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Research Report

Deprenyl enhances the striatal neuronal damage produced by quinolinic acid

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Abstract

We have tested the effect of deprenyl on the neurotoxicity induced by the injection of quinolinic acid within the striatum. Deprenyl was unable to prevent these quinolinic acid-induced damages, but enhanced the loss of several gamma-aminobutyric acid (GABA) positive subpopulations, the loss of the astroglial population and the activation of microglia produced by quinolinic acid. These effects are produced by deprenyl potentiation of dopamine actions since dopamine depletion produced by previous injection of the dopaminergic toxin 6-hydroxydopamine within the medial forebrain bundle overcomes deprenyl effects and the involvement of dopamine in the quinolinic acid-induced toxicity in striatum. In these conditions, quinolinic acid toxic action in striatum is significantly lower and similar in the animals treated with or without deprenyl. All these data justify why deprenyl worsen some pathological signals of disorders involving excitotoxicity. This also may be involved in other secondary effects described for deprenyl.

Theme: Disorders of the nervous system
Topic: Neurotoxicity

Keywords: Quinolinic acid; Huntington's disease; Deprenyl; Dopamine; Neurodegeneration

1. Introduction

Deprenyl, a specific inhibitor of monoamine oxidase B enzyme, has been used worldwide for the therapy of Parkinson's disease [61]. Blocking of dopamine metabolism is the main action of deprenyl as inhibitor of monoamine oxidase B enzyme; its metabolites (methylamphetamine, amphetamine) inhibit the re-uptake and increase the release of dopamine, which results in dopamine potentiation (for review see Ref. [41]). Deprenyl has other neuroprotective effects which might be due to induction or potentiation of various neuroprotective molecules, including free radical scavenger enzymes [10,35,62], antiapoptotic molecules [60] or neurotrophic factors [6,53,54,58]. In addition, we have previously described that deprenyl induces the tyrosine hydroxylase enzyme in the nigrostriatal dopaminergic system of the rat [48]. This could explain why deprenyl delays the requirement and doses of L-DOPA in early stages of Parkinson's disease. However, some adverse effects have been recently described for deprenyl treatment, especially in long chronic treatment along with L-dihydroxyphenylalanine (L-DOPA) [16] and also when used in other pathologies. Selegiline caused marked degenerative CNS changes and accelerated viral infection in the SIV-macaque model of human immunodeficiency virus (HIV) infection [36]. HIV infection is an emerging cause of chorea; Acquired Immuno-Deficient Syndrome-related disease should be considered in young patients presenting motor symptoms without a family history of movement disorders [43].

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Most of pathological changes in Huntington's disease are described in striatum, where up to 90% of neurons disappear [65]. Different animal models have been developed in order to study this disease; quinolinic acid, a compound produced in the kynurenine pathway from tryptophan to nicotinic acid, is an endogenous excitotoxin at the *N*-methyl-D-aspartate (NMDA) receptor [51,56,57]. Significant variations of quinolinic acid levels in the central nervous system (CNS) have been described in different pathological conditions. Neuroinflammation, a process induced in neurodegeneration, produced a significant increase in the level of quinolinic acid [40]. The increase in quinolinic acid has also been described in traumatic brain injury [5,55] and infection by agents as (HIV)-1 [29,31]. Besides quinolinic acid, other neuroactive tryptophan metabolites from the kynurenine pathway are involved in several neurological [52,57], infectious and inflammatory processes [26,28,30].

Experiments in rodents and monkey show that intrastriatal injection of quinolinic acid mimics many of the neurochemical and histological features characterizing Huntington's disease [2,20]. The neurotoxic action of quinolinic acid is due to an excitotoxic mechanism and its specificity to the selective action through the NMDA receptor. Excitotoxic damage produced by the sustained activation of NMDA receptor by quinolinic acid is currently related to increased cytosolic Ca^{2+} concentrations, ATP exhaustion, gamma-aminobutyric acid (GABA) depletion and specific GABAergic and cholinergic neural death [21,49,51]. Moreover, the neurotoxic action of quinolinic acid has been suggested to be mediated by free radicals production [4,8,50]; these findings are of particular interest since several antioxidants may represent a potential therapeutic strategy against quinolinic acid toxicity. In addition, dopamine has been suggested as a coadjuvant factor [7,46], considering that an excessive release of dopamine in vivo triggers accumulation of reactive dopamine metabolites and overproduction of reactive oxygen species (e.g., hydroxyl radicals) due to the inherent susceptibility of the catechol moiety to enzymatic and nonenzymatic oxidation [9]. Striatal dopamine release is induced by NMDA agonists [45] and also occurs in vivo during episodes of ischemia or metabolic stress that contribute to the degeneration of striatal neurons [18,24].

Taking into account the two effects of deprenyl, dopamine potentiation and antioxidant action, the aim of the present work was to carry out a comparative study of the effect produced by deprenyl on the neurotoxicity induced by an intrastriatal injection of quinolinic acid. The results show that deprenyl was not only unable to protect against the neurotoxicity of quinolinic acid but enhanced the quinolinic acid-induced damage to the nigrostriatal system. These results explain some of the adverse effects described for deprenyl and could suggest that dopamine, and especially those compounds increasing dopamine concentration or release, could potentiate neurotoxicity processes.

2. Materials and methods

2.1. Animals and surgery

Female albino Wistar rats (200–250 g) were used for these studies. The rats were kept, three or four rats per cage, at constant room temperature of 22 ± 1 °C and relative humidity (60%) with a 12-h light–dark cycle with free access to food and water. Rats were anesthetized with chloral hydrate (400 mg/kg) and positioned in a stereotaxic apparatus (Kopf Instruments, Tujunga, CA) to conform to the brain atlas of Paxinos and Watson [42]. Injections into the medial forebrain bundle were made 3.8 mm posterior, 2.4 mm lateral and 7.8 mm ventral to the bregma. Injections into the striatum were made 0.6 mm posterior, 2.6 mm lateral and 6.3 mm ventral to the bregma.

Experiments were carried out in accordance with the Guidelines of the European Union Council (86/609/EU), following the Spanish regulations (BOE 67/8509-12, 1988) for the use of laboratory animals and approved by the Scientific Committee of the University of Sevilla.

Five groups of animals were established according to the different treatments: (I) the vehicle-injected group received a single dose of 2 μl of vehicle (0.1% ascorbic acid in saline) into the left medial forebrain bundle. Two weeks later, the animals were injected 2 μl of Ringer solution in both striata and were sacrificed 1 week later (see Fig. 1 for a summary of treatments). (II) The quinolinic acid-injected group received a single dose of 2 μl of vehicle into the left medial forebrain bundle. Two weeks later, animals were injected with quinolinic acid (120 nmol/2 μl of Ringer solution) in both striata. Animals were sacrificed 1 week later. (III) The deprenyl group received a single dose of 2 μl of vehicle into the left medial forebrain bundle. One week later, animals were treated with (−)-deprenyl (2.5 mg/kg/day, i.p., Tocris) for 1 week. At the end of the deprenyl treatment, the animals received a single dose of quinolinic acid (120 nmol/2 μl) into both striata and were sacrificed 1 week later. (IV) The 6-hydroxydopamine-treated group received a single dose of 6-hydroxydopamine (8 μg/2 μl in vehicle) into the left medial forebrain bundle. Two weeks later, the animals were injected in the striata with quinolinic acid (120 nmol/2 μl in Ringer solution). Animals were sacrificed 1 week after the toxin treatment. (V) The 6-hydroxydopamine-deprenyl group received a single dose of 6-hydroxydopamine (8 μg/2 μl in vehicle) into the left medial forebrain bundle. One week later, animals were treated with (−)-deprenyl (2.5 mg/kg/day, i.p.) for 1 week. At the end of the deprenyl treatment, the animals received a single dose of quinolinic acid (120 nmol/2 μl) into both striata and were sacrificed 1 week later. From each group, at least five animals were used for immunohistological evaluation and another five for in situ hybridization.