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Antidopaminergic effects of 1,2,3,4-tetrahydroisoquinoline and salsolinol

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Summary. Immediate behavioral and biochemical effects of single doses of 1,2,3,4-tetrahydroisoquinoline (TIQ, 50 mg/kg) and salsolinol (100 mg/kg), suspected of involvement in etiology of Parkinson's disease, were investigated. Apomorphine (0.25 mg/kg) or haloperidol (1 mg/kg) were administered to TIQ or salsolinol pretreated Wistar rats. In additional experiment the displacement of [^{3}H]apomorphine by TIQ, salsolinol and dopamine receptor agonists and antagonists was tested. Both tetrahydroisoquinolines only slightly affected behavior and dopamine metabolism in naive rats, but very effectively abolished the behavioral and biochemical effects of apomorphine (hyperactivity, depression of striatal HVA level). The behavioral and biochemical effects of haloperidol were unchanged by administration of TIQ nor salsolinol. The tetrahydroisoquinolines displaced [^{3}H]apomorphine from its binding sites with effectiveness comparable to that of dopamine. The results support the hypothesis that endogenous tetrahydroisoquinolines may play an important role in regulation of dopaminergic activity in non-senescent organisms.

Keywords: Salsolinol, 1,2,3,4-tetrahydroisoquinoline, apomorphine, haloperidol, dopamine metabolism, anti-dopaminergic activity.

Introduction

Tetrahydroisoquinolines, such as 1,2,3,4-tetrahydroisoquinoline (TIQ) and its derivative (R)-1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (salsolinol), aroused a considerable interest as molecular species that may be implicated in etiology of Parkinson's disease. The compounds may be regarded both as environmental and endogenous neurotoxins. They are present in various foods, such as diary products, wines and bananas (Niwa et al., 1989b; Deng et al., 1997; Duncan et al., 1982; Strolin Benedetti et al., 1989; Riggin et al., 1976) and after ingestion may accumulate in the brain (Nagatsu, 1997; Naoi et al., 1998). Although Origitano et al. (1981) could not confirm the

earlier results of Sjöquist and Magnusson (1980) that salsolinol crosses the blood-brain barrier, its rapid and evident pharmacological action indicates that it acts on the central nervous system after intraperitoneal administration. Apart of that, they may be formed in the brain enzymatically or non-enzymatically in the Pictet-Spengler reaction from phenylalanine-derived biogenic amines and acetic aldehyde (Naoi et al., 1993). The suspicions that tetrahydroisoquinolines may be neurotoxic resulted from their ability to form tetrahydroisoquinolinium ions, analogous to MPP^+ (Maruyama et al., 1997; Naoi et al., 1994, 1989a,b), and in fact an experimental parkinsonism was induced by TIQ in marmosets (Nagatsu et al., 1988) and by N-methyl-salsolinol, a salsolinol derivative in rats (Naoi et al., 1996). In a clinical study 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 of advancement of parkinsonism (Antkiewicz-Michaluk et al., 1997).

While MPTP acts rapidly and produces irreversible neurotoxic changes after a single injection and its effects are strictly limited to nigrostriatal dopamine system (Burns et al., 1985) [although later on some changes in other systems were described, cf. (Gerlach and Riederer, 1996)], the tetrahydroisoquinolines do not produce an immediate neurotoxicity. In the animal experiment we have found 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., 2000).

In contrast to a considerable body of data concerning the effects of chronic administration of tetrahydroisoquinolines, their immediate psychopharmacological effect were studied very little, and the early study of Ginos and Doroski (1979) suggested that TIQ and its N-methyl analogue may act as neuroleptics of a new type. As our recent results indicate that these tetrahydroisoquinolines have some properties incompatible with this view (no displacement of dopamine D1 and D2 receptor antagonists from their binding sites, facilitation of morphine-induced running fit (Vetulani et al., 2000), we have presently investigated behavioral and biochemical effects of single doses of TIQ and salsolinol, with special regards to their interference with dopaminergic system.

We report here that single doses of TIQ and salsolinol inhibit changes in dopamine metabolism induced by apomorphine and haloperidol in the rat, and displace the dopamine agonist, [^{3}H]apomorphine, from its binding sites.

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. Control rats were treated with an appropriate solvent. 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-tetraphydroisoquinoline; Sigma), 50 mg/kg ip, and salsolinol (1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, Aldrich) 100 mg/kg ip, apomorphine (Sandoz) 0.25 mg/kg s.c., were dissolved in 0.9% NaCl solution, haloperidol (Sigma) 1 mg/kg i.p was suspended in 1% Tween 80. The drugs were administered in a single dose.

Behavioral tests

Locomotor activity. The activity was measured in square photoresistor actometers with two crossed light beams, in which interruptions of a light beam were counted (Bednarczyk and Vetulani, 1977). 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) as modified by Vetulani (1973). 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. Striatal tissue was obtained by dissection from animals killed by decapitation. The rats tested for locomotor activity were killed immediately after the test. The rats receiving tetrahydroisoquinolines and haloperidol were killed 100 min after haloperidol injection without carrying out the test for catalepsy. The obtained tissue was immediately frozen on solid CO_2 till used for biochemical assay.

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

The tissue samples were weighed and homogenized in ice-cold 0.1 M trichloroacetic acid containing 0.05 mM ascorbic acid. After centrifugation (10,000 × g, 5 min), the supernatants were filtered through RC 58 0.2 μm cellulose membranes (Bioanalytical Systems, West Lafayette, IN), and dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were determined by HPLC with electrochemical detection. The chromatographs (BAS-400 or Hewlett-Packard 1050) were equipped with C18 columns. The mobile phase consisted of 0.05 M citrate-phosphate buffer, pH 3.5, 0.1 mM EDTA, 1 mM sodium octyl sulfonate and 3.5% methanol. The flow rate was maintained at 0.8 ml/min. Dopamine and its metabolites were quantified by peak height comparisons with standards run on the day of analysis.

Displacement of [^{3}H]apomorphine from the binding sites in striatal synaptosomes

The animals were killed by decapitation (between 9.00 h and 11.00 h), 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 [^{3}H]apomorphine (NEN, specific activity 51 Ci/mmol) with apomorphine, dopamine, spiperone, TIQ and salsolinol was studies. The tissue was homogenized in 20 vol of an ice-cold buffer (Tris-HCl buffer pH 7.4 containing 120 mM NaCl, 5 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 10 μM pargyline and 0.1% ascorbic acid) added to obtain the final concentration of 0.5–0.6 mg/ml of protein. The homogenate was centrifuged at 1,000 × g for 15 min, the supernatant was decanted and recentrifuged at 25,000 × g for 30 min, and the resulting pellet was resuspended in the buffer and recentrifuged under the same conditions. The final pellet (fraction P2) was used for binding studies. For

incubation it was reconstituted in the buffer, to obtain a final protein concentration of approximately 0.6 mg/ml.

The incubation was carried out in the final volume of 550 μl that consisted of 450 μl of membrane suspension, 50 μl of 0.5 nM [^{3}H]apomorphine solution, 50 μl of displacer solution (6–7 concentrations, ranging from 0.1 nM to 10 μM for apomorphine and spiperone, and 1 nM to 100 μM for other displacers). The incubation was carried out at 37°C for 15 min.

Statistics

The results were analyzed by means of one-way analysis of variance followed, when appropriate, with Fisher's Least Significant Difference test; the EC_{50} values were calculated from the dose-response curves using the Prism GraphPad program.

Results

Locomotor activity

Both TIQ and salsolinol in the doses used suppressed locomotor activity only insignificantly and did not cjange appeciably the general behavior. Apomorphine produced a significant hyperactivity with mild stereotypy signs (running, rearing, and continuous sniffing), augmenting the activity score (beam crossings) almost threefold ($p < 0.01$). In rats pretreatment with TIQ (50 mg/kg) or salsolinol (100 mg/kg) apomorphine did not induce any behavioral changes (no hyperactivity nor stereotypy). In fact, after pretreatment with TIQ the effects of apomorphine were reversed, as the activity of rats receiving combined treatment was significantly lower (by almost 50%) than the locomotor activity of the saline control (Fig. 1).

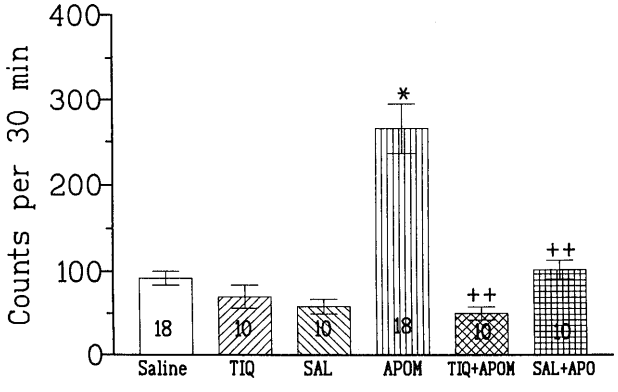

Fig. 1. The effect of TIQ and salsolinol on apomorphine hyperactivity. TIQ, 50 mg/kg, and salsolinol (SAL), 100 mg/kg were given ip 150 min before saline injection and the rats were placed 15 min after saline into actometers for 30 min. Apomorphine, 0.25 mg/kg sc (APOM) was given 150 min after saline and 15 min later the rats were placed into actometers for 30 min. In combined groups, both TIQ, 50 mg/kg ip and salsolinol, 100 mg/kg ip were administered 150 min before apomorphine, 0.25 mg/kg sc and 15 min later the rats were placed into actometers. The data are means ± SEM (n) of total motility count. *$P < 0.01$ (difference from saline control), $^{++}P < 0.01$ (difference from apomorphine group; LSD test)

Catalepsy

Neither TIQ nor salsolinol induced motor disturbances, while haloperidol in the dose used produced almost maximal cataleptic effect. In the rats pretreated with either TIQ or salsolinol the effect of haloperidol remained almost unchanged by pretreatment with isoquinolines, and in fact was insignificantly inhibited (Fig. 2).

Dopamine metabolism

While salsolinol produced a non-significant increase in HVA level in the striatum, the effect of TIQ was less consistent: in one experiment the increase in HVA level after TIQ did not reach the level of statistical significance (Table 1), while in the second one the increase was evident (by 52%, $p < 0.05$).

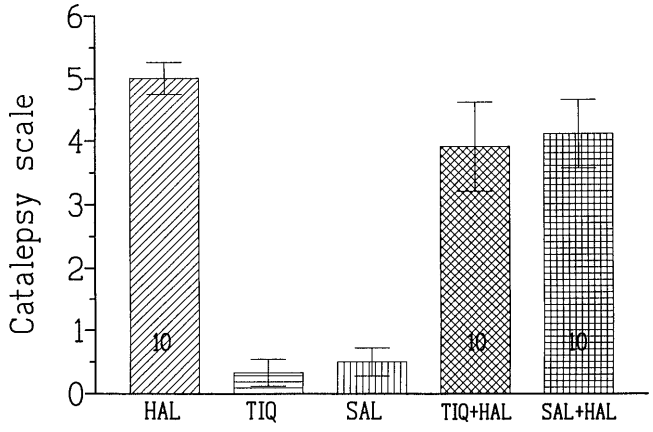

Fig. 2. The effect of TIQ and salsolinol on haloperidol-induced catalepsy. TIQ, 50 mg/kg, and salsolinol (SAL), 100 mg/kg were given ip 90 min before haloperidol (1 mg/kg ip), and 60 min later catalepsy was measured. The rats were tested for their ability to maintain the unnatural posture (left or right forepaw on a 3 and 9 cm high wooden blocks) for 15 s. The maximum score was 6. The data are means ± SEM (n) of total catalepsy score

Table 1. Modification by TIQ of apomorphine-induced changes in striatal dopamine metabolism

Treatment	Dopamine	3-MT	HVA	f
Saline	8,177 ± 355 (8)	313 ± 26 (8)	726 ± 46 (8)	9
Apomorphine	10,095 ± 580 (6)	188 ± 35 (6)*	406 ± 31 (6)**	4
TIQ	9,010 ± 541 (8)	372 ± 12 (7)	842 ± 85 (8)	9
TIQ + apomorphine	8,720 ± 459 (6)	325 ± 19 (6)$^{+}$	681 ± 79 (6)$^{+}$	8

TIQ, 50 mg/kg ip, was given 90 min before apomorphine, 0.25 mg/kg sc. The rats were decapitated 45 min after apomorphine injection. The data are means ± SEM in nanograms per gram of tissue. The number of samples given in parentheses. *f* metabolic rate index: ([HVA]/[dopamine]) × 100. *$p < 0.05$, **$p < 0.01$ (difference from saline group, LSD test), $^{+}p < 0.05$ (difference from apomorphine group, LSD test)

Table 2. Modification by salsolinol of apomorphine-induced changes in striatal dopamine metabolism

Treatment	Dopamine	3-MT	HVA	f
Saline	10,570 ± 1,380 (8)	293 ± 22 (8)	798 ± 66 (8)	7
Apomorphine	11,182 ± 1,764 (6)	202 ± 21 (6)	409 ± 43 (6)**	3
Salsolinol	11,566 ± 1,440 (8)	320 ± 26 (8)	998 ± 56 (8)	8
Salsolinol + apomorphine	9,694 ± 1,410 (6)	315 ± 35 (6)$^{+}$	693 ± 83 (6)$^{+}$	7

Salsolinol, 100 mg/kg ip, was given 90 min before apomorphine, 0.25 mg/kg sc. The rats were decapitated 45 min after apomorphine injection. The data are means ± SEM in nanograms per gram of tissue. The number of samples given in parentheses. *f* metabolic rate index: ([HVA]/[dopamine]) × 100. * $p < 0.05$, ** $p < 0.01$ (difference from saline group, LSD test), $^{+}$ $p < 0.05$ (difference from apomorphine group, LSD test)

Table 3. The effect of TIQ and salsolinol on haloperidol-induced increase in striatal dopamine metabolism

Treatment	Dopamine	DOPAC	HVA	f HVA/DA
Solvent	9,136 ± 802	1,137 ± 113	757 ± 71	8
Haloperidol	7,823 ± 392	4,191 ± 290**	3,367 ± 275**	43
TIQ	10,502 ± 269	889 ± 71*	1,159 ± 128*	11
TIQ + Haloperidol	8,131 ± 407[a]	3,576 ± 302**[a]	2,954 ± 100**[a]	36
Salsolinol	8,543 ± 673	1,123 ± 151	877 ± 93	10
Salsolinol + haloperidol	8,529 ± 246[a]	4,461 ± 171**[a]	3,298 ± 110**[a]	38

TIQ, 50 mg/kg ip, and salsolinol, 100 mg/kg ip, were given 60 min before haloperidol, 1 mg/kg i.p. The rats were decapitated 100 min after haloperidol injection. The data are means ± SEM in nanograms per gram of tissue. The number of samples in each group was 6. *f* metabolic rate index: ([HVA]/[dopamine]) × 100. * $p < 0.05$, ** $p < 0.01$ (difference from saline group, LSD test), [a] no significant difference from haloperidol group

Apomorphine in a dose used inhibited the striatal dopamine metabolism, as reflected by significant decrease in the concentrations of dopamine metabolites HVA (by 45%) and 3-MT (by 40%). Pretreatment with both TIQ and salsolinol completely prevented the deceleration of dopamine metabolism by apomorphine (Tables 1 and 2).

Haloperidol-induced acceleration of dopamine metabolism was very strong (approx. 5-fold if measured with HVA/dopamine ratio). Pretreatment with either TIQ or salsolinol did not affect significantly the effect of haloperidol on dopamine metabolism (Table 3).

[^{3}H]Apomorphine displacement

Cold apomorphine and spiperone effectively displaced [^{3}H]apomorphine (EC_{50}) in nanomolar or subnanomolar range. In contrast, dopamine displaced the radioligand with EC_{50} values higher by two orders of magnitude (225 nM).

Table 4. Displacement of [^{3}H]apomorphine from its binding sites in striatal synaptosomes by dopamine agonists, antagonist and tetrahydroisoquinolines

Drugs	EC_{50} (nmole)
Apomorphine	7
Spiperone	0.75
Dopamine	225
TIQ	180
Salsolinol	950

The EC50 values were calculated from the dose-response curves (6–7 points) with the Prism GraphPad program

The effectiveness of TIQ and salsolinol as displacers of [^{3}H]apomorphine was much lower than that of synthetic drugs, apomorphine and spiperone. However, their activity was of the same order of magnitude as that of the natural neurotransmitter, dopamine: the potency of TIQ was equal to that of dopamine (EC_{50} 180 nM), whereas salsolinol was less potent (EC_{50} 950 nM) (Table 4).

Discussion

Tetrahydroisoquinolines were mainly regarded as potential neurotoxins that might be responsible for development of Parkinson's disease (cf. Gerlach and Riederer, 1996). Although many of those compounds are non toxic by themselves, and salsolinol was even found to depress the level of free OH· radicals that indicates its neuroprotective activity, the compounds may undergo N-methylation and oxidation and owing to that form neurotoxic quinolinium ions (Maruyama et al., 1997; Naoi et al., 1994, 1989a,b). Those quarternary compounds, similarly to pyridinium ions (such as, MPP^+), accumulate in neuromelanin-containing cells and cause the disruption of the mitochondrial electron transport (cf. Gerlach and Riederer, 1996). The most neurotoxic are N-methylated derivatives of tetrahydroisoquinolines (Nagatsu, 1997), but even they are much less toxic than of MPP^+, and the course of neurodegeneration caused by them differs from the immediate neurodegeneration effect of MPTP. Even when salsolinol or TIQ are administered daily, the signs of impairment of dopaminergic system and the loss of tyrosine hydroxylase containing cells requires at least three weeks to develop (Antkiewicz-Michaluk et al., 2000; Lorenc-Koci et al., 2000).

Regardless the distant, slowly developing effects, it seems that the immediate, direct action of tetrahydroisoquinolines may be of physiological importance. Thus, in this study we investigated their acute interference with dopaminergic system of the rat brain.

In agreement with earlier results (Ginos and Doroski, 1979; Vetulani et al., 2000) we confirmed that tetrahydroisoquinoline compounds, TIQ and

salsolinol administered to rats antagonize effectively the behavioral action of a dopamine agonist, apomorphine. Similar behavioral antagonism between tetrahydroisoquinolines and amphetamine was recently described in mice (Vetulani et al., 2000). Moreover, we have now found that TIQ and salsolinol antagonize the main biochemical action of apomorphine: the profound deceleration of dopamine metabolism. Those action, as well as previously described finding that TIQ in a relatively low dose induces a considerable rigidity in rats (Lorenc-Koci et al., 2000) point at the conclusion that the investigated tetrahydroisoquinolines in some respects resemble neuroleptics. In light of these behavioral and biochemical findings, the conclusions from experiments suggesting that salsolinol administered peripherally does not reach the brain (Origitano et al., 1981) should be reconsidered, particularly that the effects observed after administration of TIQ [that undoubtedly crosses the blood-brain barrier (Nagatsu, 1997; Naoi et al., 1998)] are essentially similar (although higer doses of salsolinol are required).

Although many results point out at antidopanminergic effects of TIQ and salsolinol, several actions of these compounds are incompatible with the idea that they may have typical neuroleptic properties. Firstly, in contrast to neuroleptics, they do not produce profound sedation nor catalepsy even in the doses that produce distinctive rigidity (Lorenc-Koci et al., 2000). In contrast, typical neuroleptics, e.g., haloperidol, produce catalepsy in doses lower than those inducing rigidity (Wolfarth et al., 1985). Also, while TIQ and salsolinol specifically block the effects of dopaminergic motor stimulation in a neuroleptic-like fashion (Ginos and Doroski, 1979; Vetulani et al., 2000), they potentiate rather than inhibit the morphine-induced running fit (Vetulani et al., 2000). Moreover, in contrast to neuroleptics, whose classical biochemical effect is an increase in dopamine metabolism (e.g., Van Rossum et al., 1970; Burki et al., 1974), TIQ and salsolinol only slightly and inconsistently elevate the striatal HVA level. They also do not potentiate the cataleptogenic action of haloperidol and show no synergism with neuroleptics in the action on dopamine metabolism.

The effects opposite to those induced by haloperidol (absence of sedation and catalepsy, potentiation of morphine running fit) might be explained by the finding that TIQ increases the release of dopamine from the striatum, as shown by a microdialysis study (Lorenc-Koci et al., 2000). Similar effects were described for salsolinol (Nakahara et al., 1994). The neuroleptic-like effects are more difficult to be accounted for, as we have found earlier that neither TIQ nor salsolinol displaced [^{3}H]spiperone nor [^{3}H]SCH 23,390 from their binding sites, indicating no neuroleptic-like affinity to dopamine receptors (Vetulani et al., 2000). However, the present finding that both tetrahydroisoquinolines, particularly TIQ, interfere with the agonist binding to dopamine receptors similarly to the natural dopamine receptor ligand, dopamine, suggests that the compounds may suppress dopaminergic transmission at a site different from the neuroleptic binding site, and that this suppression is nearly completely compensated for by an increase in dopamine release under normal physiological conditions. Slight increases in the striatal HVA

levels, that are usually in 20–50% range and not always reach the level of significance, are consistent with this view.

To sum up the profile of acute effects of tetrahydroisoquinolines it should be underlined that when given in the doses that do not affect the behavior of naive animals they:

1. produce very small biochemical effects by themselves,
2. do not potentiate the action of dopamine receptor antagonists,
3. very effectively counteract the action of dopamine receptor agonist,
4. bind to agonistic sites of the dopamine receptors.

The above characteristics and the fact that they are present in the brain, accumulate in neuromelanin-containing neurons, and some of them, like salsolinol, may be synthesized from released dopamine make endogenous tetrahydroisoquinolines the ideal candidates of natural regulators of dopaminergic system, that would prevent its hyperactivity. If this assumption is true, the neurotoxic properties of tetrahydroisoquinolines could be regarded as side effects that are not eliminated in the course of evolution, because they appear only at late period of life, when several enzyme-regulating mechanisms fail.

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