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1-Methyl-1,2,3,4-tetrahydroisoquinoline protects against rotenone-induced mortality and biochemical changes in rat brain

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Abstract

The effect of single and multiple administration of the neurotoxic pesticide, rotenone, and the potentially neuroprotective compound, 1-methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ), on the concentration of dopamine and its metabolites (homovanillic acid-HVA, 3,4-dihydroxyphenylacetic acid-DOPAC, and 3-methoxytyramine-3-MT)) in three brain areas was studied by high-performance liquid chromatography (HPLC) with electrochemical detection in Wistar rats. The rate of dopamine catabolism in the striatum along the *N*-oxidative and *O*-methylation pathways was assessed by calculation of the ratio of dopamine metabolites to dopamine. In addition, the effect of rotenone on mortality and general behavior of rats was investigated. We have found that the neurotoxic pesticide, rotenone, administered in a single dose (12 mg/kg s.c.) did not produce evident behavioral or biochemical effects. In contrast, repeated administration of rotenone in doses (12–15 mg/kg) causing abnormalities in general behavior, produced considerable mortality and dramatic increases in dopamine metabolism, which may be ascribed to an increase in the oxidative pathway. Interestingly, it depressed the concentration of the extracellular dopamine metabolite, 3-MT. These behavioral and biochemical changes were effectively counteracted by administration of 1MeTIQ before each dose of rotenone. In summary, we demonstrated that multiple systemic rotenone injections are strongly toxic, and induce alterations of cerebral dopamine metabolism, and that 1MeTIQ may be considered as a potential protective agent against environmental factors affecting the function of the dopaminergic system.

Keywords: Rotenone; Mortality; HPLC (high-performance liquid chromatography); Dopamine metabolism; (Rat); Brain; 1-Methyl-1,2,3,4-tetrahydroisoquinoline

1. Introduction

Parkinson's disease, one of the devastating neurodegenerative illnesses caused by degeneration of dopaminergic neurons in the substantia nigra, is believed to be caused by a mixture of genetic and environmental factors. The environmental neurotoxins may largely contribute to the development of Parkinson's disease.

One of the most famous toxins of dopaminergic neurons is 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which gained attention after it was observed that, when injected intravenously into humans, it produces rapid, irreversible, and often fatal parkinsonism (Langston et al., 1983). MPTP, acting through its metabolite, 1-methyl-4-phenylpyridinium ion (MPP^+), induces degeneration of dopamine neurons, predominantly in the substantia nigra. The main mechanism by which MPP^+ causes neuronal damage was believed to be mitochondrial dysfunction, as MPP^+ can inhibit mitochondrial complex I activity that leads to mitochondrial depolarization and generation of reactive oxygen species (Nakamura et al., 2000). However, the recent study of Lotharius and O'Malley (2000) indicated that the main case of MPP^+-induced neurotoxicity is the generation of active oxygen species during the oxidation of dopamine released by MPP^+.

MPTP has frequently been used to provide an animal model of Parkinson's disease (Bankiewicz et al., 1986; Gerlach and Riederer 1996). It was recently shown by the Greenamyre group (Betarbet et al., 2000) that another, much

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more frequently encountered environmental toxin, rotenone may be used to produce a more realistic animal model of Parkinson's disease. Rotenone, a natural compound, is a classical, lipophilic inhibitor of mitochondrial complex I (Gutman et al., 1970; Horgan et al., 1968) and is selectively toxic to dopaminergic neurons (Marey-Semper et al., 1993). Injected directly into brain structures, rotenone acts similarly to MPTP (Heikkila et al., 1985).

Rotenone is the only neurotoxin known today that induces the formation of Lewy bodies, which are the most characteristic histopathological feature of Parkinson's disease (Betarbet et al., 2000). As in the case of MPTP, a defect of mitochondrial function due to complex I inhibition was postulated to be the cause of rotenone-induced neurodegeneration (Betarbet et al., 2000; Jenner, 2001; Greenamyre et al., 2001). Rotenone also causes dopamine release, as evidenced by microdialysis and neurochemical data (Santiago et al., 1995; Thiffault et al., 2000), and this may also contribute to the degeneration of dopaminergic neurons.

In addition to exogenous neurotoxins, endogenous neurotoxins are implied in the etiology of Parkinson's disease. Of these, tetrahydroisoquinolines, such as salsolinol and 1,2,3,4-tetrahydroisoquinoline (TIQ), have attracted most attention. There are several other tetrahydroisoquinolines in the brain, with different biological properties. Some of them, such as salsolinol, TIQ and 1-benzyl-1,2,3,4-tetrahydroisoquinoline (1BnTIQ) have definite neurotoxic properties (Antkiewicz-Michaluk et al., 2000a; Kotake et al., 1996, 1998; Lorenc-Koci et al., 2000; Nagatsu 1997) though are much less toxic than MPTP or rotenone. Some of the tetrahydroisoquinolines present in the brain manifest neuroprotective activity. One of the most investigated is 1-methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ), which partially antagonizes the behavioral symptoms of dopaminergic neurodegeneration induced by MPTP, TIQ (Tasaki et al., 1991) and 1BnTIQ (Kotake et al., 1995, 1996).

Dopamine is catabolized along two different routes: by the action of intracellular monoamine oxidase it undergoes oxidative deamination (oxidative pathways), while the action of extracellular catechol-*O*-methyltransferase (COMT) results in its *O*-methylation (*O*-methylation pathway). The products of both routes, 3,4-dihydroxyphenylacetic acid (DOPAC) and 3-methoxytyramine (3-MT), undergo further metabolism to yield homovanillic acid (HVA) as the final product. While the *O*-methylation pathway is not dangerous to the dopaminergic neuron, DOPAC formation by the oxidative route may be connected with the generation of reactive oxygen species that may be deleterious for the neuron.

We have previously reported that 1MeTIQ inhibits the formation of DOPAC during dopamine catabolism and shifts metabolism toward the *O*-methylation route (Antkiewicz-Michaluk et al., 2001), while the neurotoxic 1BnTIQ produces the opposite effect. Because of this, we undertook a study of the effects of 1MeTIQ on rotenone-induced changes in the dopamine metabolism and catabolism along the oxidative and *O*-methylation pathways.

2. Materials and methods

2.1. Animals and treatment

The subjects were male Wistar rats, of initial body weight 220–240 g, kept under standard laboratory conditions, six 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 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 Bioethics Commission as complying to the Polish law.

2.2. Drugs

1-Methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ) was synthesized in the Department of Medicinal Chemistry of the Institute of Pharmacology of the Polish Academy of Sciences in Kraków; rotenone was obtained commercially (Sigma). 1MeTIQ was dissolved in 0.9% NaCl solution; rotenone was administered as a suspension prepared in 1% Tween 80 solution by sonification.

2.3. Biochemistry

The rats were treated with rotenone, 12 mg/kg s.c., once or daily for 7 days. 1MeTIQ, 50 mg/kg i.p., was administered 90 min before rotenone injection. The rats were killed by decapitation 4 h after the last rotenone injection. The substantia nigra, striatum, and nucleus accumbens were dissected immediately and frozen on solid CO_2 till used

Table 1
The effect of 1MeTIQ on rat mortality induced by repeated rotenone administration

Rotenone dose (mg/kg s.c.)	Rotenone + saline	Rotenone + 1MeTIQ	Chi-square
0	0/25	0/12	0
10	0/15	0/5	0
12	2/12	0/12	2.18
15	10/25	1/12	3.89[a]

Rotenone was administered daily for 7 days. 1MeTIQ, 50 mg/kg i.p., was given 90 min before each rotenone injection. Mortality was assessed 24 h after the last rotenone injection. The significance of results was assessed using chi-square test.

[a] $P < 0.05$.

Table 2
The effect of 1MeTIQ on rotenone-induced changes in the levels of dopamine and its metabolites in the substantia nigra of the rat

Groups	Dopamine	DOPAC	3-MT	HVA
Control	1074 ± 59 (6)	243 ± 14 (5)	54 ± 2 (5)	197 ± 25 (5)
Rotenone single	1504 ± 117 (6)[a]	332 ± 57 (6)	33 ± 11 (6)	233 ± 32 (6)
Rotenone repeated	817 ± 86 (6)[a]	683 ± 222 (5)[b]	12 ± 4 (5)[b]	336 ± 34 (5)[b]
1MeTIQ repeated	1136 ± 65 (6)	91 ± 7 (6)	107 ± 11 (6)[b]	139 ± 22 (6)
1MeTIQ + rotenone repeated	1024 ± 155 (6)	165 ± 33 (6)[c]	46 ± 9 (6)[d]	138 ± 25 (6)[c]

Rotenone, 12 mg/kg s.c., was given once (single) or daily for 7 days (repeated), and 1MeTIQ, 50 mg/kg i.p., was given 90 min before each rotenone injection. The animals were killed 4 h after the last rotenone injection. The data are concentrations in ng/g tissue, means ± S.E.M. (*N*).

[a] $P < 0.05$ in comparison with control.

[b] $P < 0.01$ in comparison with control.

[c] $P < 0.01$ in comparison to rotenone group (LSD test).

[d] $P < 0.05$ in comparison to rotenone group (LSD test).

for biochemical assay. Dopamine and its metabolites, homovanillic acid (HVA), 3,4-dihydroxyphenylacetic acid (DOPAC), and 3-methoxytyramine (3-MT), were assayed by means of HPLC with electrochemical detection. 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). The chromatograph (Hewlett-Packard 1050) was 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.

2.4. Calculations and statistics

The significance of the protective effect of 1MeTIQ against rotenone toxicity was assessed with the chi-square test. The results of biochemical experiments were analyzed by means of one-way analysis of variance followed, when appropriate, by Fisher's Least-Significant Difference test (LSD). The metabolic indices were calculated as reported previously (Antkiewicz-Michaluk et al., 2001). The total catabolism rate was assessed from the ratio of the concentration of the common final dopamine metabolite, HVA to the dopamine concentration and expressed as the index of catabolism rate ([HVA]/[DA]) × 100. To assess the participation of the monoamine oxidase-dependent oxidative pathway in dopamine catabolism, the ratio of DOPAC to dopamine was calculated and presented as the index ([DOPAC]/[DA]) × 100. The COMT-dependent methylation pathway was assessed similarly, and the index ([3-MT]/[DA]) × 100 was calculated. The indices were calculated using concentrations from individual tissue samples.

3. Results

3.1. General condition of rotenone-treated rats

Administration of rotenone for 7 days produced dose-dependent changes suggestive of toxic effects. The body weight gain of the rats treated with rotenone (10–15 mg/kg) declined, and the general appearance deteriorated. The movements were slowed down, and disturbances in the coordination of movements were observed. Repeated administration of rotenone in the highest dose (15 mg/kg) caused death.

Table 3
The effect of 1MeTIQ on rotenone-induced changes in the levels of dopamine and its metabolites in the striatum of the rat

Groups	Dopamine	DOPAC	3-MT	HVA
Control	9580 ± 393 (7)	986 ± 38 (8)	198 ± 4 (8)	787 ± 63 (8)
Rotenone single	9748 ± 403 (6)	1333 ± 37 (6)	210 ± 13 (6)	925 ± 64 (6)
Rotenone repeated	8850 ± 563 (6)	3815 ± 275 (5)[b]	23 ± 4 (5)[b]	4609 ± 447 (5)[b]
1MeTIQ repeated	9562 ± 241 (7)	587 ± 25 (6)	368 ± 15 (6)[b]	969 ± 69 (6)
1MeTIQ + rotenone repeated	11,333 ± 1417 (6)	1743 ± 497 (6)[c]	89 ± 13 (6)[d]	1567 ± 418 (6)[c]

Rotenone, 12 mg/kg s.c., was given once (single) or daily for 7 days (repeated), and 1MeTIQ, 50 mg/kg i.p., was given 90 min before each rotenone injection. The animals were killed 4 h after the last rotenone injection. The data are concentrations in ng/g tissue, means ± S.E.M. (*N*).

[a] $P < 0.05$ in comparison with control.

[b] $P < 0.01$ in comparison with control.

[c] $P < 0.01$ in comparison to rotenone group (LSD test).

[d] $P < 0.05$ in comparison to rotenone group (LSD test).

Table 4
The effect of 1MeTIQ on rotenone-induced changes in the levels of dopamine and its metabolites in the nucleus accumbens of the rat

Groups	Dopamine	DOPAC	3-MT	HVA
Control	9250 ± 74 (5)	1391 ± 92 (5)	141 ± 24 (5)	544 ± 40 (5)
Rotenone single	9836 ± 832 (6)	1882 ± 98 (6)	160 ± 35 (6)	609 ± 68 (6)
Rotenone repeated	9318 ± 397 (5)	3726 ± 965 (5)[a]	51 ± 10 (5)[b]	2806 ± 635 (5)[a]
1MeTIQ repeated	9564 ± 503 (6)	996 ± 40 (6)	309 ± 58 (6)[b]	668 ± 52 (6)
1MeTIQ + rotenone repeated	9521 ± 1255 (6)	1944 ± 609 (6)[c]	85 ± 10 (6)	1099 ± 395 (6)[c]

Rotenone, 12 mg/kg s.c., was given once (single) or daily for 7 days (repeated), and 1MeTIQ, 50 mg/kg i.p., was given 90 min before each rotenone injection. The animals were killed 4 h after the last rotenone injection. The data are concentrations in ng/g tissue, means ± S.E.M. (*N*).

[a] $P<0.01$ in comparison with control.

[b] $P<0.05$ in comparison with control.

[c] $P<0.05$ in comparison to rotenone group (LSD test).

Concomitant administration of 1MeTIQ did not prevent the loss of body weight gain, but apparently improved the general appearance and motor coordination of the rats, and significantly ($P<0.05$) prevented rotenone-induced mortality (Table 1).

3.2. Levels of dopamine and its metabolites in the substantia nigra, striatum, and nucleus accumbens

Single administration of rotenone tended to increase the dopamine level in the investigated structures, and a significant elevation (by 40%, $P<0.05$) was noted in the substantia nigra. The changes in the levels of dopamine metabolites did not reach the level of significance, although a tendency to increase was observed in all structures for DOPAC (by over 30%) and for HVA (12–19%) (Tables 2–4).

In contrast to the effects of single rotenone administration, the repeated treatment resulted in clear changes in dopamine metabolism. While the decrease in dopamine content was significant only in the substantia nigra (74% of the control level, $P<0.05$), the direction of the changes in metabolite levels was similar in all structures. The level of the intraneuronal metabolite, DOPAC, was strongly increased (by 200–300%, $P<0.01$) in all investigated structures, while the level of the extraneuronal metabolite, 3-MT was depressed to 10–40% ($P<0.01$) of the control level. The total metabolism of dopamine was augmented, especially in dopamine nerve ending-containing structures, as evidenced by a significant increase in HVA in the striatum (by 500%, $P<0.01$) and the nucleus accumbens (by 400%, $P<0.01$).

Repeated administration of 1MeTIQ in a dose of 50 mg/kg did not change the levels of either dopamine or its final metabolite, HVA. However, the metabolic route of dopamine was changed in the direction of 3-methylation, as evidenced by a significant, about two-fold increase in 3-MT level in all investigated structures (98% in the substantia nigra, 86% in the striatum, and 119% in the nucleus accumbens, $P<0.05$).

Administration of 1MeTIQ before each rotenone injection antagonized the effects of rotenone on dopamine metabolism: it significantly counteracted the rotenone-induced increase in DOPAC and HVA levels, and prevented the decrease in 3-MT concentrations.

3.3. Indices of dopamine catabolic pathway in the striatum

A single dose of rotenone (12 mg/kg) did not produce any significant changes in the concentrations of dopamine

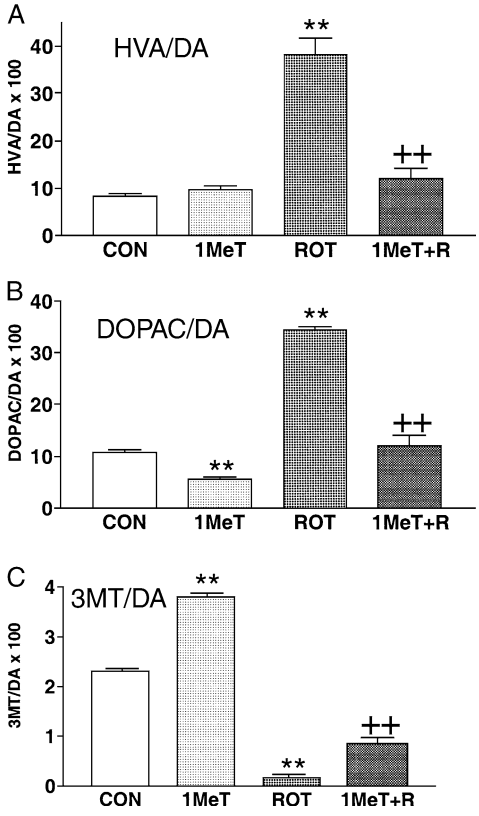

Fig. 1. Modification by 1MeTIQ of rotenone-induced changes in dopamine metabolism in rat striatum. (A) The index of the rate of total dopamine catabolism ([HVA]/[DA]) × 100. (B) The index of the rate of oxidative dopamine catabolism (monoamine oxidase-dependent) ([DOPAC]/[DA]) × 100. (C) The index of the rate of *O*-methylation dopamine catabolism ([3-MT]/[DA]) × 100. Each bar represents the mean ± S.E.M. from five to seven individually calculated ratios. Rotenone (ROT), 12 mg/kg s.c., was given for 7 days, and 1MeTIQ (1MeT), 50 mg/kg i.p., was administered 90 min before each rotenone injection. The animals were killed 4 h after the last rotenone injection. $^{**}P<0.01$ in comparison with control, $^{++}P<0.01$ in comparison to rotenone group (LSD test).

and its main metabolite HVA, and did not influence dopamine metabolism (Table 3). In contrast, repeated rotenone administration induced dramatic changes in the rate and pathways of dopamine metabolism (Fig. 1A–C). Total dopamine metabolism, measured as HVA/dopamine ratio, increased approximately four-fold ($P<0.01$). Catabolism was potently shifted to oxidative deamination (a three-fold increase in DOPAC/dopamine ratio, $P<0.01$), while the 3-*O*-methylation pathway was virtually blocked (decrease in 3-MT/dopamine ratio by a factor of 8, $P<0.01$).

1MeTIQ did not change the total dopamine metabolism (HVA/dopamine ratio), but increased *O*-methylation by about two-fold ($p<0.01$) and inhibited the oxidative pathway by a factor of 2 ($P<0.01$). Given before each dose of repeatedly administered rotenone, 1MeTIQ effectively antagonized the metabolic effects of rotenone and nearly normalized total dopamine metabolism and the rate of metabolism along both catabolic routes.

4. Discussion

It is currently believed that Parkinson's disease is caused not only by genetic, but also, to a large extent, by environmental factors, of which herbicides may play an important, though not exclusive, role (Gorell et al., 1998). One of the pesticides which may be involved in the development of Parkinson's disease is rotenone. Two lines of reasoning support the role of rotenone. Firstly, both in hereditary and spontaneous Parkinson's disease the activity of mitochondrial complex I is decreased (Schapira et al., 1990; Swerdlow et al., 1996), and rotenone is a potent, lipid-soluble inhibitor of this complex (Gutman et al., 1970; Horgan et al., 1968). Secondly, oxidative damage is strongly implied in the neurodegeneration of dopaminergic neurons (Lamensdorf et al., 2000a,b), and, as shown by us previously (Antkiewicz-Michaluk and Vetulani, 2001) and in this paper, rotenone potently activates dopamine metabolism along the oxidative pathway.

We report here that while a single dose of rotenone did not produce evident behavioral or biochemical effects, repeated administration of this compound induced important changes both at behavioral and biochemical levels that were counteracted by administration of 1MeTIQ before each rotenone injection.

Rotenone was toxic when applied in doses of 12–15 mg/kg repeatedly for a short period, causing considerable mortality. Those rats that survived the treatment showed clear abnormalities in general behavior, such as bradykinesia, abnormal gait, and loss of body weight gain. Mortality and behavioral abnormalities were effectively counteracted by 1MeTIQ.

Part of the observed behavioral abnormalities may be explained by the action rotenone on the dopaminergic system. Repeated rotenone administration was found to strongly increase dopamine metabolism, as measured by the increase in concentrations of the intraneuronal dopamine metabolite, DOPAC, and the final metabolite, HVA. Interestingly, it depressed the concentration of the extracellular dopamine metabolite, 3-MT. These changes were effectively counteracted by administration of 1MeTIQ before each dose of rotenone.

A single dose of rotenone did not produce changes in dopamine metabolism, but repeated doses caused dramatic increases in total dopamine metabolism, due to an increase in oxidative deamination. The effects were most marked in the striatum, while they were much less marked in the substantia nigra.

The lack of evident changes after a single dose of rotenone suggest that the effects of rotenone in a dose of 12 mg/kg do not depend on a direct action on dopaminergic receptors or transporters. With higher peripheral doses (Thiffault et al., 2000), or with brain perfusion (Santiago et al., 1995), rotenone was found to induce dopamine release. With lower doses, the changes evolved progressively, most probably due to damage of intracellular structures caused by a permanent energy deficit resulting from the inhibition of mitochondrial complex I (Horgan et al., 1968; Greenamyre et al., 2001). These changes seem to be responsible for the shift in dopamine metabolism toward the oxidation pathway, as indicated by the dramatic increase in DOPAC concentration, with concomitant potent inhibition of the *O*-methylation pathway, but with negligible changes in the level of dopamine.

The reason for the very strong increase in DOPAC concentration may be explained by the inhibitory action of rotenone on the dopamine vesicular transporter described by Vaccari and Saba (1995). Inhibition of the vesicular transporter will make the dopamine taken up by the nerve ending an unprotected substrate for monoamine oxidase. This would result in an increased formation of DOPAC which, after diffusion into the synaptic cleft, may be *O*-methylated by COMT. This leads to the observed strong increase in HVA concentration. Moreover, in this situation DOPAC may compete with released dopamine for COMT and, as a result, the synthesis of extraneuronal dopamine metabolite, 3-MT, is diminished.

The rotenone-induced increase in the oxidative pathway of dopamine metabolism results in an increased generation of free oxygen radicals, which are formed during monoamine oxidase-dependent oxidative deamination. In our other experiments with mice, we have demonstrated that administration of rotenone (5 mg/kg i.p.) for 4 days leads to an increase in the formation of 2,3-dihydroxybenzoic acid, a marker for the hydroxyl radical, from sodium salicylate (unpublished results). This radical may be an important factor in the neurodegeneration caused by rotenone (Betarbet et al., 2000).

Tetrahydroisoquinolines, which are usually regarded as noxious endogenous compounds (Nagatsu 1997), may play an important physiological role, one of which may be their antidopaminergic activity (Antkiewicz-Michaluk et al., 2000b; Vetulani et al., 2001). At least one of them, namely 1MeTIQ, was found to protect animals against the behavioral toxicity of MPTP and similarly acting compounds, such as 1BnTIQ (Tasaki et al., 1991; Yamakawa et al., 1999; Yamakawa and Ohta 1999). We have previously demonstrated that 1MeTIQ has a biochemical profile of action opposite to that of 1BnTIQ: the former shifted dopamine metabolism toward *O*-methylation, while 1BnTIQ shifted it toward the oxidative pathway. We have shown here that rotenone induces biochemical changes similar to those induced by 1BnTIQ, and that 1MeTIQ effectively counteracts them.

The mechanism of 1MeTIQ-induced protection against the behavioral and biochemical changes brought about by rotenone or other neurotoxins has not been elucidated yet. Our results suggest that one of the components of this protective action may be prevention of the rotenone-induced shift in dopamine catabolism toward oxidation, and therefore a reduction in the generation of free radicals. The pattern of biochemical changes after 1MeTIQ administration may suggest that the compound is a monoamine oxidase A inhibitor. We have, indeed, found in a separate experiment that 1MeTIQ inhibits both monoamine oxidase A and monoamine oxidase B activity, with IC_{50} values of 32 and 130 μmol, respectively. Monoamine oxidase inhibition by 1MeTIQ may explain both the shift in dopamine metabolism toward the *O*-methylation pathway and the antagonism of the rotenone-induced shift in the direction of oxidation pathway. This may explain not only the normalization of dopamine metabolism in the investigated brain structures, but also the prevention of some of the behavioral abnormalities that seem to result from malfunction of the dopaminergic system (e.g. abnormal gait and bradykinesia). Not all effects of rotenone, e.g. inhibition of body weight gain, are inhibited by 1MeTIQ. However, the inhibition of rotenone-induced mortality by 1MeTIQ suggests that the compound may also antagonize some of the toxic effects related to the peripheral actions of rotenone, which seem to cause less mortality than the central actions of rotenone after its direct injection into several cerebral structures (unpublished results).

In summary, we demonstrated that rotenone strongly shifts dopamine metabolism toward the oxidative pathway, along which reactive oxygen species are also generated. These biochemical effects may be responsible for the Parkinsonian-like changes caused by chronic exposure to the pesticide. As 1MeTIQ antagonized the behavioral and neurochemical effects of rotenone, the compound may be considered as a potential protective agent against environmental factors affecting the function of the dopaminergic system.

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