Role of Monoamines in Behavior of Reserpinized Rats Given Tranylcypromine Stereoisomers

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With 1 Figure

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Summary

The effects of tranylcypromine stereoisomers [(+)-TCP and (−)-TCP] on behavior were studied in reserpinized rats. Rats given reserpine showed a behavioral syndrome characterized by hypoactivity. Administration of (+)-TCP to reserpinized rats led to a dose-dependent increase in their locomotor activity. At a dose of 15 mg/kg, (+)-TCP produced activation, stereotypy and hyperstimulation in reserpinized rats. In contrast, (−)-TCP failed to influence the behavior of reserpinized rats reliably. Pharmacological studies using agonists and antagonists of monoaminergic functions showed the actions of (+)-TCP to depend on presynaptic serotonergic and catecholaminergic functions. The results provide another example of stereoselective effects of tranylcypromine stereoisomers on behavior mediated mainly by monoaminergic neurotransmission.

Introduction

Rats given reserpine show a behavioral syndrome characterized by ptosis, akinesia, catatonia and a hunch-backed appearance (Rubin, Malone, Waugh, and Burke, 1957; Andén and Johnels, 1977). Actions of reserpine on monoaminergic neurotransmission are involved in the syndrome (Brodie, Finger, Orlans, Quinn, and Sulser, 1960; Brodie, Comer, Costa, and Dlabac, 1966). Reversal of the syndrome is often used to study actions of drugs on monoaminergic mechanisms (Carlsson, Lindsjö, and Magnusson, 1957; Costa, Garattini, and
Tranylcypromine stereoisomers [(+)- and (−)-trans-2-phenylcyclopropylamine] have stereoselective actions on monoaminergic mechanisms; the (+)-isomer [(+)-TCP] appears to influence mainly tryptaminergic mechanisms in addition to inhibition of monoamine oxidase, while the (−)-isomer [(−)-TCP] seems to act primarily on catecholaminergic mechanisms as an indirect agonist (see Smith, 1980; Reigle, Orsulak, Avni, Platz, and Schildkraut, 1980). The present study was carried out to investigate further the actions of tranylcypromine stereoisomers on monoaminergic neurotransmission using reserpine-reversal as the behavioral test.

Methods

Male albino Wistar rats weighing 250—350 g were used. They were housed individually in clear plastic cages (40×25×15 cm) in a thermostatically controlled room (21 °C) on a 12-hour light-dark cycle (lights on 6 a.m. to 6 p.m.). They were injected i.p. with reserpine (10 mg/kg; 2 ml/kg) and deprived of food 20 hours before tests.

Pretreatments were given by i.p. injection in a volume of 2 ml/kg, unless otherwise stated. Synthesis of dopamine and norepinephrine was inhibited by (±)-alpha-methyl-p-tyrosine methylester HCl (AMPT) (2×150 mg/kg) given 22 and 2 hours before tests. Synthesis of norepinephrine was inhibited by bis-(4-methyl-1-homo-piperazinyl-thiocarbonyl) disulfide (FLA 63) (25 mg/kg) given 2 hours before tests. Serotonin synthesis was inhibited by (±)-p-chlorophenylalanine methylester HCl (PCPA) (300 mg/kg) given 72 hours before tests or by (±)-alpha-(3, 4-dihydroxyphenyl)-valeramide (H 22/54) (500 mg/kg; 16 ml/kg) given 3 hours before tests. Dopaminergic receptors were antagonized by pimozide (5 mg/kg) given 2 hours before tests. Noradrenergic receptors were antagonized by phenoxybenzamine HCl (10 mg/kg) given 2 hours before tests. Catecholaminergic neurotransmission was antagonized by oxypertine (5 mg/kg) given 2 hours before tests. Serotonin receptors were antagonized by either methysergide bimaleate (16.6 mg/kg) or cyproheptadine HCl (50 mg/kg) given 2 hours before tests. Monoamine oxidase was inhibited by nialamide (50 mg/kg) given 2—3 hours before tests. Peripheral decarboxylation was inhibited by benserazide (50 mg/kg) given 30 min before tests.

An intragastric load (10 ml/kg) of either distilled water (vehicle), (+)-TCP (0.15, 1.5, or 15 mg/kg), (−)-TCP (0.15, 1.5, or 15 mg/kg), L-tryptophan (400 mg/kg), isocarboxazid (23.7 mg/kg), nialamide (30 mg per kg), or DL-5-hydroxytryptophan (50 mg/kg) was administered at the start of tests. Isocarboxazid and nialamide were used to inhibit monoamine oxidase. L-tryptophan and DL-5-hydroxytryptophan were used to enhance serotonergic neurotransmission.