

ROLE OF NORADRENERGIC SYSTEM IN THE MECHANISM OF ACTION OF ENDOGENOUS NEUROTOXIN 1,2,3,4-TETRAHYDROISOQUINOLINE: BIOCHEMICAL AND FUNCTIONAL STUDIES

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It is well recognized that 1,2,3,4-tetrahydroisoquinoline (TIQ) is a substance capable of inducing in animals a syndrome, regarded as an animal model of Parkinson's disease. This study was designed to evaluate the effect of the endogenous neurotoxin TIQ on the brain noradrenaline (NA) metabolism in mice and on an arterial blood pressure in rats. It was shown for the first time that TIQ significantly increased NA metabolism, induced NA release and raised the level of its final metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG), in mouse brain. The comparative biochemical studies using specific agonist (clonidine) and antagonist (yohimbine) of α_2 -adrenergic receptors ligands have shown that observed biochemical effects were similar to those produced by α_2 -adrenergic antagonist, yohimbine. In functional studies, the systolic and diastolic blood pressure was measured using a non-invasive blood pressure transducer. Both acute and multiple treatment with TIQ produced a strong hypotensive effect, having decreased both systolic and diastolic blood pressure in rats. Development of tolerance to the hypotensive effect was observed after multiple treatment with TIQ. The data coming from these experimental studies apparently suggest an important role of the noradrenergic system in the mechanism of action of endogenous compounds from TIQ group. The results may also support the hypothesis assuming a causal relationship between noradrenergic denervation, activity of the nigrostriatal dopamine system, and some clinical manifestation of Parkinson's disease.

Key words: *1,2,3,4-tetrahydroisoquinoline, endogenous neurotoxin, noradrenaline metabolism, mouse brain, arterial blood pressure in rats*

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INTRODUCTION

Idiopathic Parkinson's disease is characterized by a relatively selective degeneration of dopaminergic cells in the substantia nigra, a loss of striatal dopamine, and intracellular inclusions known as Lewy bodies [12, 13]. Since the discovery that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) may produce a clinical syndrome similar to Parkinson's disease [6, 17, 19], it has been postulated that some exogenous or endogenous toxins may be involved in the pathogenesis of this disease [14]. Endogenous tetrahydroisoquinoline (TIQ) derivatives that are structurally related to the selective dopaminergic neurotoxin MPTP and its active metabolite 1-methyl-4-phenylpyridine (MPP+) may contribute to dopaminergic neurodegeneration in Parkinson's disease [1–4, 21, 27–29]. 1,2,3,4-TIQ is an endogenous amine found in the brain of both humans and rats [2, 34, 36], but it is also frequently encountered in a variety of foods [22, 35]. Moreover, this compound easily crosses the blood-brain barrier [16]. TIQ administered chronically to monkeys, mice and rats produces parkinsonian-like disturbances such as tremor, bradykinesia, rigidity [3, 4, 21, 42, 43], but only a slight decrease in the concentration of dopamine in the nigrostriatal pathways [4, 21]. While MPTP acts rapidly and produces irreversible neurotoxic changes after a single injection into the nigrostriatal pathways, the TIQs do not produce an immediate neurotoxicity [3, 4, 21]. Interestingly, our earlier experiments have shown that TIQs, which may be engaged in the etiopathogenesis of Parkinson's disease, show a high affinity for α_2 -adrenergic receptors in rodents brain [41]. Such high affinity of TIQ to α_2 -adrenergic receptors suggests the direct influence of this compound on both noradrenaline (NA) metabolism in the brain, and the arterial blood pressure. Recently, the biochemical data obtained from postmortem studies have shown the involvement of pigmented noradrenergic neurons in the neurodegeneration in the course of Parkinson's disease [1, 5]. The authors have shown a significant decline in the NA level in the locus coeruleus of parkinsonian patients which was paralleled by the decline in the density of α_2 -adrenoreceptors. Attention has been focused on the role of noradrenergic system in the area of locus coeruleus, which may precede neurodegenerations in the nigrostriatal system in the course of Parkinson's disease [1, 5, 8, 9]. Interestingly, there have been reports in the litera-

ture that arterial blood pressure in Parkinson's disease patients is frequently lower than in healthy persons of the same age [33, 37–40]. The cause of development of cardiovascular changes in patients suffering from idiopathic Parkinson's disease is still unknown.

The present experimental studies were undertaken to determine whether the endogenous neurotoxin TIQ altered arterial blood pressure in rats and affected NA metabolism in the mouse brain.

MATERIALS and METHODS

Animals and treatment

The subjects were male Wistar rats with initial body weight of 220–240 g, and Albino Swiss mice (body weight 25–30 g), kept under standard laboratory conditions, with free access to standard laboratory food and tap water, at the room temperature (22°C) on a natural day-night cycle. The experiment was carried out between 10.00 and 15.00 h. All the tests were held in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals, and were approved by the Bioethical Committee.

Drugs

The following drugs were used: TIQ (1,2,3,4-tetrahydroisoquinoline hydrochloride, Sigma), yohimbine (hydrochloride, Sigma), clonidine (hydrochloride, Sigma), 3-methoxy-4-hydroxyphenylglycol (MHPG, Sigma). The compounds were dissolved in 0.9% NaCl solution.

Biochemistry – noradrenaline metabolism

A brain tissue (minus cerebellum) was collected from mice killed by decapitation. The mice were treated with clonidine (1 mg/kg *ip*), TIQ (25 and 50 mg/kg *ip*) and yohimbine (20 mg/kg *ip*), and were killed 1, 2 and 4 h after the injections, respectively. The obtained tissue was immediately frozen on solid CO₂ until further use in biochemical experiments. NA and its metabolite MHPG were assayed by a high-performance liquid chromatography (HPLC) with electrochemical detection. The tissue was weighed and homogenized in an ice-cold 0.1 M perchloric 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, USA). A Bioanalytical System (BAS)

chromatograph was equipped with an Alltech Adsorbosphere Catecholamine column (3 μ m, 100 \times 4.6 mm). The mobile phase consisted of 0.05 M citrate-phosphate buffer, pH 3.8, 0.1 mM EDTA, 1 mM sodium octyl sulfonate and 3.5% methanol. The flow rate was maintained at 1 ml/min. NA and MHPG were quantified by a peak height comparison with standards, run on the day of experiment. A concentration of MHPG in the brain is often used as a measure of central NA metabolism and noradrenergic activity [11]. In rat brain, MHPG takes the form of the sulphate conjugate MHPG-SO₄, while in mice it is mainly present in an unconjugated form. It is suggested that a useful index of NA turnover is the formation of free MHPG in mice and conjugated MHPG-SO₄ in rats. Under our experimental conditions, we were unable to measure MHPG-SO₄. In order to determine the index of NA turnover, we examined free MHPG in the whole mouse brain, where it reflects the major cerebral NA transformation.

Blood pressure

Systolic and diastolic blood pressure was measured with a non-invasive blood pressure transducer (Stoelting) connected to a Knauer recorder. The rats that were habituated to the procedure were hand-held during the measurement, and their blood pressure was recorded from the tail at 1, 4, and 24 h after acute treatment with TIQ (50 mg/kg *ip*). In the case of the multiple treatment with TIQ, the measurement was carried out 2 h after the 1st, 4th and 10th injections. The reference drugs, clonidine (1 mg/kg *ip*) and yohimbine (20 mg/kg *ip*), were also tested.

Calculations and statistical analysis

Analysis of variance, followed by Dunnett's test or the Least Significant Difference test (LSD), were used to assess the significance of differences between groups. In addition, an individual ratio of [MHPG/NA \times 100] was calculated as an index of the rate of NA metabolism.

RESULTS

Biochemical effects

The level of noradrenaline and its metabolite

Clonidine, an agonist of α_2 -noradrenergic receptors, produced a slight increase (approximately 15%) in the concentration of NA and a significant decline

in that of its metabolite MHPG (20%, $p < 0.05$) in the mouse brain. Yohimbine, an antagonist of α_2 -noradrenergic receptors, produced effects opposite to those of clonidine: a significant decline in NA concentration (30%, $p < 0.05$), and a substantial increase (80%, $p < 0.01$) in MHPG level (Tab. 1). TIQ at doses of 25 and 50 mg/kg produced biochemical effects very similar to those of the antagonist of α_2 -noradrenergic receptors, yohimbine: a decrease in NA concentration and a pronounced increase in the level of its metabolite MHPG. The effect of TIQ was dose-dependent (Tab. 1).

Metabolic rate index

The rate of total NA metabolism was expressed as a ratio of the final metabolite (MHPG) to the neurotransmitter (NA). Clonidine, being an α_2 -noradrenergic receptor agonist, produced a significant decrease in NA turnover (by 35%, $p < 0.01$). In contrast to clonidine, yohimbine, an antagonist of α_2 -noradrenergic receptors, produced an about 3-fold acceleration of NA metabolism (Tab. 1). TIQ dose-dependently mimicked the effect of yohimbine, and accelerated NA metabolism from 2 to 2.5-fold ($p < 0.05$ and < 0.01 , respectively, Tab. 1).

Table 1. The effect of 1,2,3,4-tetrahydroisoquinoline (TIQ), clonidine and yohimbine on the level of noradrenaline (NA) and its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in mouse brain

Treatment	N	NA	MHPG	<i>f</i>
Saline	17	459 \pm 23	55 \pm 3	12 \pm 3
Clonidine	8	530 \pm 35	45 \pm 3*	8 \pm 0.4**
Yohimbine	7	325 \pm 36*	99 \pm 15**	32 \pm 5**
TIQ ₂₅	8	367 \pm 28	88 \pm 8*	25 \pm 4*
TIQ ₅₀	9	349 \pm 37*	106 \pm 10**	30 \pm 3**
F		F _{4/44} = 5.39, p < 0.01	F _{4/44} = 3.83, p < 0.01	F _{4/44} = 15, p < 0.01

Clonidine (1 mg/kg *ip*), yohimbine (20 mg/kg *ip*), and TIQ (25 mg/kg and 50 mg/kg *ip*) were given 1, 2, and 4 h, respectively, before decapitation. The data are means \pm SEM in ng/g of tissue. N – the number of samples. *f* – metabolic rate index [MHPG/NA \times 100]. * $p < 0.05$, ** $p < 0.01$ (difference from saline group, LSD test)

Blood pressure

When given acutely, the classic hypotensive drug clonidine significantly depressed both systolic and diastolic arterial blood pressure in conscious

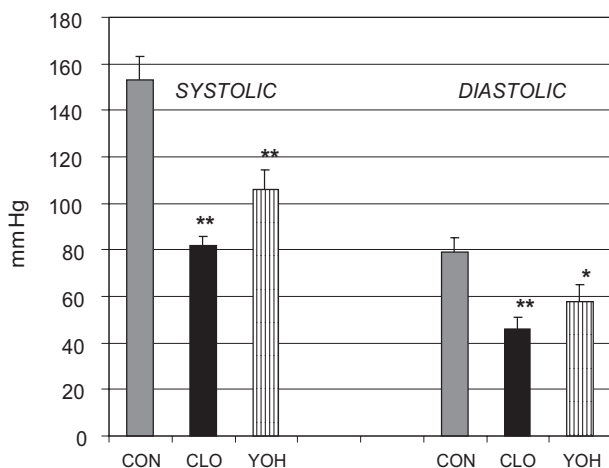


Fig. 1. The effect of reference hypotensive drugs on systolic and diastolic arterial blood pressure in the rat. Clonidine (CLO) 2 mg/kg *ip* and yohimbine (YOH) 20 mg/kg *ip*, were given 2 h before the test. Each group contained from 8 to 10 rats. * $p < 0.05$, ** $p < 0.01$ (the difference vs. the saline-treated control group, LSD-test)

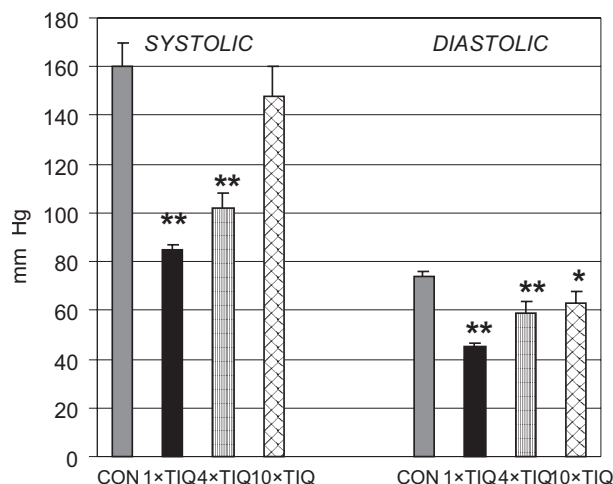


Fig. 3. The development of tolerance to TIQ-induced hypotension after multiple treatment. TIQ was given once, 4 days, and 10 days, and the measurements were made always 2 h after the last injection. Each group contained 10 rats. * $p < 0.05$, ** $p < 0.01$ (the difference vs. the saline-treated control group, LSD-test)

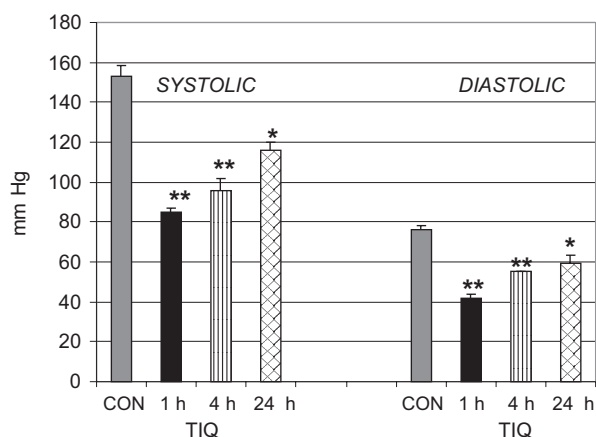


Fig. 2. The effect of acute TIQ administration on systolic and diastolic arterial blood pressure measured in conscious rats. TIQ (50 mg/kg *ip*) was administered 1, 4, and 24 h before the test. Each group contained from 8 to 10 rats. * $p < 0.05$, ** $p < 0.01$ (the difference vs. the saline-treated control group, LSD-test)

rats. A hypotensive effect, considerably less pronounced than that of clonidine though, was also observed after administration of the α_2 -noradrenergic receptor antagonist yohimbine (Fig. 1). Acute administration of TIQ produced a marked decline (by about 40–45%) in both systolic and diastolic arterial blood pressure, which lasted up to 24 h after injection (Fig. 2). Multiple treatment with TIQ (10 days, once daily) resulted in development of tolerance to its hypotensive effect (Fig. 3).

DISCUSSION

The main finding of this study was that TIQ, an endogenous parkinsonism-inducing compound, strongly affected NA metabolism in way similar to yohimbine, α_2 -noradrenergic antagonist, and at the same time produced deep fall in the arterial blood pressure. On the other hand, our earlier investigations have shown strong antidopaminergic effect of TIQs but rather incompatible with the idea that they may have typical neuroleptic properties [3, 4, 21, 41]. Firstly, in contrast to neuroleptics, they do not produce profound sedation or catalepsy even at the doses that produce distinctive rigidity [3, 21], and they also do not potentiate the cataleptogenic action of haloperidol and show no synergism with neuroleptics in the action on dopamine metabolism [3]. The above characteristic, and the fact that they are present in the brain in neuromelanin-containing neurons [34–36] make endogenous TIQs the ideal candidates of natural regulators of dopaminergic activity. However, TIQs were mainly regarded as potential neurotoxins that might be responsible for development of Parkinson's disease [3, 4, 21, 31, 32, 43]. Although many of those compounds are nontoxic 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 MAO-dependent oxidation and owing to that form neurotoxic quinolinium ions [23, 30, 31]. Those quarternary compounds, similarly to pyridinium ions (such as MPP⁺) accumulate in neuromelanin-containing cells and cause the disruption of the mitochondrial electron transport [10]. The most neurotoxic are N-methylated derivatives of TIQs [27] but even they are much less toxic than MPP⁺, and the course of neurodegeneration caused by them differs from the immediate neurodegeneration evoked by MPTP. Even when salsolinol and TIQ are administered daily, the signs of impairment of dopaminergic system and loss of tyrosine hydroxylase-containing cells requires at least three weeks to develop [4, 21]. Regardless of the distant slowly developing effects, it seems that the immediate, direct action of TIQ may be of physiological importance. Thus, in this study we investigated its acute interference with noradrenergic system of the mouse brain. Additionally, the effect of TIQ on the arterial blood pressure in conscious rat was measured as a functional factor connected with affecting the noradrenergic system.

Present results clearly indicate direct participation of the noradrenergic system in cardiovascular disorders following administration of the endogenous neurotoxin TIQ. Thus, compounds belonging to the TIQ group can be used as model substances for studying disturbances in various neurotransmitter systems, which are likely to occur in this neurodegenerative disease. Present biochemical studies have shown that TIQ strongly affects noradrenergic system in the brain. Acute administration of TIQ potentiates approximately three times NA metabolism in the mouse brain, which leads to a decrease in the level of the amine and increases in the content of its final metabolite MHPG. A biochemical effect similar to that of TIQ is produced by yohimbine, an α_2 -adrenergic receptor antagonist. On the other hand, clonidine, an α_2 -adrenergic receptor agonist, attenuates NA metabolism and reduces its release, which is manifested as a substantial decrease in MHPG level and a slight increase in NA content. The present results have shown for the first time a visible effect of TIQ on NA metabolism, which means that this endogenous compound may play a role in the feedback control of the activity of noradrenergic system. At the same time, it has been found that TIQ produces significant decrease in both systolic and diastolic arterial blood pressure in the rat. The hypotensive effect of TIQ is the most

pronounced after single treatment (blood pressure decreases exceeding 45%), whereas repeated administration produces a weaker effect, which points to the development of tolerance in the latter case. It should be stressed that the changes in blood pressure evoked by both, the agonist (clonidine) and the antagonist (yohimbine), go in the same direction: both these α_2 -adrenergic receptor ligands cause falls in blood pressure in rats, however the hypotension produced by clonidine is much more pronounced, what is in agreement with literature [7, 15, 24]. The experimental studies discussed above seem to support the hypothesis that orthostatic hypotension in the patients with Parkinson's disease [18, 20, 25, 26] may be connected with disturbances occurring in the noradrenergic system. To sum up the profile of acute effect of TIQ, its strong influence on NA metabolism and activity of noradrenergic neurons in the brain should be underlined.

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