D₁, not D₂, dopamine receptor activation dramatically improves MPTP-induced parkinsonism unresponsive to levodopa

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Abstract

Levodopa is the standard-of-care for Parkinson’s disease, but continued loss of dopamine neurons with disease progression decreases its bioconversion to dopamine, leading to increased side effects and decreased efficacy. In theory, dopamine agonists could equal levodopa, but no approved oral “dopamine agonist” matches the efficacy of levodopa. There are consistent data in both primate models and in Parkinson’s disease showing that selective high intrinsic activity D₁ agonists can equal levodopa in efficacy. There are, however, no data on whether such compounds would be effective in severe disease when levodopa efficacy is low or absent. We compared two approved antiparkinson drugs (levodopa and the D₂/₃ agonist bromocriptine) with the experimental selective D₁ full agonist dihydrexidine in two severely parkinsonian MPTP-treated non-human primates. Bromocriptine caused no discernable improvement in parkinsonian signs, whereas levodopa caused a small transient improvement in one of the two subjects. Conversely, the full D₁ agonist dihydrexidine caused a dramatic improvement in both subjects, decreasing parkinsonian signs by ca. 75%. No attenuation of dihydrexidine effects was observed when the two subjects were pretreated with the D₂ antagonist remoxipride. These data provide evidence that selective D₁ agonists may provide profound antiparkinson symptomatic relief even when the degree of nigrostriatal degeneration is so severe that current drugs are ineffective. Until effective disease-modifying therapies are discovered, high intrinsic activity D₁ agonists may offer a major therapeutic advance in improving the quality of life, and potentially the longevity, of late stage Parkinson’s patients.
Keywords
MPTP; parkinsonism; Parkinson’s disease; dopamine; dopamine D<sub>1</sub> receptors; dopamine D<sub>1</sub> agonists; dihydrexidine

1. INTRODUCTION: 492

The motor signs of Parkinson’s disease (PD) (Parkinson, 1817) are a result of dopamine deficiency due to progressive degeneration of dopamine neurons in the substantia nigra pars compacta (Ehringer and Hornykiewicz, 1960; Hornykiewicz, 1963). Despite recent insights into the biology of PD, no preventative or restorative therapy is yet available, thus the gold-standard therapy remains levodopa (Cotzias et al., 1969), a dopamine precursor that dramatically increases the dopamine levels in the brain (Davidson et al., 1971). Bioconversion of levodopa in situ depends on the residual dopamine terminals that are lost with disease progression, causing a decrease in efficacy and an increase in side effects such as wearing off and freezing (Connolly and Lang, 2014). Ultimately, a patient will often be wheelchair- or bed-bound if they do not succumb to injury, infection, or another disorder.

Levodopa indirectly activates six dopamine receptors in two pharmacological groups: D<sub>1</sub>-like (D<sub>1</sub> and D<sub>5</sub>); and D<sub>2</sub>-like (D<sub>2L</sub>, D<sub>2S</sub>, D<sub>3</sub>, D<sub>4</sub>) (Neve and Neve, 1997). In theory, a dopamine agonist should equal or exceed the efficacy of levodopa by targeting the essential dopamine receptors, yet all approved “dopamine agonists” (selective for D<sub>2</sub>-like receptors) are less efficacious than levodopa, especially in late stages of PD (Mailman and Huang, 2007; Rothman et al., 2000). Although data with the partial agonist SKF38393 (Setler et al., 1978) showed little efficacy (Boyce et al., 1990; Close et al., 1985), the first full D<sub>1</sub> agonist dihydrexidine (Brewster et al., 1990; Lovenberg et al., 1989; Mottola et al., 1992) caused profound antiparkinson effects in MPTP-treated African green monkeys, essentially eliminating all parkinsonian signs acutely (Taylor et al., 1991b). Later full D<sub>1</sub> agonists, such as A-77636 (Kebabian et al., 1992) and A-86929, a structural and pharmacological cousin of dihydrexidine (Michaelides et al., 1995), also produced profound antiparkinson effects (Shiosaki et al., 1996). Importantly, ABT-431 (an A-86929 prodrug), was equi-efficacious to levodopa in two clinical trials (Rascol et al., 1999; Rascol et al., 2001).

Levodopa efficacy decreases as dopamine terminals are lost with PD progression (Lewis et al., 2011; Lewis et al., 2007), thus selective activation of D<sub>1</sub> receptors might provide profound symptomatic relief even in late-stage PD patients who are unresponsive to levodopa. Goulet and Madras (2000) reported that D<sub>1</sub> agonists (including dihydrexidine) were more effective in severe than in moderate parkinsonian MPTP-treated cynomolgous monkeys. We had the opportunity to study two MPTP-treated African green monkeys with severe MPTP-induced parkinsonism that was unresponsive to levodopa. We designed a rigorous case study in which each animal was given four different treatments (two standard of care PD drugs; the D<sub>1</sub> agonist dihydrexidine; and dihydrexidine plus a D<sub>2/3</sub> antagonist). This design not only permitted qualitative evaluation of the relative effects, but also added rigor by having eight possible results that would all have to be true to support the initial hypothesis that a D<sub>1</sub> agonist is markedly superior to either levodopa or a D<sub>2</sub> agonist in very
severe parkinsonism, and concomitant D$_{2/3}$ activation is unimportant for the antiparkinson response.

2. MATERIALS & METHODS

2.1 Materials

Dihydrexidine was synthesized as described previously (Brewster et al., 1990; Ghosh et al., 1996). Bromocriptine was a gift from Novartis (formerly Sandoz Pharmaceuticals, East Hanover, NJ), and remoxipride was a gift from AstraZeneca (formerly Astra AB, Södertälje Sweden). Levodopa and benserazide were purchased commercially.

2.2 MPTP treatment and animal care

A group of adult male monkeys (Cercopithecus aethiops sabaicus) from St. Kitts, West Indies were injected intramuscularly with 0.3 to 0.4 mg/kg MPTP given four or five times over a five-day period. They were housed individually in standard primate cages in natural daylight. Access to food and water was unlimited. Care and treatment of these monkeys were in compliance with the US Public Health Service Guide for the Care and Use of Animals (1985), and the protocols were approved by the Axion/St. Kitts Biomedical Research Foundation committee. All experimental monkeys were carefully monitored for their general level of function, motor coordination, and oral intake before and after MPTP treatment, and any monkey failing to take established minimums of fluid or food was assisted as necessary to ensure adequate nutrition and hydration. Daily physiotherapy consisting of regular passive range of motion exercises and monitoring of temperature and respiration rates was done based on severity of impairment. Medical complications of severe parkinsonism, when they occur, were evaluated and treated as necessary to minimize the impact of non-parkinsonian disease or disability on the function of the animal. Details of the handling of these animals have been published previously (Taylor et al., 1994; Taylor et al., 1997).

Of this group, several animals became unusually parkinsonian, and were no longer able to sit upright or to feed themselves. When the excess parkinsonism was noted, these subjects received special care that included special padded bedding to minimize contact with the hard cage surfaces, and feeding assistance and special nursing care that included may feeding by humans of a softened commercial monkey chow via a large syringe. Of these animals, some were used for assessment with nigral fetal tissue grafts into the striatum [see for example (Taylor et al., 1991a), and two monkeys (subjects T236 and T201) were selected for this pharmacological rescue study reported here. After these animals failed to improve spontaneously over several weeks, levodopa was tried as a rescue medication, but there was no adequate response in either. Prior studies in this model have shown that similar animals have parkinsonism scores of ca. 60–70, and unlike moderate or mildly parkinsonian animals (scores of 8–17) do not recover with time (Elsworth et al., 2000). Such severe animals have an overall dopamine depletion in the striatum of >99%, whereas moderate animals, such as used in our earlier study of dihydrexidine (Taylor et al., 1991b) have depletions of 90–95%.
The recommendation from the attending veterinarian was to euthanize the subjects. It was recognized, however, that these two subjects represented a model of end-stages of Parkinson’s disease in which patients are bed-ridden, can no longer self-feed, and for which there is no currently available effective therapy. Based on data showing the large effect size of dopamine D₁ full agonists in the MPTP model of moderate PD, it was felt that these subjects provided the unusual opportunity to determine if a D₁ agonist might offer hope in advanced PD. Thus, a controlled cross-over acute comparison of current standards of care (levodopa and D₂ agonists) with dihydrexidine, a full D₁ agonist, was felt to be warranted. There was a one-day interval between each drug trial. The two subjects were tested on the same day. The order of treatment was levodopa, bromocriptine, dihydrexidine, and dihydrexidine plus remoxipride.

2.3 Videotaping and rating

The subjects were videotaped, and the complete and unedited videotapes rated by two trained observers who were blinded to the order of the drug challenges. These observers had achieved a coefficient of concordance (Kendall’s) greater than 0.95 on all behaviors. The ratings used an observation scale that has been reported in detail (Taylor et al., 1994; Taylor et al., 1997), the components of which are summarized in Fig. 1.

3. RESULTS

3.1 Treatment design

Typically, evaluating drug effects would be done by group comparisons in which the group sizes would be established a priori using a power analysis based on predicted effect size. Because only two subjects were available, this design was impossible. Instead, each subject was challenged on different days with four drug treatments, and the videotapes were rated by two trained observers who were completely blinded to treatment. The ratings in Figs. 2 and 3 were made from complete and unedited videotapes. Several factors supported the feasibility of this design. Prior research in moderately parkinsonian MPTP-treated non-human primates (NHPs) of the same species had shown a very large effect size of the full D₁ agonist dihydrexidine (Taylor et al., 1991b). Second, dihydrexidine and levodopa have relatively rapid metabolism, thus there would be essentially no carry-over effects from residual drug, and a single drug challenge was unlikely to induce marked adaptive responses that would compromise interpretation. Third, inter-subject design would allow using each subject as its own control.

Four specific hypotheses were tested in each animal. Since it was known that these two animals had shown minimal response to levodopa/benserazide during their routine care prior to this experiment, the first hypothesis was that responses to levodopa using blinded raters would show minimal improvement. The second challenge was with bromocriptine that, like other D₂/₃ agonists, has very little efficacy in severe Parkinson’s disease. The hypothesis was that these two animals would similarly show little response. The third challenge was the selective D₁ agonist dihydrexidine, testing the hypothesis that direct D₁ activation would, unlike either levodopa or a D₂/₃ agonist, cause a large antiparkinson effect. Because dihydrexidine is only ca. ten-fold D₁:D₂, the last hypothesis used pretreatment with the D₂/₃
antagonist remoxipride before administration of dihydrexidine to test whether D₁ activation alone is adequate for any antiparkinson response.

3.2 Effect of drugs

The first part drug challenge was with levodopa plus benserazide, a combination that causes a robust response in moderately parkinsonian MPTP-NHPs and in PD. As noted, prior uncontrolled rescue studies in these two subjects showed minimal response. This was confirmed by the relative lack of response to levodopa plus benserazide in subject 236, and only a modest response in subject 201 (Fig. 2-left panel).

The second phase of the trial was the challenge with the D₂ agonist bromocriptine (Jouvent et al., 1983; Lees and Stern, 1981). Bromocriptine failed to elicit any detectable improvement in ether subject (Fig. 2, right panel).

The next phase was treatment with the short-acting selective D₁ agonist dihydrexidine. A dose of 0.6 mg/kg was chosen based on prior study of moderately parkinsonian MPTP-NHPs (Taylor et al., 1991b). Prior to treatment, the monkeys could neither sit, stand, or feed themselves, but after drug administration they were moving significantly and taking food (Fig. 3, left panel).

Dihydrexidine has no major off-target affinity for non-dopamine receptors, but is only ca. ten-fold selective for D₁-like versus D₂ like receptors (Mottola et al., 1992). The activity of dihydrexidine at the D₂ receptor has been extensively studied, and it has both agonist and antagonist activity at D₂-like signaling pathways, making it the first /functionally selective/ highly-biased ligand that was characterized (Gay et al., 2004; Kilts et al., 2002; Mailman and Gay, 2004; Mailman et al., 1998; Mottola et al., 1991; Mottola et al., 2002). Thus, it was possible that low levels of D₂ receptor occupancy might contribute to the effects of dihydrexidine. To test the hypothesis that the antiparkinson effects of dihydrexidine was mediated almost essentially by D₁ receptors, the monkeys were pretreated with the D₂ antagonist remoxipride, and then challenged with dihydrexidine. The pretreatment with remoxipride did not attenuate the effects of dihydrexidine in either subject (Fig. 3, right panel).

4. DISCUSSION

4.1 Profound antiparkinson effects of a D₁ full agonist

We had previously reported that dihydrexidine essentially eliminated all parkinsonian signs in moderately parkinsonian MPTP-treated African green monkeys (Taylor et al., 1991b). The current data provide evidence that selective D₁ agonists may provide profound antiparkinson symptomatic relief even when the degree of nigrostriatal degeneration is so severe that levodopa is ineffective. This is in partial agreement with Goulet and Madras (2000) who reported that two D₁ agonists (dihydrexidine and SKF81397) both had significant, but not dramatic, effectiveness in four severely affected MPTP-treated cynomologous monkeys. Conversely, they saw no major effects in “mild” subjects, contrary to our earlier report showing consistent dramatic effects in nine subjects (Taylor et al., 1991b). Goulet and Madras (2000) also reported a large effect size of two D₂-like agonists.
(PHNO and quinelorane), albeit with side effects, whereas we saw no effect with the D₂-like agonist bromocriptine. Their study did not compare these dopamine agonists with levodopa, whereas ours showed that there was no effect of a large dose of levodopa. Another difference was that we saw very large effects at 0.6 mg/kg of dihydrexidine (consistent with doses to get maximal effects in rat models), whereas they required doses five times higher. Because of the practical and ethical difficulties in working with severely parkinsonian non-human primates, both studies had small numbers of subjects, and used animals of different species and with different scoring systems. Nonetheless, despite these limitations, our results are consistent with what is seen in very advanced PD patients where levodopa and D₂ agonists are both largely ineffective.

4.2 Are these effects mediated by the D₁ receptor?

The major off-target activity of dihydrexidine is at other dopamine receptors (Mottola et al., 1992). Dihydrexidine has little selectivity for D₁ vs. D₅ receptor, but expression of the D₁ receptor in high in the basal ganglia, whereas very low for the D₅ (Ciliax et al., 2000; Laurier et al., 1994; Montague et al., 2001), decreasing the possible importance of the D₅ receptor. Similar logic decreases a role for the low-striatal expressed of the D₄ receptor (Ariano et al., 1997). Conversely, both D₂ and D₃ receptors are expressed in the striatum, yet pretreatment with remoxipride failed to attenuate the actions of dihydrexidine. Thus, the evidence points to a primary role of the D₁. This hypothesis is supported by the basal ganglia neurocircuitry (Albin et al., 1989; DeLong, 1990) that posits that coordinated movement is regulated by two parallel and segregated pathways (direct and indirect). We had shown that the striatum had the highest expression of D₁ receptors (Schulz et al., 1985), and that D₁ antagonism could block dopaminergic motor stimulation (Mailman et al., 1984), suggesting that the D₁ receptor-mediated direct pathway might facilitate movement stimulatory actions, whereas the D₂ receptor-mediated indirect pathway would be inhibitory (Gerfen et al., 1990). The current data show that, at least in severe parkinsonism, activation of only D₁ would be entirely adequate for marked antiparkinson effects in advanced PD, contrary to common dogma about the importance of the D₂-like receptors in levodopa actions (Cedarbaum and Schleifer, 1990; Konta and Frank, 2008; Schachter et al., 1980).

4.3 Parkinson's disease versus the MPTP model

The overall impact of these data depends on the ability to translate to the clinic. Although the MPTP-model has not led to translatable breakthroughs in understanding PD etiology, symptomatically there has been excellent correlation of the motor efficacy of drugs used in PD with its motor improvement in MPTP-treated NHPs (Langston, 2017; Mailman and Huang, 2007). Although both PD and MPTP-NHP models have depleted dopamine, in PD this occurs more in the putamen, whereas MPTP decreases dopamine levels in both the caudate and putamen (Elsworth et al., 1989). Our earlier report showed profound efficacy of dihydrexidine in moderately parkinsonian MPTP-NHPs (Taylor et al., 1991b). Later, ABT-431 [whose active metabolite A-68929 is structurally and pharmacologically similar to dihydrexidine (Michaelides et al., 1995)] was found to have clinical efficacy essentially equal to levodopa (Rascol et al., 1999; Rascol et al., 2001), as predicted by Taylor et al. (1991b). The MPTP model and PD, however, differ in their temporal progression. MPTP treatment causes acute damage, whereas the long course of PD involves dynamical

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pathophysiological changes that even differ between individuals (Du et al., 2018; Lewis et al., 2018). Striatal D₁ receptors are, however, post-synaptic to degenerating dopamine neurons, and may maintain near-normal function, but more data in advanced PD patients is needed.

4.4 D₁ signaling mechanisms and drug action

There are two mechanistic issues that are relevant for future study. The first selective D₁ agonist SKF38393 had low intrinsic activity (Setler et al., 1978), possibly explaining why it failed in both MPTP-NHP and human trials (Boyce et al., 1990; Close et al., 1985). Dihydrexidine and many later compounds had full or high efficacy (Kebabian et al., 1992; Lovenberg et al., 1989; Michaelides et al., 1995; Shiosaki et al., 1996) and were effective antiparkinson agents. Although this suggested high intrinsic activity was critical, a new series of partial agonist D₁ agonists discovered by Pfizer (Brodney et al., 2014; Davoren et al., 2014) have shown significant antiparkinson effects in mid-stage disease (Papapetropoulos et al., 2018; Sohur et al., 2018). These Pfizer compounds also are interesting because they are functionally selective/highly-biased (Urban et al., 2007) at D₁ receptor signaling, as partial agonists of the D₁ cAMP pathway, and antagonists of D₁-mediated β-arrestin2 recruitment (Gray et al., 2018). This differs from dihydrexidine-like molecules (Lee et al., 2014; Yang et al., 2018). Interestingly, in vitro studies of Yano et al. (Yano et al., 2018) suggested that dihydrexidine actually is only a partial agonist when the D₁ receptor couples to GαOLF, the critical striatal G. This hypothesis is, however, inconsistent with prior studies in both murine and primate striatum (Gilmore et al., 1995; Lovenberg et al., 1989; Mottola et al., 1992; Watts et al., 1993; Watts et al., 1995). Potential dose-limiting side effects (Blanchet et al., 1998) may be decreased by understanding these mechanisms more fully.

4.5 Summary and future directions

If our data translate to clinical PD, D₁ agonists may change the landscape of the therapy of advanced PD. This hypothesis already may have some support in the existing clinical literature. Although all approved dopamine agonists are D₂/₃ selective, two have differentiated themselves from others when used in later stages of PD. Apomorphine is currently approved, although it is limited by short duration of action and by being only injectable. Although D₂/₃ selective, apomorphine has modest D₁ affinity, but relatively high D₁ intrinsic activity. This may explain why it provides motor relief in later stages of PD not seen with any other approved dopamine agonist. A second case is the formerly approved drug, pergolide, an ergoline-based D₂/₃ selective agonist like bromocriptine that we used. Although pergolide and bromocriptine are D₂/₃ selective, both have modest affinity for the D₁ receptor, yet pergolide is a partial D₁ agonist, whereas bromocriptine has only D₁ antagonist activity. This may explain why pergolide retains antiparkinson activity over time in patients who have stopped responding to bromocriptine (Goetz et al., 1985). These clinical data are consistent with the conclusions drawn from the current data.

Because very advanced Parkinson’s patients have no available treatment, they suffer from many secondary effects of the disease resulting from inactivity or physical instability, as well as many non-motor symptoms. For these reasons, to our knowledge there had never been an
interventional study in patients in this very advanced state, probably because no potential therapy justified such clinical trials. Based on the results of the current study and influenced by that of Goulet and Madras (2000), we initiated an acute challenge of the oral partial D\textsubscript{1} agonist PF-06412562 in very advanced PD patients (Huang et al., 2020). To our knowledge, it was the first acute Phase I study in very advanced PD patients, and it used a strategy like that described in the current work. The results show that even very advanced patients (Hoehn & Yahr >4) can be studied effectively, and that at least one D\textsubscript{1} agonist was well-tolerated (Huang et al., 2020). In the absence of a cure on the horizon, and with development of D\textsubscript{1} agonists finally accelerating (Mailman et al., 2001), the possibility that we can bring new hope to PD patients at the bleakest part of their journey cannot be disregarded, especially because D\textsubscript{1} receptors also play important roles in other processes like cognition (Arnsten et al., 2017; Sawaguchi and Goldman-Rakic, 1991). Thus, D\textsubscript{1} agonists have the potential of revolutionizing treatment of advanced PD until, and if, a cure can be found.

Lastly, it may be useful for neurologists to retire the phrase “dopamine agonist.” It misleadingly suggests all dopamine receptors are involved, when current drugs largely target D\textsubscript{2}-like receptors (Millan et al., 2002). Receptor-specific labels will offer more pharmacological precision, and will help physicians evaluate evidence-based medicine.

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Dr. Mailman is an inventor of D\textsubscript{1} agonist technology, the conflicts-of-interest of which are managed by the Pennsylvania State University College of Medicine. He is the past recipient of research funds and consulting compensation from Pfizer, Inc. Dr. Huang is an inventor of D\textsubscript{1} agonist-related technology whose interests were assigned to the University of North Carolina. Dr. Huang has also received nominal transportation and per diem expenses from Acadia, Medtronics, and Cerevel Therapeutics, and research support from Pfizer, Biogen, and Biohaven. Drs. Mailman and Huang have no other conflicting interests. Dr. Yang has no conflicting interests. The opinions in this review are those of the authors alone and do not reflect those of the university or any other party.

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Fig. 1.
Scale for rating of parkinsonian signs in these subjects [from (Taylor et al., 1994; Taylor et al., 1997)]
Fig. 2.
(Left) Time course of effects of levodopa in two MPTP-treated NHPs (T236 and T201) after injection of benserazide, a decarboxylase inhibitor (arrow indicates injection of benserazide). (Right). Time course of effects of the D2 agonist, bromocriptine. Shaded area denotes time after injection of active drug (i.e., levodopa in left panel; bromocriptine-right panel). Results are the average of the scores of two raters.
Fig. 3.
(Left). Effects of the full D$_1$ agonist dihydrexidine on parkinsonian signs in two MPTP-treated NHPs (subjects T236 and T201). (Right) Effects of pretreatment with D$_2$ antagonist remoxipride (arrow indicates the time of remoxipride injection) on subsequent treatment with dihydrexidine. Shaded area denotes time after injection of dihydrexidine.