that single doses of TIQ and salsolinol inhibit biochemical and behavioral changes induced by apomorphine, and displace dopamine agonists ([³H]apomorphine, [³H]dopamine) from their binding sites. In the case of chronic treatment.
tetrahydroisoquinolines may be considered as attractive model substances to induce experimental parkinsonism.

MATERIALS AND METHODS

Animals and Treatment. The subjects were male Wistar rats, of initial weight 220-240 g, kept under standard laboratory conditions, 8 to a large animal cage, with free access to standard laboratory food and tap water, at room temperature (22°C) with a natural day-night cycle. The experiments were carried out between 10:00 h and 15:00 h. All experiments were carried out according to the National Institutes of Health Guide for Care and Use of Laboratory Animals (publication No. 85-23, revised 1985) and were approved by the internal Bioethics Commission.

Drugs. TIQ (1,2,3,4-tetrahydroisoquinoline), 50 mg/kg i.p., and salsolinol (1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline) 100 mg/kg i.p., apomorphine 0.25 mg/kg s.c., were dissolved in 0.9% NaCl solution, haloperidol 1 mg/kg i.p.) was suspended in 1% Tween 80. In the case of chronic treatment TIQ (50 mg/kg i.p.) and salsolinol (100 mg/kg i.p.) were administered once daily for 18 days with the last dose given 72 h before decapitation. The brains were rapidly removed and dissected on the ice-cold glass plate. Substantia nigra, striatum and nucleus accumbens were taken and immediately frozen in dry ice until used.

Behavioral Tests

Locomotor Activity. The activity was measured in square photoresistor actometers. The rats were injected with TIQ or salsolinol and apomorphine was given 150 min later. Fifteen minutes after apomorphine the rats were placed into actometers individually for 30 min, and counting commenced immediately after introduction of the animals.

Catalepsy. The rats were injected with TIQ or salsolinol, followed 90 min later with haloperidol, and catalepsy was measured 60 min after haloperidol injection, according to the method of Delini-Stula and Morpurgo (1968). The rats were tested for their ability to maintain the unnatural posture (left or right forepaw on a 3 and 9 cm high wooden blocks) for 15 s. The maximum score was 6.

Biochemistry

Dopamine Metabolism. Dopamine and its metabolites, homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) or 3-methoxytyramine (3-MT), were assayed by means of high-performance liquid chromatography (HPLC) with electrochemical detection.

Displacement of Dopamine Agonists ([3H]apomorphine, [3H]dopamine) and Antagonists ([3H]spiperone, [3H]SCH23390) from Their Binding Sites in Striatal Synaptosomes. The animals were killed by decapitation the brain was rapidly removed, placed on an ice-chilled porcelain plate, and the striata were dissected out and placed in dry ice till the binding assay. The displacement of dopamine agonists; [3H]apomorphine in concentration 0.5 nM and [3H]dopamine in concentration 3 nM and dopamine antagonists; [3H]SCH23390 (D1 receptor ligand, 0.5 nM) and