

Chapter 2

Isoquinolines as Neurotoxins: Action and Molecular Mechanism

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Abstract Derivatives from the isoquinoline group were found in many plants, food as well as in the mammalian brain. The interest with these substances appeared about 20 years back, after the exploration of their chemical structures similar to the well-known exogenous neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Tetrahydroisoquinolines such as 1-benzyl-1,2,3,4-tetrahydroisoquinoline (1BnTIQ) and 1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (salsolinol) show the neurotoxic activity to the dopamine neurons and this way it has been proposed as endogenous factors leading risks to Parkinson's disease. In animals, research indicates that chronic administration of 1BnTIQ as well as salsolinol induced parkinsonian-like symptoms. Both compounds produce disturbances in the function of dopaminergic neurons, intensify oxidative stress, and inhibit mitochondrial complex I and/or II activity. In consequence, this mechanism of action leads to

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cell death via apoptosis. This review briefly describes the properties of 1BnTIQ and salsolinol in mammalian brain. This chapter presents the chemical structures of both compounds and possible pathways of their synthesis in the brain. A special focus was put on neurochemical effects of acute and chronic administration of 1BnTIQ and salsolinol on dopamine release as well as their metabolism in rat brain. Additionally, the effects of dopamine metabolism have been shown as a source of free radical generation in the brain.

Keywords 1-Benzyl-1,2,3,4-tetrahydroisoquinoline • Salsolinol • Rat brain • Oxidative stress • Neurotoxins • Dopamine metabolism • In vivo dopamine release • Parkinson's disease

Abbreviations

BBB	Blood–brain barrier
1BnTIQ	1-Benzyl-1,2,3,4-tetrahydroisoquinoline
COMT	Catechol- <i>O</i> -methyltransferase
CSF	Cerebrospinal fluid
DA	Dopamine
DAT	Dopamine transporter
DOPAC	3,4-Dihydroxyphenylacetic acid
H ₂ O ₂	Hydrogen peroxide
HVA	Homovanilic acid
L-DOPA	3,4-Dihydroxy-L-phenylalanine
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MAO	Enzyme monoamine oxidase
PEA	Phenylethylamine
PD	Parkinson's disease
ROS	Reactive oxygen species
TH	Tyrosine hydroxylase
TIQ	1,2,3,4-Tetrahydroisoquinoline

2.1 Introduction

Isoquinoline derivatives, e.g. tetrahydroisoquinolines, are widely distributed in the environment, being present in many plants and foods such as cheese, milk, red wine, bananas, etc. The exogenously administered tetrahydroisoquinolines easily cross the blood–brain barrier (BBB) and migrate into the brain, producing behavioral and biochemical effects in monoamine systems (Antkiewicz-Michaluk et al.

2000a, b, 2001; Kikuchi et al. 1991; Michaluk et al. 2002). These compounds belong to the isoquinoline group and their structure closely resembles the well-known exogenous toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The neurotoxic role of MPTP depends crucially on its metabolite MPP⁺, formed in glial cells in a reaction catalyzed by the MAO_B enzyme. The assumption that tetrahydroisoquinolines may be neurotoxic is based on their ability to form tetrahydroisoquinoline ions, analogous to MPP⁺ (Maruyama et al. 1997; Naoi et al. 1994, 1989a, b), in fact an experimental parkinsonism was induced by TIQ in monkeys (Nagatsu and Yoshida 1988) and by a salsolinol derivative in rats (Naoi et al. 1996). While MPTP acts rapidly and produces irreversible neurotoxic changes after a single injection and its effects are strictly limited to the nigrostriatal dopamine system (Burns et al. 1985), tetrahydroisoquinolines produce no immediate neurotoxic effects; after acute administration, they produce marginal biochemical effects. Furthermore, tetrahydroisoquinolines do not potentiate the action of dopamine receptor antagonists but very effectively counteract the action of dopamine receptor agonists. In addition, tetrahydroisoquinolines bind to the agonistic sites of dopamine receptors.

2.2 The Chemical Structure of the Endogenous Neurotoxins: 1-Benzyl-1,2,3,4-Tetrahydroisoquinoline and 1-Methyl-6,7-Dihydroxy-1,2,3,4-Tetrahydroisoquinoline (Salsolinol) (Fig. 2.1)

2.3 The Synthesis of 1BnTIQ and Salsolinol in the Brain

1BnTIQ can be formed in vivo by mammalian brain enzymes from PEA and phenylacetaldehyde (metabolite of PEA) generated by MAO-B.

The biosynthetic pathway of 1BnTIQ (Fig. 2.2).

In vivo 1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (salsolinol) can be formed in the mammalian brain by three different mechanisms: (1) via the

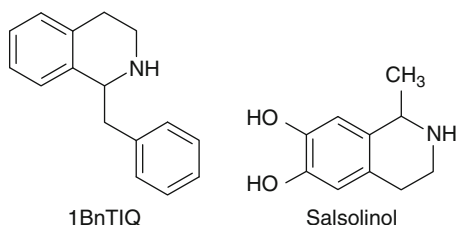


Fig. 2.1 Chemical structures of 1BnTIQ and salsolinol based on Naoi et al. 2004; Waşık et al. 2009

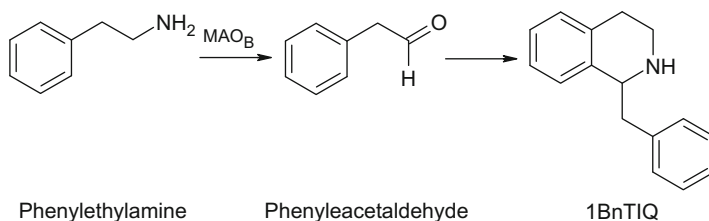


Fig. 2.2 Synthetic route of 1BnTIQ based on Kotake et al. 1995

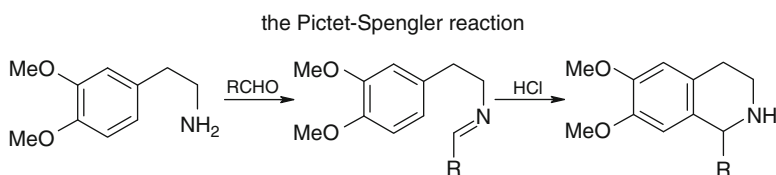


Fig. 2.3 The Pictet–Spengler reaction based on Whaley and Govindachari 1951

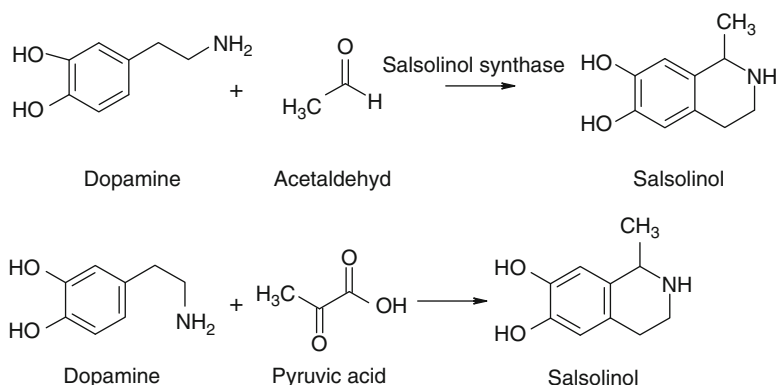


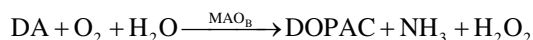
Fig. 2.4 Salsolinol synthesis based on Naoi et al. 2004

nonenzymatic Pictet–Spengler condensation of dopamine and aldehydes producing salsolinol in two racemic isomers (*R* or *S*); (2) by the nonenzymatic condensation of dopamine and pyruvate yielding 1-carboxyl-tetrahydroisoquinoline, followed by decarboxylation and reduction, which produce (*R*)-salsolinol; (3) by the selective synthesis of (*R*)-salsolinol from dopamine and acetaldehyde.

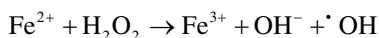
The original Pictet–Spengler reaction was a reaction of β -phenylethylamine with the dimethyl acetal of formaldehyde and hydrochloric acid, which yielded tetrahydroisoquinoline (Figs. 2.3 and 2.4).

2.4 The Oxidation of Dopamine

There are many natural sources of oxidative stress e.g., environmental toxins (herbicides, pesticides, heavy metals), heat shock, UV radiation, and inflammation. Reactive oxygen species (ROS) are products of normal cellular metabolism. Also, dopamine can generate ROS via enzymatic and nonenzymatic pathways (Cohen et al. 1997; Berman and Hastings 1999; Gluck et al. 2002). During a dopamine catabolism process, ROS are formed which are very dangerous to living cells. A high concentration of ROS leads to damage to a number of biomolecules, such as DNA, proteins, and lipids. In consequence, cell death is induced via apoptosis. Complexes I, II, and III of the mitochondrial respiration, pyruvate dehydrogenase, and α -ketoglutarate complexes are highly sensitive to the blocked effect of ROS (Vinogradov et al. 1976; Bunik et al. 1990; Bulteau et al. 2003; Bunik 2003). Gluck et al. (2002) reported that dopamine at low concentrations inhibited mitochondrial respiration, predominately by a MAO-dependent mechanism involving H_2O_2 and downstream hydroxyl radical formation. The production of superoxide anion occurs mostly within cell mitochondria (Cadenas and Sies 1998). In neurons, dopamine is nonenzymatically oxidized by the molecular oxygen to form hydrogen peroxide (H_2O_2) and the corresponding *O*-quinone (Oq). Then, this Oq undergoes intramolecular cyclization which is immediately followed by a cascade of oxidative reactions resulting in the formation of neuromelanin – a black pigment characteristic of dopaminergic neurons (Graham 1978; Graham et al. 1978). Additionally, dopamine can also be enzymatically deaminated by monoamine oxidase (MAO) to form H_2O_2 and 3,4-dihydroxyphenylacetaldehyde. This process is shown by the following formula:



Subsequently, 3,4-dihydroxyphenylacetaldehyde is oxidized by aldehyde dehydrogenase to form 3,4-dihydroxyphenylacetic acid (DOPAC), which is methylated by catechol-*O*-methyltransferase (COMT) to yield homovanilic acid (HVA), which is a final dopamine metabolite. Therefore, both autooxidation and MAO-mediated metabolism of dopamine lead to the production of H_2O_2 . This compound can be subject to the Fenton reaction, which consists in reducing H_2O_2 in the presence of ferrous iron (Fe^{2+}). Further, in consequence come into the being the hydroxyl radical ($\cdot OH$), which is considered the most damaging free radical to living cells.



The formation of a free radical during both the biosynthesis and the turnover of dopamine leads to a loss of many dopaminergic neurons (Fornstedt et al. 1990). It is evident that the subsequent excessive autooxidation and catabolism of dopamine are involved in the development of many neurodegenerative and age-related disorders (e.g., Parkinson's disease). Furthermore, these phenomena are enhanced by the presence of neuromelanin in dopaminergic neurons due to its reported ability to

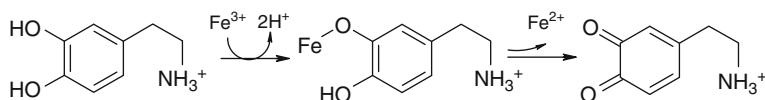


Fig. 2.5 Dopamine autoxidation based on Hermida-Ameijeiras et al. 2004

accumulate iron (Enoch et al. 1994); consequently, neuromelanin can act by promoting the Fenton reaction. Hermida-Ameijeiras et al. (2004) reported that the continuous production of $\cdot\text{OH}$ during the dopamine incubation with mitochondrial preparations obtained from rat brain was maintained under the physiological conditions of pH and temperature. That production was reduced when MAO activity was blocked by the preincubation of mitochondrial preparations with the MAO inhibitor, pargyline. Thus, on the one hand the dopamine protects against both the hazardous Fenton reaction and the propagation of lipid peroxidation but, on the other, it generates $\cdot\text{OH}$ and promotes protein oxidation. Furthermore, these properties are differently enhanced by the presence of Fe^{2+} and Fe^{3+} . The hydroxyl ion OH^- , also produced in the Fenton reaction, is considerably less toxic (10^{14}) than the hydroxyl radical. Iron plays an important role in this reaction. It may originate from neuromelanin or ferritin. It should be emphasized that in the course of Parkinson's disease, neuromelanin-containing dopaminergic neurons are those which die, which suggests that Fe^{2+} , essential for the Fenton reaction to occur, can be released from this compound by unknown toxic factors (Antkiewicz-Michaluk 2002; Ben-Shachar et al. 1991a, b). Thus, dopamine metabolism leads to the formation of the toxic hydroxyl radical, which poses a serious threat to nervous cells causing their damage and death in the process of apoptosis.

The process of dopamine autoxidation in the presence of Fe^{3+} is shown by the following formula (Fig. 2.5).

2.5 The Effect of Acute and Chronic Treatment with 1BnTIQ and Salsolinol on Dopamine Metabolism in Rat Brain

1-Benzyl-1,2,3,4-tetrahydroisoquinoline (1BnTIQ) is an endogenous neurotoxin which has been proposed as one of the etiological factors of idiopathic Parkinson's disease (PD) (Kotake et al. 1995). The level of 1BnTIQ in the CSF of patients with idiopathic PD was found to be three times higher than that in CSF of neurological control subjects (Kotake et al. 1995). Chronic administration of 1BnTIQ induced parkinsonian-like symptoms in rodents and primates (Kotake et al. 1995; 1996). In vitro studies showed that 1BnTIQ is toxic to human SH-SY5Y neuroblastoma cells and cultured primary neurons (Kotake et al. 2003; Shavali and Ebadi 2003; Shavali et al. 2004). Some evidence demonstrated that 1BnTIQ dose-dependently elevated

the level of the pro-apoptotic protein Bax and decreased the concentration of the anti-apoptotic protein Bcl-xL. Additionally, 1BnTIQ produced an increase in the formation of active caspase-3 protein fragments (Shavali and Ebadi 2003). 1BnTIQ induced cell death via apoptosis. A morphological analysis of SH-SY5Y cells treated with 1BnTIQ showed nuclear defects and the presence of apoptotic-like bodies and nuclear fragments (Shavali et al. 2004). Dopaminergic cells deteriorated and slowly died, their number being gradually reduced. The neurotoxicity of 1BnTIQ was correlated with the overall exposure (concentration multiplied by time of exposure). The prolonged exposure of dopaminergic neurons to a low concentration of 1BnTIQ initially induced a decrease in the dopamine level, after which the shrinkage of the cell body led to cell death (Kotake et al. 2003). Different TIQ derivatives inhibited mitochondrial respiration and electron transfer complexes. 1BnTIQ was found to be a more potent inhibitor than MPTP and MPP⁺ (Morikawa et al. 1996, 1998). 1BnTIQ also blocked the dopamine transporter (DAT) leading to inhibition of dopamine uptake. Okada et al. (1998) reported that 1BnTIQ can be taken up via DAT into dopaminergic neurons similarly to MPP⁺ in vivo. Otherwise, those agents can only bind to the DAT like cocaine. However, since salsolinol (structurally similar to THP) seems to be taken up into rat striatal slices (Hirata et al. 1990) and PC 12h cells (Maruyama et al. 1993) 1BnTIQ can also be accumulated in DAT-HEK. 1BnTIQ, which is synthesized endogenously in the body and/or is obtained exogenously in the diet, can be taken up by neurons via DAT; furthermore, it accumulates in dopaminergic neurons and exerts some pathological effects leading to parkinsonism, and it disturbs the efficacy of L-DOPA chemotherapy in parkinsonian patients. Kotake et al. (2003) showed that the exposure to 1BnTIQ for 24 h or 7 days caused a dose-dependent decrease in dopamine content in mesencephalic slices. Kohta et al. (2010) found that 1BnTIQ bound to tubulin β in mid-brain neurons and reduced the formation of high-molecular-weight polyubiquitinated tubulin β . The latter findings suggest that 1BnTIQ may impair tubulin β ubiquitination, similarly to mutant parkin in AR-JP. Even low concentrations of 1BnTIQ can decrease the polyubiquitination of tubulin β if present for a long time (Kohta et al. 2010). The overexpression of tubulin β is toxic (Burke et al. 1989) and causes disturbances in the functioning of dopaminergic neurons. 1BnTIQ acts by inhibiting the enzymes involved in dopamine biosynthesis. Ex vivo biochemical studies showed that a single dose of 1BnTIQ (50 mg/kg) produced a dramatic fall in the dopamine level in rat brain (approx. 40%) and increased the concentration of its metabolites, DOPAC and HVA. Additionally, 1BnTIQ markedly reduced the level of extraneuronal dopamine metabolite, 3-MT. 1BnTIQ evoked strong (nearly three-fold) activation of the oxidative MAO-dependent catabolic pathway (Wąsik et al. 2009). Dopamine oxidation is directly connected with the production of free radicals, oxidative stress, as well as with cell death and neurodegeneration (Schapira et al. 1990; Adams and Odunze 1991; Miller et al. 1996; Chan 1998; Dykens 1999). At the same time, 1BnTIQ significantly inhibits the COMT-dependent O-methylation pathway. Striatum and nucleus accumbens represent brain regions where the depression of dopamine produced by 1BnTIQ is most powerfully expressed, this effect being specific to dopaminergic neurons. The biochemical effects of the chronic

administration of 1BnTIQ are considerably weaker. This pattern of changes suggests that during chronic 1BnTIQ administration some tolerance to its dopamine-depressing effect develops, while the impairment of dopamine synthesis ensues (Wąsik et al. 2009). After chronic (14 doses) 1BnTIQ administration the decrease in dopamine level was weaker (approx. 20%). However, in the mixed group in which rats received L-DOPA with the last dose of 1BnTIQ, the effects of L-DOPA were significantly reduced. Such an effect was observed 2 h after the last 1BnTIQ injection, as well as after its 24-h withdrawal. Hence, dopamine production was disturbed after chronic 1BnTIQ administration, the effect being long lasting (Antkiewicz-Michaluk et al. 2010).

It is common by known that enantiomer (*R*)-salsolinol is synthesized in human and mammalian brain, whereas enantiomer (*S*) penetrates into the organism with foods. A low concentration of salsolinol was detected in normal human cerebrospinal fluid (Moser and Kompf 1992), brain, and urine (Dostert et al. 1989). In contrast, both parkinsonian patients treated with L-DOPA and chronic alcoholics showed a significant elevation in the concentration of salsolinol in CSF and urine (Cohen and Collins 1970; Collins et al. 1979; Moser and Kompf 1992; Sandler et al. 1973). Salsolinol is a dopamine metabolite and its toxicity is closely connected with catecholaminergic nerve terminals. Salsolinol is structurally similar to MPTP which produces a parkinsonian-like syndrome in human and nonhuman primates. It was suggested that under special conditions salsolinol may act as a false neurotransmitter, causing – among other effects – neurodegeneration. It was found that tetrahydroisoquinoline may produce parkinsonism-like symptoms in primates (Nagatsu and Yoshida 1988). Salsolinol acts as inhibitor both of tyrosine hydroxylase (TH) and MAO. Patsenka and Antkiewicz-Michaluk (2004) have reported that different TIQs inhibited MAO activity in a dose-dependent manner. Salsolinol inhibited MAO_A activity most effectively in rat frontal cortex, and less efficiently in other rat and mouse brain structures. Moreover, from different TIQs only salsolinol was effective as an inhibitor of TH activity. This compound is regarded as an inhibitor of catecholamine uptake in rat brain synaptosomes and it causes the release of catecholamines stored in rat brain (Heikkilä et al. 1971). Storch et al. (2000) concluded that salsolinol was toxic to dopaminergic neuroblastoma SH-SY5Y cells by blocking the cellular energy supply via inhibition of mitochondrial complex II activity. The latter authors found that incubation of human SH-SY5Y dopaminergic neuroblastoma cells with salsolinol resulted in a rapid, dose- and time-dependent decrease in the intracellular level of ATP and ATP/ADP ratio of intact cells. In vitro studies showed that salsolinol induced specific changes in cellular energy metabolism, similar to those caused by MPP⁺, which consistently preceded cell death (Storch et al. 2000). As reported by Morikawa et al. (1998) salsolinol inhibited mitochondrial complex II activity. It caused a rapid loss of intracellular ATP and maximal turnover of glycolysis without compensating fast energy depletion. Additionally, the blockade of complex II did not change the level of NADH. Selective binding of salsolinol was confirmed not only in dopaminergic structures such as e.g., the striatum, but also in the pituitary gland, cortex, and hypothalamus (Homicsko et al. 2003). Salsolinol also inhibited vesicular monoamine transporters in dopaminergic terminals.

The latter findings suggest that salsolinol may regulate the function of dopamine neurons as a neurotransmitter and may act as a mediator in the neuroendocrine system, through its specific binding sites and via intervention in the dopamine system (Naoi et al. 2004). Salsolinol antagonized behavioral action of L-DOPA and apomorphine, a dopamine agonist (Ginos and Doroski 1979; Antkiewicz-Michaluk et al. 2000a, b). Binding studies demonstrated that salsolinol displaced [^3H]apomorphine, but not dopamine D_1 ([^3H]SCH23,390) and D_2 ([^3H]spiperone) receptor antagonists, from their binding sites, its effectiveness being comparable to that of dopamine (Antkiewicz-Michaluk et al. 2000a, b). The above data suggest that salsolinol may suppress dopaminergic transmission by acting on the agonistic sites of dopaminergic receptors, which are different from neuroleptic binding sites. Salsolinol showed an antidopaminergic profile since it induced only a weak effect on spontaneous locomotor activity; moreover, it produced effective antagonism to behavioral and biochemical effects of apomorphine and induced muscle rigidity (Antkiewicz-Michaluk et al. 2000a, b; Lorenc-Koci et al. 2000; Vetulani et al. 2001). Ex vivo biochemical studies demonstrated that a single dose of salsolinol (100 mg/kg) produced no changes in dopamine concentration as well as its metabolites in different rat brain structures. On the other hand, administration of salsolinol jointly with L-DOPA enhanced its effect. In fact, the level of dopamine and all its metabolites was significantly higher compared to a group treated with L-DOPA (data not shown). Chronic (14 doses) salsolinol administration did not produce any changes in dopamine concentration and in the level of its metabolites. However, in a mixed group of rats which were given, the last dose of salsolinol jointly with L-DOPA, the effect of L-DOPA was significantly reduced. Similar to experiment with 1BnTIQ, the latter effect was observed 2 h after the last salsolinol injection as well as after its 24-h withdrawal. Hence, it has been demonstrated that chronic injection of salsolinol produces long-lasting disturbances in dopamine production in the brain (Antkiewicz-Michaluk et al. 2010).

2.6 The Effect of 1BnTIQ and Salsolinol on In Vivo Dopamine Release in Rat Striatum

An in vivo microdialysis study demonstrated that 1BnTIQ given systemic markedly reduced dopamine release into the synaptic cleft of freely moving rats, and produced a long-lasting decrease in extracellular dopamine in rat striatum (about 30%). In contrast, the concentration of all the dopamine metabolites was significantly elevated after acute 1BnTIQ administration (approx. 100%) (Wąsik et al. 2009). The above findings suggest that 1BnTIQ may show injury properties to vesicular transporter in dopaminergic neurons, leading to a pathological release of dopamine into the cytosol. In contrast, an acute dose of salsolinol produced only a slight reduction of dopamine level. The latter findings indicate that both acute and repeated administration of 1BnTIQ results in the development of abnormalities in the function of dopamine neurons (Wąsik et al. 2009). Such disturbances are particularly observed in

animals treated with 1BnTIQ concomitant with L-DOPA, because chronic administration of 1BnTIQ in contrast to its acute injection significantly reduces the increase in dopamine release, produced by L-DOPA; furthermore, it completely antagonizes the L-DOPA-induced rise in DOPAC and 3-MT levels in rat striatum (Antkiewicz-Michaluk et al. 2010). In the light of all these data we suggest that therapy with L-DOPA may not be efficient in PD patients with an elevated endogenous 1BnTIQ level in the brain.

2.7 Conclusions

It is reported that both isoquinoline derivatives (1BnTIQ and salsolinol) are endogenous neurotoxins synthesized in human and mammalian brain. The action of both these compounds is closely connected with dopaminergic neurons. Their exogenous administration elevates dopamine oxidation which leads to an increase in the formation of ROS in dopaminergic neurons. In consequence, these substances inhibit the mitochondrial complex I or/and II and induce cell death via apoptosis. Chronic administration of 1BnTIQ as well as salsolinol produced parkinsonian-like symptoms both in rodents and rhesus. Both acute and chronic administration of 1BnTIQ and salsolinol leads to the development of the abnormalities in the functioning of dopamine neurons. The accumulated evidence suggests that isoquinoline derivatives may be one of the etiological factors of idiopathic PD and additionally a therapy with L-DOPA may not be efficient in PD patients with a high endogenous level of 1BnTIQ and/or salsolinol in the brain.

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