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RESEARCH****Research Report****Behavioral and morphological effects of minocycline in the 6-hydroxydopamine rat model of Parkinson's disease**

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ABSTRACT

The neuropathology in many neurodegenerative diseases is mediated by inflammatory cascades that influence neuronal dysfunction and death. Minocycline reduces the neurodegeneration observed in various models of Parkinson's. We exploited the unilateral 6-hydroxydopamine (6-OHDA) lesion model to assess the effect of minocycline on related neurodegeneration. Thirty Fisher 344 rats were divided into three daily treatment groups: (1) after: 45 mg/kg of minocycline beginning 24 h after lesioning; (2) before: 45 mg/kg of minocycline beginning 3 days before 6-OHDA lesioning; (3) control: corresponding saline-treated controls. Animals were assessed for apomorphine-induced rotations for 4 weeks. A longitudinal model for repeated measures showed that both after and before groups had significantly lower rotations than controls ($P < 0.001$ for both comparisons). Pair-wise group comparisons showed that the before animals rotated less compared to controls (mean rotations: 164 ± 38 versus 386 ± 49 , respectively, $P = 0.001$). After animals also rotated significantly less than controls (mean rotations: 125 ± 41 versus 386 ± 49 , respectively, $P < 0.001$). Animals receiving minocycline displayed reduced tyrosine hydroxylase-positive cell loss in the lesioned nigra versus contralateral nonlesioned nigra, compared to controls (mean differences: 5065 for after, 3550 for before, and 6483 for controls; $P = 0.158$ for after versus controls, $P = 0.019$ for before versus controls). The remaining lesioned nigral cells of both minocycline-treated groups were larger than controls, with the most robust cell size and fiber density observed in the after group. These data suggest that the therapeutic potential of minocycline may depend on the time of drug administration relative to neuropathogenic event.

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1. Introduction

Neuroinflammation mediated by activated glial cells has recently been investigated as a causatory factor for Parkinson's disease (PD), an age-related neurodegenerative disease (Barcia et al., 2003; Dawson and Dawson, 2003). Studies have shown that activated microglial cells surround dopaminergic neurons in patients with this disease and produce damaging

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cytokines that may be directly responsible for the demise of the dopamine (DA) neurons (Hirsch et al., 2003; Hunot and Hirsch, 2003). Activated glia (astrocytes and microglia) also contribute towards the rampant oxidative stress that is associated with the neurodegenerative process via excessive production of neurotoxic free radicals (Abramov et al., 2004; Leblhuber et al., 2003). Although astrocytes normally protect neurons through their production of growth and trophic molecules, “aging” astrocytes, because of their expression of pro-oxidant enzymes such as MAO-B and a high content of free iron, can promote enzymatic and nonenzymatic oxidation of DA, generating toxic levels of reactive oxygen species (Johnstone et al., 1999; Hirsch et al., 2003).

Minocycline, a second generation tetracycline, has recently fallen under close scrutiny as having possible therapeutic value for treating several neurodegenerative disorders, including Huntington's disease (Chen et al., 2000), amyotrophic lateral sclerosis (Zhu et al., 2002), and autoimmune encephalomyelitis (Popovic et al., 2001). Studies in models of PD, including the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model (Du et al., 2001; Wu et al., 2002) and the 6-hydroxydopamine (6-OHDA) model (He et al., 2001), have provided compelling evidence that minocycline possesses vast potential for attenuation of the neurodegenerative changes that occur in the brain. In particular, He et al. (2001) compared the effects of minocycline treatment to saline controls on nigral dopaminergic neuronal and microglial status in male mice lesioned in the right striatum with 6-OHDA. Tyrosine hydroxylase (TH) immunohistochemistry revealed a significant sparing of dopamine neurons in animals receiving minocycline treatment. In addition, the number of activated microglia was significantly decreased in those animals that received minocycline compared to their saline counterparts. Lin et al. (2003) reported that minocycline reduced the susceptibility of cultured rat cerebellar granule neurons to 6-OHDA-induced death and prevented the production of free radicals following 6-OHDA administration. These two studies clearly demonstrate that minocycline impacts the toxicity associated with 6-OHDA administration and establish the possibility of manipulating the degenerative cascade that follows upon introduction of this toxin. However, 6-OHDA studies in the rat model combined with minocycline have been sparse. The allure of this phenomenon becomes apparent when one considers that the biochemical and cellular events associated with 6-OHDA toxicity may be, at least in part, similar to the molecular neuroinflammatory cascades that are engaged in the onset of neurodegenerative diseases such as Parkinson's disease (Hirsch et al., 1998; Jenner and Olanow, 1998).

Since its first use by Ungerstedt in the late 1960s (Ungerstedt, 1968), the utilization of the catecholaminergic neurotoxin 6-hydroxydopamine (6-OHDA) to experimentally destroy dopaminergic neurons in the brain has been well documented and is regarded as the gold standard for studying mesencephalic dopamine (DA)-containing neurons (Schwartz and Huston, 1996a,b; Glinka et al., 1997; Blum et al., 2001; Deumens et al., 2002). By stereotactically introducing 6-OHDA into individual components of the nigrostriatal pathway, we have gained enormous insight into the neuroanatomical, neurochemical, and electrophysiological parameters of DA-containing neurons and their interaction with other sys-

tems. The most common application of this toxin is the creation of a unilateral lesion in mesencephalic DA neurons or their ascending fibers, which will result in a loss of target striatal DA, or into the striatum directly. Consequently, the efficacy of a 6-OHDA unilateral lesion can be demonstrated by DAergic compounds, such as apomorphine or amphetamine (Ungerstedt and Arbuthnott, 1970). The number of apomorphine-induced turns per hour has been directly correlated to the extent of DA loss when 6-OHDA is injected into the medial forebrain bundle (Hudson et al., 1993). This strategy has been proven to be an invaluable tool in studying how diseases, such as PD, may encroach upon the nigrostriatal pathway and how experimental manipulation of this system may provide clues for possible clinical intervention.

For this study, we hypothesize that minocycline will reduce the number of lesioned nigral dopaminergic cells and will reduce the number of apomorphine-induced rotations in rats when administered prior to or after receiving a unilateral 6-OHDA lesion. In order to test the preventive effects of this drug, daily intraperitoneal injections of saline or minocycline were initiated 3 days prior to neurotoxic lesioning and continued for 4 weeks postlesioning. We also assessed the rescue effects of minocycline by administering the drug (as well as saline control counterparts) 24 h following 6-OHDA lesioning and continuing for 4 weeks after surgery. In order to obtain behavioral evidence of the neuroprotective properties of this tetracycline, weekly apomorphine-induced rotational behavior was assessed on all subjects, and histological analysis of surviving dopaminergic neurons was performed following sacrifice of all animals.

2. Results

2.1. Effects of minocycline on apomorphine-induced rotations

Apomorphine-induced rotational analysis was performed in order to examine the effect of minocycline treatment on the survival of dopaminergic neurons exposed to 6-OHDA. All animals were analyzed for apomorphine-induced rotations for 1 h, once a week, for 4 weeks following lesioning (previous studies indicate that 6-OHDA requires 4 weeks before the full rotational potential of each animal is realized (Ungerstedt and Arbuthnott, 1970; Sauer and Oertel, 1994; Gerlach and Riederer, 1996). Fig. 1 is a graphical representation of the rotational assessments for the saline-treated animals (control group), minocycline 3 days before lesioning (before group), and minocycline 24 h after lesioning (after group) over the 4-week testing period following 6-OHDA administration. The control group consistently rotated the most number of times at each weekly time point, compared to those animals that received minocycline. At 1 week, the mean rotation rate for the controls was 202 turns per hour compared to 140 turns in the before and 34 turns in the after groups ($n = 10$). At 2 weeks postlesion, the controls rotated 381 turns per hour, whereas the before and after animals rotated 138 and 114 turns per hour, respectively. Three weeks following toxin administration resulted in 359 turns in the controls, 246 turns in the before

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