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## Metabotropic glutamate receptors and nitric oxide in dopaminergic neurotoxicity

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### Abstract

Dopaminergic neurotoxicity is characterized by damage and death of dopaminergic neurons. Parkinson's disease (PD) is a neurodegenerative disorder that primarily involves the loss of dopaminergic neurons in the substantia nigra. Therefore, the study of the mechanisms, as well as the search for new targets for the prevention and treatment of neurodegenerative diseases, is an important focus of modern neuroscience. PD is primarily caused by dysfunction of dopaminergic neurons; however, other neurotransmitter systems are also involved. Research reports have indicated that the glutamatergic system is involved in different pathological conditions, including dopaminergic neurotoxicity. Over the last two decades, the important functional interplay between dopaminergic and glutamatergic systems has stimulated interest in the possible role of metabotropic glutamate receptors (mGluRs) in the development of extrapyramidal disorders. However, the specific mechanisms driving these processes are presently unclear. The participation of the universal neuronal messenger nitric oxide (NO) in the mechanisms of dopaminergic neurotoxicity has attracted increased attention. The current paper aims to review the involvement of mGluRs and the contribution of NO to dopaminergic neurotoxicity. More precisely, we focused on studies conducted on the rotenone-induced PD model. This review is also an outline of our own results obtained using the method of electron paramagnetic resonance, which allows quantitation of NO radicals in brain structures.

**Key Words:** Dopaminergic neurotoxicity; Metabotropic glutamate receptors; Nitric oxide; Rotenone; Parkinson's disease

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**Core Tip:** Dopaminergic neurotoxicity is characterized by damage and death of

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dopaminergic neurons. Chronic systemic exposure to rotenone (an inhibitor of mitochondrial complex I and a commonly used pesticide) induced dopaminergic degeneration and reproduced many features of human Parkinson's disease in rats. The current paper aims to review the involvement of metabotropic glutamate receptors and the contribution nitric oxide to dopaminergic neurotoxicity.

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## INTRODUCTION

The dopaminergic system is a part of the brain that plays a key role in the control of locomotor activity, stress reactions, aggressive behavior, and mechanisms of the formation of dependence in humans and animals[1,2]. Dopaminergic neurotoxicity is characterized by damage and death of dopaminergic neurons. The contribution of dopaminergic neurotoxicity to the pathogenesis of several disorders of the central nervous system (CNS), such as Parkinson's disease (PD)[3,4], Tourette syndrome[5], drug abuse[6,7], and schizophrenia[8,9], has been postulated. Currently, neurodegenerative diseases are a major cause of disability around the world. PD is the second-leading cause of neurodegenerative disorder after Alzheimer's disease (AD)[4]. PD is manifested primarily by movement disturbances. Mental health disorders are also a serious nonmotor feature of PD[10,11]. Thus, psychotic symptoms are not uncommon among individuals with PD, with a prevalence rate of approximately 25%-30%[12,13]. In this regard, the study of mechanisms, as well as the search for ways to prevent and treat PD, is not only an important medical problem but also a social problem[14].

A growing body of evidence has demonstrated that glutamatergic neurotransmission plays an important role in the mechanisms of dopaminergic brain damage[15,16]. Previous studies have shown that modulation of metabotropic glutamate receptors (mGluRs) may be considered a more promising way to alter the activity of the brain glutamatergic system than direct action on ionotropic glutamate receptors of the N-methyl-D-aspartate and amino-methyl-phosphonic acid subtypes[17]. However, the neurochemical and neuropsychological effects of mGluRs on dopaminergic neurotoxicity remain poorly understood.

The association between the neurotransmitter function of glutamate and the formation of neuronal messenger nitric oxide (NO) has received increased attention in recent years. NO is considered to be the first representative of a novel family of signaling molecules with neurotransmitter properties[18,19]. NO is a labile free radical that is involved in many physiological processes[20]. It is assumed that together with some important physiological functions in the CNS, NO can have either neuroprotective or neurotoxic actions, depending on its redox state[21]. There are growing numbers of studies concerning the involvement of NO in the mechanisms of dopaminergic neurotoxicity[22-24]. Measurement of NO is technically difficult due to its rapid chemical reactions with a wide range of molecules, such as free radicals, metals, thiols, etc[25]. Thus, accurate detection and quantification are critical to understanding health and disease[26]. Most of the NO measurement techniques in the literature are indirect[27,28]. In our work, we used the direct electron paramagnetic resonance (EPR) method, which allows us to estimate the generation of NO radicals directly in brain tissue[29-31]. The current paper aims to review the involvement of mGluRs and the contribution of NO to dopaminergic neurotoxicity. More precisely, we focused on studies conducted on the rotenone-induced Parkinson's disease model. This review is also an outline of our own results obtained using the EPR method, which allows quantitation of NO radicals in brain structures.

## MODELS OF DOPAMINERGIC NEUROTOXICITY

The use of animal models to study neurological diseases associated with dopaminergic neurotoxicity allows for in-depth study of their neuropathophysiology[32,33]. Patholo-

gically, the hallmark of idiopathic PD is the loss of dopaminergic neurons in the substantia nigra (SN). However, in the absence of nigral involvement, noncatecholaminergic neurons are also affected[34]. Agents that selectively damage or disrupt catecholaminergic systems, such as reserpine, methamphetamine (METH), 6-hydroxydopamine (6-OHDA), and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), have been used to develop PD models of PD[35,36]. Based on experimental and clinical evidence, PD was the first neurological disease to be modeled and subsequently treated with neurotransmitter replacement therapy[35]. Recent studies have shown that nigrostriatal dopamine degeneration can be induced *via* overexpression of  $\alpha$ -synuclein using viral vectors or transgenic techniques. In addition, protein aggregation pathology can be triggered by inoculating preformed fibrils of  $\alpha$ -synuclein in the SN or the striatum[37,38]. Transgenic animals that overexpress  $\alpha$ -synuclein were used to study the role of this protein in dopaminergic degeneration[39,40]. Nevertheless, although transgenic models offer insight into the causes of the pathogenesis of PD or Lewy body (LB)-like formation, the lack of sequential loss of neurons in the SNc remains a major limitation for these models[40]. Conversely, toxin-based models recreate selective nigrostriatal cell death and show extensive motor dysfunction. However, these toxin models do not reproduce the extranigral degeneration that also occurs as part of the disease and lack the pathological hallmark of LB inclusions[39, 41]. Betarbet *et al*[42] reported that chronic, systemic introduction of rotenone, an inhibitor of mitochondrial complex I, accurately replicates many aspects of the pathology of PD. Additionally, in rotenone-treated animals,  $\alpha$ -synuclein-and polyubiquitin-positive aggregates were observed in dopamine neurons of the SN[43,44]. The advantages of this model include a slow and specific loss of DA neurons. The disadvantages of the model include the duration of drug administration, as well as sometimes high animal mortality[36]. Currently, several modifications of rotenone-induced Parkinson's disease models have been created. These modifications are different in the mode of administration as well as in the dosage and duration of treatment with rotenone[44-46]. The fact that rotenone is still widely used in agriculture as a pesticide increases the relevance of studying this model[47-49]. However, while the behavioral effects of rotenone administration are well characterized, the mechanisms of rotenone action are still poorly understood.

## MGLURS IN MODELS OF DOPAMINERGIC NEUROTOXICITY

A significant number of studies have revealed that the excitotoxicity of glutamate contributes to the development of dopaminergic neurotoxicity[50-52]. It has been reported that various neurotoxic agents, including rotenone and METH, can severely damage both ionotropic and metabotropic glutamate receptors, which leads to the progression of toxic effects[53]. An important functional interplay between the dopaminergic and glutamatergic systems has stimulated the consideration of mGluRs as potential therapeutic targets in PD[54-56]. Eight mGluRs (GRM1 to GRM8) have been identified and divided into three groups based on their sequence similarity and pharmacology[57,58]. All mGluRs are family C G-protein-coupled receptors that participate in the modulation of synaptic transmission and neuronal excitability throughout the CNS[59]. Studies have shown that mGluR-mediated mechanisms have been implicated in both neuroprotection and neurotoxicity. The involvement of mGluRs in the control of movement, spatial and olfactory memory and nociception has been demonstrated[57,60,61]. Studies have shown the antiparkinsonian potential of mGluR modulation in groups I, II and III in experimental MPTP and 6-OHDA models of PD[56,62]. It has been reported that group I mGluR antagonism and groups II and III mGluR activation improve some motor symptoms of PD by regulating excitatory and inhibitory transmission in the basal ganglia[55]. However, the mechanism by which these mGluR ligands may alleviate the symptoms of parkinsonism in animal models is largely unknown.

### *Involvement of mGluRs in neurotoxicity induced by rotenone*

Because the rotenone model of PD has attracted much attention, we searched the PubMed and Google Scholar databases for articles concerning the effect of mGluR on the rotenone model of neurotoxicity. In the end, by consensus, primary articles were selected as relevant to our goals (Table 1). Thus, it has been reported that the application of a group III mGluR agonist (L-AP-4) significantly reduced the toxicity of rotenone in a culture of TH+ midbrain neurons[63]. The authors hypothesized that activation of group III mGluR decreases the selective toxicity of rotenone to dopamine

**Table 1 Main findings on metabotropic glutamate receptors involvement in rotenone-induced neurotoxicity**

Ref.	Object of study	mGluR type	Ligand
Luo <i>et al</i> [67], 2019	Cell culture; rats	mGluR5	Antagonist MPEP
Bai <i>et al</i> [66], 2018	Cell culture	mGluR5	Agonist CHPG; antagonist MPEP
Xia <i>et al</i> [65], 2015	Cell culture, rats	mGluR5	Antagonist MPEP
Bashkatova <i>et al</i> [69], 2012	Rats	mGluR5	Antagonist MPEP
Sun <i>et al</i> [64], 2012	Cell culture, rats	Group I mGluR	Agonist DHPG
Zhu <i>et al</i> [68], 2012	Cell culture, rats	mGluR5	Antagonist MPEP
Alam <i>et al</i> [70], 2009	Rats	mGluR5	Antagonist MPEP
Jiang <i>et al</i> [63], 2006	Cell culture	Group III mGluR	Agonist L-AP-4

mGluR: Metabotropic glutamate receptors; MPEP: 2-methyl-6-(phenylethynyl) pyridine; CHPG: (RS)-2-chloro-5-hydroxyphenylglycine; DHPG: (S)-3,5-dihydroxyphenylglycine.

neurons by activating the MAP kinase pathway to stabilize microtubules[63]. In contrast, activation of group I mGluRs enhances rotenone-induced toxicity in MN9D cells[64]. The modulation of the mGluR5 type in rotenone-induced PD models has attracted much attention from researchers. Pharmacological inhibition of mGluR5 has beneficial anti-akinetic effects in animal models of PD; however, the mechanism by which these antagonists alleviate PD symptoms is largely unknown[65]. Previous studies have shown that downregulation of mGluR5 promotes cell apoptosis in a model of rotenone-induced cellular PD. Moreover, conditioned media derived from rotenone-treated dopaminergic MN9D neuronal cells have been found to enhance the production of reactive oxygen species (ROS), which can be further attenuated by an mGlu5 agonist[66]. The selective mGluR5 antagonist 2-methyl-6-(phenylethynyl) pyridine (MPEP) prevented rotenone-induced DNA damage in MN9D dopaminergic neurons through a mechanism involving ROS-related mitochondrial dysfunction[65]. It has been demonstrated that mGluR5 expression is decreased in a time- and dose-dependent manner in rotenone-treated MN9D cells[67]. It has been reported that oxidized extracellular cysteine/cystine redox potential plays a role in mGluR5 activity in the rotenone rat model of PD[68]. In our studies, MPEP (3 mg/kg) reduced the intensity of catalepsy in rats after long-lasting administration of rotenone at a dose of 1.5 mg/kg[69]. We observed that the mGluR5 antagonist partially prevented the increase in NO generation evoked by rotenone[69]. In another study, it was shown that the behavioral effects of MPEP (2.5 mg/kg) were less pronounced in rats receiving a higher dose of rotenone (2.5 mg/kg) following the same duration of neurotoxin administration[70]. It has been reported that coadministration of MPEP with rotenone reduces the descent latency in the grid test at day 60 but does not block the decrease in DA and serotonin levels induced by treatment with this neurotoxin[70]. Thus, the behavioral effects of mGluR5 were notably dependent on the dose of rotenone administered. The above findings indicate that mGluR5 inhibition produces an inhibitory effect on ROS and NO activity[65,66,69]. In summary, an analysis of the literature data supports the notion that antagonists of mGluR5 are considered promising targets for the treatment of pathological conditions induced by dopaminergic neurotoxicity.

## INVOLVEMENT OF NO IN DOPAMINERGIC NEUROTOXICITY

### *NO as neuronal messenger*

Currently, mitochondrial dysfunction is thought to be associated with NO pathways in glutamate neurotoxicity[71]. NO is a gaseous chemical messenger that modulates many functions of the nervous system, including the release of neurotransmitters, interneuronal communication, synaptic plasticity, receptor state, and intracellular signal transduction[20,72]. The role of NO as a biological mediator is primarily determined by its physical and chemical properties. NO is generated by the enzyme NO synthase (NOS), which is widely distributed in the brain[19,73]. One of the possible mechanisms of the neurotoxic effect of NO may be the reaction of NO with



ROS, leading to the formation of a highly toxic product peroxynitrite[24,74,75]. The short half-life of the NO radical is 2-5 s[20]. There are several indirect methods for determining NO and its products/metabolites in biological fluids and tissues. One of the most frequently used indirect methods for the determination of NO is the measurement of nitrite and nitrate by spectroscopy using the Griess reagent[27]. Another well-known method for indirect measurement of NO is the quantitative determination of 3-nitrotyrosine (a product of tyrosine nitration)[76]. The applicability of these indirect methods seems to be problematic. Quantitative determination of nitrites by the Griess method is falsified in the presence of reducing agents as well as thiol groups[77]. These data are consistent with our opinion that only direct methods may be used for reliable determination of NO levels. One of the most accurate and correct ways to measure these data is through use of the EPR method[26,31,78,79].

### ***Participation of no in dopaminergic neurotoxicity***

Recent reports claim that NO is involved in neurotoxicity elicited by dopaminergic neurotoxins[24,74,79]. Over the past two decades, significant advances have been made in improving knowledge about the role of NO in the mechanisms of PD pathogenesis[21,80,81]. Thus, in brains from victims of PD, a nitrosyl species, identified as nitrosyl hemoglobin, has been observed in the SN[82]. Previous studies have shown that neurotoxic agents such as MPTP[83], 6-OHDA[84] or METH[74] induce a significant increase in the production of 3-nitrotyrosine in the striatum. The protective effect of neuronal NOS inhibitors has been demonstrated in the MPTP neurotoxicity model in mice[85].

### ***Involvement of no in neurotoxicity induced by rotenone***

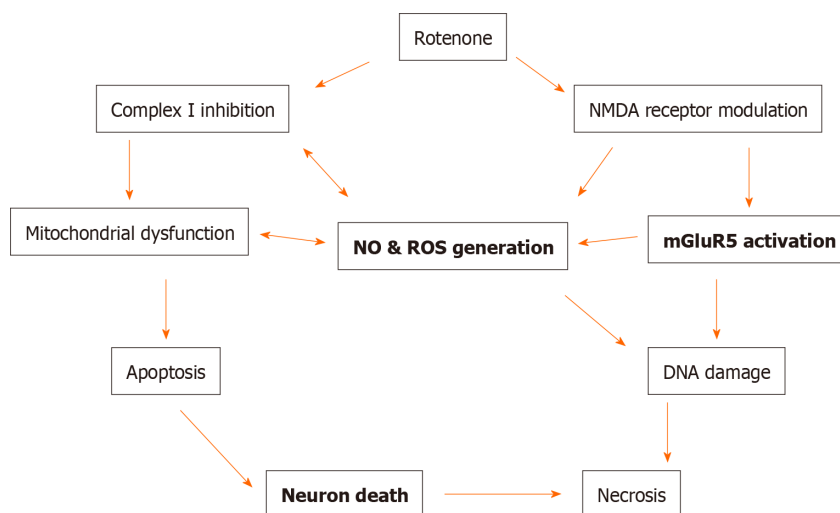
NO is cytotoxic, partly due to its effects on mitochondria[86]. Research reports have shown that NO is involved in rotenone-induced neurotoxicity (Table 2). However, the detailed mechanisms of this process are not well understood. Our data indicate that following a single injection of rotenone (1.5 mg/kg), the levels of NO in all studied brain areas were indistinguishable from those in control animals[78]. The data obtained correspond with the results of other authors. Thus, acute administration of rotenone at a significantly higher dose (15 mg/kg) did not affect the level of hydroxyl radical generation[87]. The NO level reached its maximum in dopaminergic structures, the prefrontal cortex, and the NAc 60 d after administration of rotenone[78]. We observed a more than 2-fold elevation in NO generation in all studied brain structures of rats only after repeated injections of rotenone[78]. These results are consistent with other studies investigating NO metabolites/products in the brains of rats treated with rotenone (Table 2). Thus, a significant increase (by 200.0%) in the concentration of nitrite determined by the spectrophotometric method was observed[88]. Authors suggest that overproduction of NO may be associated with Snitrosylation or nitration of certain important proteins[88]. It was reported that the production of 3-nitrotyrosine in the brains of rats treated with rotenone for 40 d increased significantly[76]. In recent years, several studies have investigated the potential neuroprotective properties of various plant extracts[89-91], polyphenolic agents[92] and flavonoids[93] in a rotenone model of PD. The authors measured the level of nitrites as a marker of neurotoxicity in the dopaminergic brain structures of animals after long-lasting administration of rotenone (Table 2). The above studies indicate that the content of NO and its metabolites in the brain is currently considered one of the markers of rotenone-induced neurotoxicity.

In our opinion, it seems to be critical to study the dynamics of NO changes in various brain structures during long-term administration of rotenone. This issue is practically not studied. Our results demonstrated a significant enhancement of NO generation in the NAc after 20 d of treatment with rotenone, while the NO level was not elevated yet in the frontal cortex[78]. These data may indicate that dopaminergic neurons in the NAc may be intrinsically susceptible to oxidative damage compared to other neurons. Taken together, our results, as well as literature data, allow us to conclude that rotenone can produce a neurotoxic effect and cause an increased production of free radicals, including NO, only with long-lasting chronic administration. This, in turn, confirms the assumption that the cascade of biochemical reactions causing the development of neurotoxic processes can be triggered only after repeated injections of rotenone[35,78,87,94]. In summary, the data obtained indicate prospects for further research on the interaction of dopaminergic, mGluR and NO systems in rotenone models of PD to search for and study the mechanism of action of substances with neuroprotective properties (Figure 1).

**Table 2 Main finding on the determination of nitric oxide and its products/metabolites in the rotenone model of neurotoxicity**

Ref.	Dose of rotenone	Duration	NO or its products/metabolites	Method of NO determination
Kumar <i>et al</i> [91], 2021	2.0 mg/kg	28	Nitrite	Spectrophotometry
Parkhe <i>et al</i> [92], 2020	2.0 mg/kg	21	Nitrite	Spectrophotometry
Sharma <i>et al</i> [93], 2020	2.0 mg/kg	28	Nitrite	Spectrophotometry
Sun <i>et al</i> [80], 2019	1.5 mg/kg	28	Nitrate/nitrite	NO assay kit
Jayaraj <i>et al</i> [90], 2019	1.5 mg/kg	28	Nitrite	Spectrophotometry
Abdel-Salam <i>et al</i> [89], 2017	1.5 mg/kg × 3	7	Nitrite	Spectrophotometry
Javed <i>et al</i> [86], 2016	2.5 mg/kg	28	Nitrite	Spectrophotometry
Xiong <i>et al</i> [88], 2015	1.5 mg/kg	6	Nitrite	Spectrophotometry
Tapias <i>et al</i> [23], 2014	3.0 mg/kg	Individually <sup>1</sup>	3-NT (3-nitrotyrosine)	Immunofluorescence
Bashkatova <i>et al</i> [69], 2012	1.5 mg/kg	60	NO (Nitroxyl radical)	EPR
Bashkatova <i>et al</i> [78], 2004	1.5 mg/kg	60	NO (Nitroxyl radical)	EPR
He <i>et al</i> [76], 2003	2 mg/kg × 3	40	3-NT (3-nitrotyrosine)	HPLC

<sup>1</sup>Tissue collection was carried out when each individual animal had reached endpoint (when the behavioral phenotype became debilitating, *i.e.*, when akynesia, rigidity, and postural instability were manifested)[23]. NO: Nitric oxide; EPR: Electron paramagnetic resonance; HPLC: High performance liquid chromatography.



**Figure 1 Proposed scheme for the involvement of nitric oxide and metabotropic glutamate receptor subtype 5 in rotenone-induced dopaminergic neurotoxicity.** It is now generally accepted that rotenone in low doses of rotenone specifically binds complex I and induces mitochondrial dysfunction. The action of rotenone can be mediated by an increase in the N-methyl-D-aspartate current, which leads to the activation of metabotropic glutamate receptor subtype 5. Complex I, in combination with excitation of glutamate receptors, induces the generation of reactive oxygen species and nitric oxide. In summary, these key cellular events induce progressive death of dopaminergic neurons in the substantia nigra pars compacta *via* apoptosis and necrosis. It is important to note that at each stage, the action of rotenone becomes regionally limited so that inhibition of complex I ultimately lead to highly selective degeneration and loss of dopaminergic neurons of the nigrostriatal pathway. NO: Nitric oxide; ROS: Reactive oxygen species.

## CONCLUSION

This review summarizes several newly discovered mechanisms of dopaminergic neurotoxicity (Figure 1). Current treatments for PD are mainly the administration of dopaminergic drugs. However, dopaminergic drugs are only symptomatic treatments and are limited by several side effects. Understanding the pathogenetic mechanisms of the onset and development of PD is of great clinical importance. Recent studies on drug development have focused on emerging new molecular mechanisms, including modulation of mGluRs and NO formation. Despite the growing number of studies demonstrating the positive effect of some mGluR ligands on motor symptomatology in PD models, there are still no drugs in clinical practice targeting mGluRs to restore

neurological disorders of PD. Treatment with NO scavengers/NOS inhibitors may be another potential neuroprotective strategy for diseases associated with dopaminergic neurotoxicity. In addition, our preliminary results and literature data suggest that an increase in the formation of NO radicals in some brain structures may precede the onset of behavioral disorders in rats treated with rotenone. Therefore, finding a possible correlation between the generation of NO radicals and the onset of neurological disturbances during long-term application of rotenone can be an important step in understanding the pathogenesis of rotenone-induced neurotoxicity. We can assume that in the future, the determination of NO generation may become a test for the early diagnosis of PD in patients who do not yet have specific symptoms of the disease.

Additionally, long-term application and widespread use of synthetic insecticides have resulted in the accumulation of their residues in food, milk, water, and soil and have adverse health effects for humans[95]. Although all natural insecticides are not completely safe, it seems necessary to phase out the use of rotenone pesticides in agriculture and replace them with natural ("organic") pesticides with maximum safety.

In summary, alternative treatment strategies beyond dopaminergic drugs might be a major topic of future PD therapy. In conclusion, the findings demonstrate that modulation of mGluR and NO formation suggests the possibility of developing new treatment strategies for PD.

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