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ORIGINAL INVESTIGATION

Comparison of the D_1 dopamine full agonists, dihydrexidine and doxanthrine, in the 6-OHDA rat model of Parkinson's disease

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Abstract
Rationale Preclinical evidence indicates that D_1 dopamine receptor full agonists have potential as therapeutic agents for a variety of neurological conditions. Dihydrexidine (DHX) was the first high potency selective D_1 dopamine receptor full agonist and has been studied as a possible treatment for Parkinson's disease (PD). Recently, we discovered doxanthrine (DOX), an oxygen bioisostere of DHX that has even greater selectivity for the D_1 dopamine receptor.
Objectives Using the unilateral 6-hydroxydopamine-lesioned rat model of PD, DOX and DHX were compared at several doses (0.625, 1.25, 2.5, or 5.0 mg/kg) for their ability to elicit contralateral rotation by either intraperitoneal injection or oral gavage.
Results After intraperitoneal administration, both DOX and DHX showed robust contralateral rotation at doses of 2.5 and 5.0 mg/kg compared to vehicle. In addition, after intraperitoneal administration at doses of 2.5 and 5.0 mg/kg, DHX had a significantly longer duration of action than DOX ($p<0.05$). Areas under the curves (AUC) for DOX and DHX were not significantly different, however, indicating that DOX and DHX have similar potency after intraperitoneal administration. By contrast, after oral administration, 2.5 and 5.0 mg/kg of DOX produced significant contralateral rotations ($p<0.05$), whereas DHX showed no significant activity after oral administration of any dose.
Conclusion These results demonstrate that although DHX and DOX have similar activity after intraperitoneal administration, DOX demonstrated greater activity after oral administration compared to DHX. Despite its catechol functionality, DOX may possess sufficient oral availability for development as a human therapeutic agent.

Keywords Parkinson's disease · Dopamine D_1 receptor · Dihydrexidine · Doxanthrine · 6-Hydroxydopamine · Rat · Contralateral rotation

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative condition that affects millions of people worldwide (Hickey and Stacy 2011). PD involves loss of motor control that includes symptoms such as a resting tremor, rigidity, bradykinesia, and postural instability (Rodriguez-Oroz et al. 2009) but also can include cognitive dysfunctions such as deficits in working memory (Lewis et al. 2003). The etiology of PD is still not well understood but most of the symptoms arise as a result of cell death in the substantia nigra (Foltynie et al. 2002), which provides dopaminergic input into the basal ganglia responsible for voluntary motor control.

Although current therapies do not slow the progression of the disease or treat non-motor symptoms, the most effective long-term control of the motor symptoms is presently achieved using L-DOPA as a dopamine replacement therapy, which after several years of treatment can result in periodic "on-off" states that make PD therapy very difficult to manage (Fahn et al. 2004). The length of time that L-DOPA remains efficacious also is a severe limiting factor in PD therapy, where the progression of the disease can last for decades after diagnosis (Silver 2006).

As a result of these problems with L-DOPA, initial monotherapy with dopamine receptor agonists active at

the D_2 or D_3 receptor subtypes (Meissner et al. 2011) is now commonly initiated to delay the need for L-DOPA (Gottwald and Aminoff 2011). Current D2 family agonists (e.g., pramipexole and ropinirole) can have undesirable side effects such as nausea, orthostatic hypotension, fatigue, and even compulsion and hypersexuality (Perez-Lloret and Rascol 2010) consistent with the localization of dopamine D2 subfamily receptors in the chemoreceptor trigger zone (Yoshikawa et al. 1996) and nucleus accumbens (Lahti et al. 1995). More problematic, however, is the fact that D_2-like agonists do not remain efficacious after a few years of use, with the number of patients remaining on agonist monotherapy decreasing to less than 50% after 3 years of treatment (Bonuccelli and Pavese 2006).

Although no current therapeutic agents are available for PD that are targeted to the D_1 dopamine receptor, D_1 receptors consistently have been implicated in controlling the "direct pathway" of the basal ganglia (Wooten 1997). Consistent with this hypothesis, dihydrexidine (DHX), a D_1 dopamine full agonist, reversed the motor dysfunction induced by MPTP lesions in monkeys (Taylor et al. 1991).

Recently, we reported the discovery of doxanthrine (DOX), a highly D_1 receptor-selective full agonist (Cueva et al. 2006). Doxanthrine was designed as a potential bioisostere of dihydrexidine, where an oxygen atom replaces a methylene unit, as illustrated in Fig. 1. Compared to DHX, DOX showed greater than 100-fold selectivity for D_1-like over D_2-like receptors in porcine striatal tissue and similar potency in stimulating cAMP accumulation in recombinant human D_1 dopamine receptor-expressing HEK cells (Cueva et al. 2006). Initial in vivo characterization of the enantiomers of DOX showed that the (+) isomer increased locomotor activity in mice (Przybyla et al. 2009), but to date there still has been no in vivo evidence for potential utility of DOX in PD.

The present experiments sought to explore the in vivo activity of DOX compared to DHX using the unilateral 6-hydroxydopamine-lesioned rat model of PD. This model, originally developed by Ungerstedt (1976), has become widely used for prediction of effective therapies for PD (Jenner 2008). The unilateral 6-hydroxydopamine-lesioned model produces asymmetric movement ipsilateral to the lesion, but upon challenge with a direct-acting dopamine agonist, contralateral rotation occurs (Deumens et al. 2002). It was known that DHX lacked significant oral bioavailability, but no information was available for DOX. Therefore, the purpose of this investigation was to use the 6-hydroxydopamine-lesioned rat model to compare the rotational activity of two full agonists selective for the D_1 dopamine receptor, DOX and DHX, given both systemically and by oral gavage.

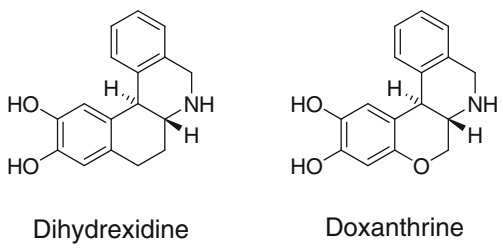

Fig. 1 Comparison of the structures of dihydrexidine with its oxygen bioisostere doxanthrine

Methods

Drugs

Racemic DHX and DOX were previously synthesized in our laboratory (Brewster et al. 1990; Cueva et al. 2006) and were used as the hydrochloride salts. Desipramine HCl, *R*-(−)-apomorphine HCl, chloral hydrate, and 6-hydroxydopamine (6-OHDA) HCl were all purchased from Sigma-Aldrich (St. Louis, MO, USA) and dissolved in physiological saline (0.9% NaCl). For DOX and DHX studies, the vehicle for the intraperitoneal route of administration was physiological saline, and the vehicle for the oral route was distilled water. Desipramine and chloral hydrate were both administered intraperitoneally and *R*-(−)-apomorphine was administered subcutaneously. All drugs, with the exception of 6-OHDA, were administered in a volume of 1 mL/kg.

Unilateral 6-hydroxydopamine lesioning

Adult male Sprague–Dawley rats were used for this study, approximately 8 weeks of age and weighing between 275–325 g at the time of surgery. Rats were housed individually in polycarbonate cages with free access to food and water under a 12:12 h light/dark schedule with lights on at 0700 hours and off at 1900 hours. Rats were purchased either from Harlan (Indianapolis, IN, USA) or, if prelesioned, from Taconic (Surgery model #SU048, NY, USA). Thirty minutes before surgery, rats were administered 25 mg/kg i.p. desipramine to protect norepinephrine neurons. Rats were anesthetized with 400 mg/kg chloral hydrate i.p., and stereotaxic coordinates were set to the medial forebrain bundle (4.3 mm posterior, 1.2 mm medial to bregma, and 8.3 mm ventral from dura relative to bregma) according to Paxinos and Watson (1998). A solution of 8 μg of 6-OHDA (calculated as the free base) in a total volume of 4 μL was infused at 1 μL/min with an additional 5 min for diffusion. Surgical procedures were nearly identical for prelesioned

rats obtained from Taconic, except the anesthesia used was isoflurane. There were no significant differences in rotation responses between rats lesioned in our laboratory, and prelesioned rats from Taconic, in response to administration of 0.5 mg/kg apomorphine (data not shown; this dose of apomorphine produced similar total contralateral rotations with a mean of 257±34 turns). All surgical and animal care procedures conformed to the Association for Assessment and Accreditation of Laboratory Animal Care and were approved by the Purdue Animal Care and Use Committee.

Drug administration

Rats were handled and weighed daily for at least 2 weeks post-surgery to ensure stable weight before experiments. Two weeks after surgery, 0.5 mg/kg apomorphine was administered subcutaneously and rotations were measured as described. Rats were chosen for further study if they exhibited >100 contralateral rotations per 120-min session, a magnitude of apomorphine response that has been consistently validated as resulting from >90% loss of dopamine in the striatum (Robin et al. 1985). Afterwards, rats were randomly assigned to receive one of four doses, 0.625, 1.25, 2.5, or 5.0 mg/kg of DOX or DHX or vehicle. Each rat received the assigned drug dose on separate occasions by two routes of administration: oral gavage (PO) and intraperitoneal injection (IP), in order to determine individual oral versus intraperitoneal rotational responses. The first exposure to drug by route of administration was counterbalanced for each drug dose group, and sessions for each individual rat were separated by at least 3 days.

Rotation procedure

On the day of experiments, groups of rats were weighed and transported to the rotation room in individual cages. Rats were placed into the rotation field where a harness was fastened around their torso immediately behind their forelegs. The harness had enough space for at least one finger between the harness and the torso, and all four paws of the rat were fully in contact with the surface of the rotation field. The experimenter was absent from the room during all measurements. After an initial 30-min baseline measure was recorded, rats were removed from the rotation harness and drug was administered either IP or PO. Rats were placed back into the harness and the session was started and recorded for exactly 120 min. Rats were then removed from the harness and taken back to the colony room. Rotation chambers were cleaned with 70% ethanol after every session. All experiments were performed between 1200 and 1700 hours.

Rotation field apparatus and data analysis

Equipment and software were purchased from Accuscan Instruments (Columbus, OH, USA). Rotation fields were cylindrical polycarbonate chambers measuring approximately 30 cm in diameter with a wire harness measuring approximately 27 cm from the top of the chamber, and placed on a flat square polycarbonate surface of 2,500 cm^2. The wire harness was attached to a flexible swivel switch at the top of the chamber that recorded 360° rotations using RotoMax v.1.40 software. Contralateral rotation data for each subject were sorted into 5-min time bins. Total contralateral rotations were defined as the sum of all 5-min bin rotations during the 120-min session. The total AUC was calculated, duration was determined by the last minute at which rotational behavior stopped, and all statistical analyses were performed using Graphpad Prism 4 Software (San Diego, CA, USA).

Results

Contralateral rotations following IP administration of 2.5 and 5.0 mg/kg DOX and DHX are shown in 5-min time bins in Fig. 2. At 2.5 mg/kg IP (Fig. 2a), both DHX and DOX produced a rapid increase in the number of contralateral rotations within 10 min, with rotations gradually decreasing at 60 to 90 min. At 5.0 mg/kg IP (Fig. 2b), DOX showed a sharp increase in rotations within the first 5 min with an effect that tapered off at about 80 min, whereas the action of DHX continued for about another 30 min.

The 2.5 mg/kg oral dose of DHX (Fig. 2c) produced little to no response, similar to vehicle, suggesting low oral availability. The same dose of DOX given orally, however, produced an evident contralateral rotation, although this effect was less robust and shorter than when this DOX dose was given IP. When 5.0 mg/kg of DHX was given orally (Fig. 2d), it produced a modest rotation, whereas DOX showed a much greater rotational response at this dose. Compared to the 2.5 mg/kg PO dose of DOX, the 5.0 mg/kg PO dose produced a more robust response with a longer duration than DHX.

To examine further the differences in time course of action, as seen in Fig. 2, the duration of DOX and DHX at each dose was calculated and is shown in Table 1. With IP administration, two-way ANOVA revealed a significant interaction between DOX and DHX ($F_{4,45}=10.09$, $p<0.0001$), and Bonferroni's multiple comparisons showed significant differences in duration between DOX and DHX at the 1.25, 2.5, and 5.0 mg/kg doses. These results indicate that following IP administration, DHX rotational behavior persists longer at the 2.5 and 5.0 doses compared to DOX, but at the 1.25 dose, DOX has a longer duration than DHX. In contrast to this finding,

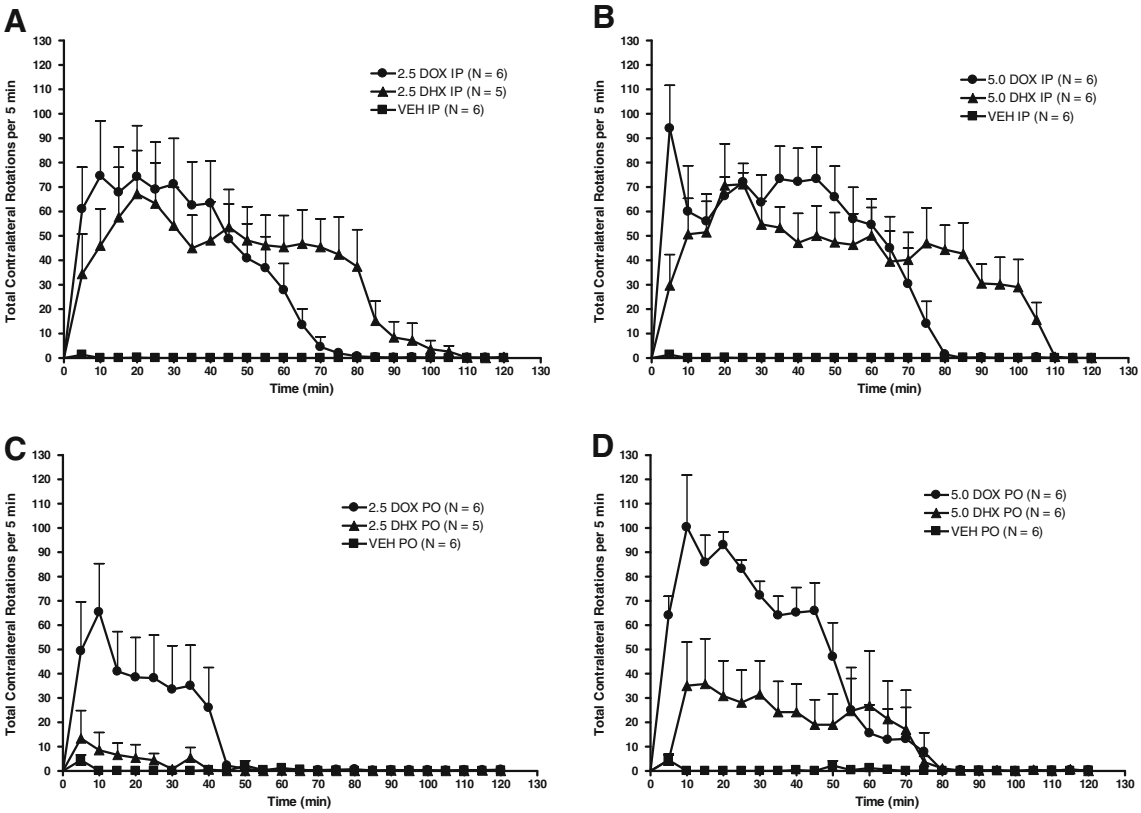

Fig. 2 Contralateral rotations produced by vehicle (*VEH*), dihydrexidine (*DHX*), and doxanthrine (*DOX*) at 2.5 mg/kg IP (**a**), 5.0 mg/kg IP (**b**), 2.5 mg/kg PO (**c**), and 5.0 mg/kg PO (**d**). Each data point represents the mean of total contralateral rotations per 5-min time bin and *error bars* represent SEM, with n=5 or 6

no significant interaction ($F_{4,45}$=1.09, p>0.05) was detected following oral dosing, indicating that, despite the more robust response to DOX after oral administration, the two drugs did not differ in duration of action when given orally.

Table 1 Duration in minutes of DOX and DHX at dose and route of administration

Dose (mg/kg)	Drug	Route of administration	
		IP	PO
5.0	DOX	79 (3)*	63 (6)
	DHX	108 (6)	43 (16)
2.5	DOX	67 (7)*	45 (9)
	DHX	99 (6)	25 (7)
1.25	DOX	52 (7)*	23 (4)
	DHX	20 (8)	23 (7)
0.625	DOX	29 (5)	22 (2)
	DHX	22 (7)	18 (4)
0	VEH	8 (4)	7 (2)

Data represent means, and parenthesis represent SEM, n=5 or 6

DOX doxanthrine, *DHX* dihydrexidine, *VEH* vehicle

*p<0.001 comparing the same dose of DOX to DHX

In order to account for the differences in duration and to examine the magnitude of the overall rotational response, the AUC was utilized as a measure of efficacy. The AUC provides a good estimate of a drug's pharmacokinetic profile and has been used to compare the efficacy of antiparkinson drugs such as ropinirole after administration of different dosage forms (Tompson and Oliver-Willwong 2009). Dose–response curves using the AUC for DOX and DHX are shown in Fig. 3 for both routes of administration. Figure 3a shows a similar dose–response relationship for DOX and DHX when given IP, and a two-way ANOVA revealed no significant interaction between DOX and DHX at any dose ($F_{4,45}$=0.31, p>0.05) indicating that although there were significant differences in duration, DHX and DOX did not differ in their AUC after IP administration.

The dose–response for the AUC after PO drug administration shows that DOX produces a greater AUC response than DHX (Fig. 3b). A two-way ANOVA detected a significant interaction between DOX and DHX by the PO route ($F_{4,46}$=5.22, p<0.01), and Bonferroni's multiple comparisons indicated a significant difference between DOX and DHX at the 2.5 mg/kg (p<0.05) and 5.0 mg/kg (p<0.001) doses. These results demonstrate that although DOX and DHX did not differ in their AUC when administered

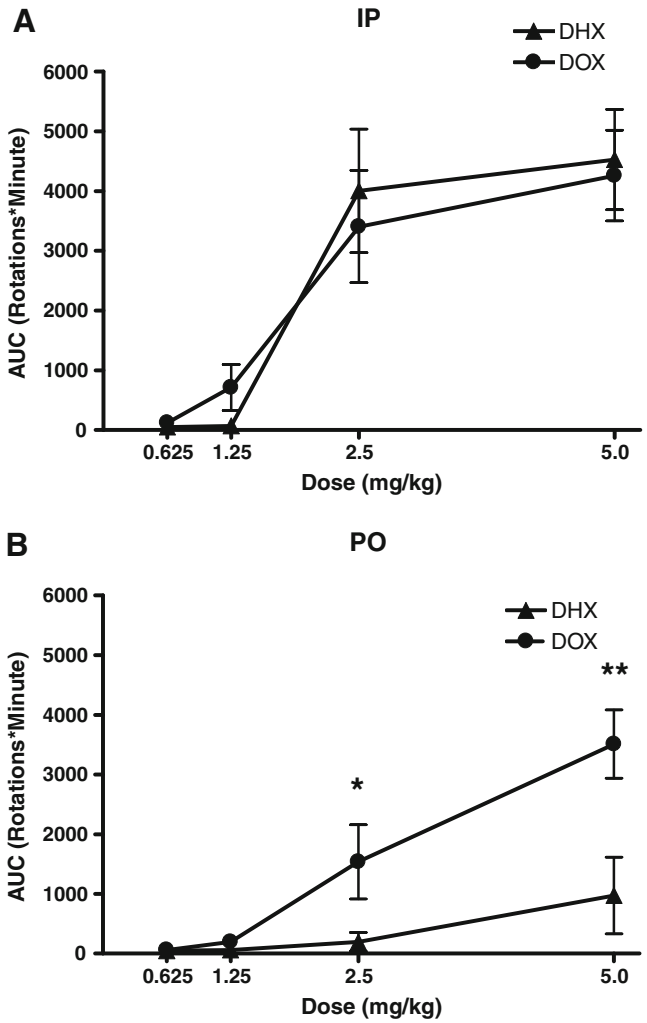

Fig. 3 Dose–response of area under the curve (*AUC*) for doses of DOX and DHX given IP (**a**) or PO (**b**). Data represent means, and *error bars* represent SEM, $n=5$ or 6. *$p<0.05$, **$p<0.001$ comparing the same dose of DOX to DHX. *DHX* dihydrexidine, *DOX* doxanthrine, *IP* intraperitoneal, *PO* oral. These data are derived from the experiments illustrated in Fig. 2

IP, DOX had a significantly greater AUC than DHX when either dose was given orally.

Finally, we wished to examine each subject's response to oral drug administration as a percentage of total rotations exhibited after intraperitoneal administration. This measure reflects relative oral bioavailability by controlling for large individual rotational responses in order to assess the intraindividual rotational response. Figure 4 shows contralateral rotations after oral drug administration as a percentage of total contralateral rotations after IP dosing at either 2.5 or 5.0 mg/kg. Both doses of DOX showed a greater percentage of oral to intraperitoneal response compared to DHX, and in fact, 5.0 mg/kg of DOX approaches closely to a 100% response. A one-way ANOVA shows a significant difference among the DOX and DHX dose groups ($F_{3,19}=12.02$, $p<0.0001$). Bonferroni's multiple comparisons detect a significant difference between DOX and DHX at 2.5 mg/kg ($p<0.05$) and an even greater difference between DOX and DHX at 5.0 mg/kg ($p<0.01$).

Discussion

Our experiments provide three major findings regarding the in vivo activity of DOX compared to DHX in the unilateral 6-hydroxydopamine-lesioned rat. First, both DOX and DHX produced robust contralateral rotations when administered IP, and this response for both drugs was dose-dependent. Second, although DHX had a significantly longer duration of action when administered IP, analysis of the AUC showed that there was no significant difference between DHX and DOX at each dose. Finally, but most importantly, only DOX elicited any dose-dependent contralateral rotation after oral drug administration, and this effect was significantly different from DHX, especially when individual differences in the IP drug responses were taken into account.

The finding that the effect of IP-administered DHX lasted approximately 100 min or longer is consistent with studies of the time course of rotational effect after DHX in the unilateral MPTP-lesioned primate (Johnson et al. 1995). In the present rat model, DOX had a significantly shorter duration of effect compared to DHX. Although it is unknown whether a relatively brief duration of action would be a drawback for clinical use, a more significant problem may be a prolonged duration of action. For example, the D_1 dopamine receptor-selective agonist, A-77636, showed a

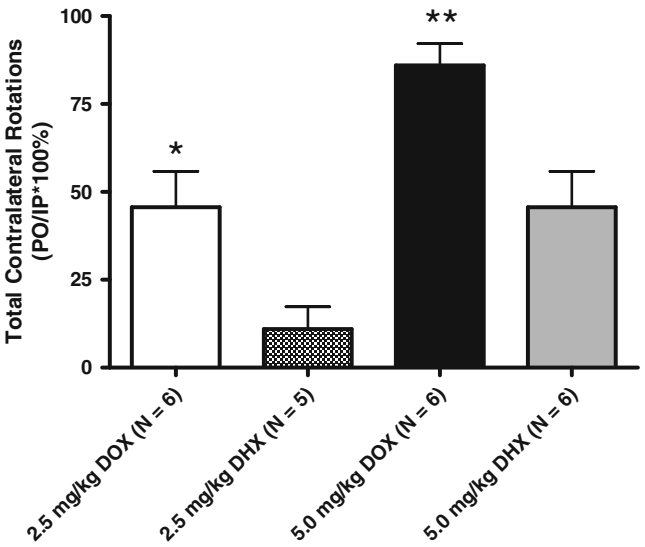

Fig. 4 Contralateral rotations after oral drug administration as a percentage of total contralateral rotations after IP dosing at either 2.5 or 5.0 mg/kg. *$p<0.05$, **$p<0.01$ comparing the same doses of DOX to DHX

greater than 20-h long contralateral rotational response in the MPTP-lesioned marmoset (Kebabian et al. 1992), and led to tolerance (Asin and Wirtshafter 1993), most likely resulting from D_1 receptor desensitization and slow dissociation from the receptor (Lin et al. 1996). A short-acting compound would avoid that problem and could be easily managed, for example, with a controlled release formulation.

Our results show that DHX and DOX have similar activity profiles as measured by the AUC when given IP, but only DOX showed a significant response following oral administration. Moreover, full intrinsic activity remains an important pharmacodynamic feature for any potential dopaminergic antiparkinson drug, as evident in the clinical failure of the D_1 dopamine receptor-selective partial agonist, SKF 38393, to ameliorate PD symptoms (Braun et al. 1987). DOX exhibits full intrinsic activity at D1 receptors in several in vitro models (recombinant human D_1, porcine D1-like, and native D1-like in MCF7 cells (Cueva et al. 2006; Przybyla et al. 2009)), and as we demonstrate here, possesses substantial dopaminergic activity in vivo, thus exhibiting potential utility as a therapeutic agent for PD. Although we did not perform antagonist studies here, Johnson et al. (1995) have previously shown that DHX elicited dose-dependent contralateral rotational behavior in hemiparkinsonian monkeys was blocked by the selective D_1 antagonist SCH 23390, but not by the D_2 antagonist raclopride.

We have previously demonstrated that the (−) enantiomer of DOX possesses potent alpha-2 adrenergic agonist activity and causes a decrease in mouse locomotor activity (Przybyla et al. 2009). Alpha-2 adrenergic agonists such as clonidine also have been shown to inhibit contralateral rotation in the 6-hydroxydopamine model (Chopin et al. 1999), yet the racemic DOX used in this study still produces a robust rotational response, indicating that any motor inhibition produced by the (−) enantiomer is not sufficient to block significantly the activity-inducing effect of the (+) enantiomer in the racemate. We felt this finding was important because alpha-2 agonists have been shown to improve aspects of working memory in PD patients (Riekkinen et al. 1999), so the use of the racemate rather than the (+) isomer might offer that advantage.

An important feature of a potentially marketable drug is its oral availability, particularly in the case of drugs for PD that must be given on a daily basis and often multiple times a day. The conventional wisdom in drug development circles has been that catechols, because of poor oral bioavailability, do not make good drugs, a consideration that was a major factor in preventing the further development of DHX as a therapy for PD. Our results here indicate that, by contrast, DOX does, indeed, exhibit significant activity after oral administration, whereas DHX does not. This finding is especially surprising in view of the fact that DOX differs from DHX only in that it has an oxygen atom replacing a CH_2 moiety (Fig. 1).

We initially hypothesized that the differences in oral activity might lie in differing susceptibility to catechol-*O*-methyl transferase (COMT). That idea was not supported, however, following preliminary experiments in this model where pretreatment with the COMT inhibitor OR-486 lengthened the duration of action only slightly but had little effect on the response after oral administration of either DHX or DOX (data not shown). The underlying basis for differences in oral availability of catechol-containing drugs would therefore seem to be a fruitful area for further investigation.

In summary, we compared the first high-potency selective D_1 dopamine receptor full agonist DHX to its recently synthesized oxygen bioisostere DOX in the unilateral 6-hydroxydopamine-lesioned rat model of PD. Our results show that DOX and DHX have similar efficacy in this model following IP administration, whereas only DOX has significant oral activity. Considered together with its full D_1 dopamine receptor agonist activity, and its high D_1 vs D_2 receptor selectivity, DOX presents as a possible candidate for further development as a medication for Parkinson's disease. Furthermore, these properties of DOX may make it valuable as a new tool to study D_1 dopamine receptor mechanisms of tolerance, metabolism, and absorption in order to advance our understanding of the role of D_1 dopamine receptors in Parkinson's disease and its treatment.

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