Pharmacology, Biochemistry and Behavior 105 (2013) 26–33

Contents lists available at SciVerse ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Abnormal involuntary movement (AIM) expression following D2 dopamine agonist challenge is determined by the nature of prior dopamine receptor stimulation (priming) in 6-hydroxydopamine lesioned rats

Jonathan D. Drake, Laura N. Kibuuka, Kroum D. Dimitrov, Alexia E. Pollack *

Department of Biology, University of Massachusetts-Boston, United States

ARTICLE INFO

Article history:
Received 18 September 2012
Received in revised form 9 January 2013
Accepted 16 January 2013
Available online 28 January 2013

Keywords:
Behavioral sensitization
Abnormal involuntary movements (AIM)
6-Hydroxydopamine
D1 dopamine
D2 dopamine

ABSTRACT

Rats with unilateral 6-hydroxydopamine (6-OHDA) lesions show sensitization (priming) of rotational behavior upon repeated treatment with dopamine agonists. To relate these observations to dyskinesias exhibited by Parkinson's Disease patients, we assessed abnormal involuntary movements (AIMs) in 6-OHDA rats, which were primed with three injections of either the following: water, D1/D2 agonist apomorphine (Apo) (0.5 mg/kg), D1 agonist SKF38393 (SKF) (10 mg/kg) or D2 agonist quinpirole (Quin) (1 or 2.5 mg/kg). The rats were challenged one week later with Quin (0.25 mg/kg). Axial, limb, orolingual, locomotor, and grooming AIMs were scored (0–4) every 5 min. Priming with water did not produce AIMs. Priming with Quin (1 mg/kg) produced axial and locomotor AIMs, while priming with Apo, SKF or Quin (2.5 mg/kg) produced axial, locomotor, limb, and grooming AIMs. The disparity in AIM profiles between Quin (1 mg/kg) and (2.5 mg/kg) was not the result of D1 receptor stimulation since there was little striatal Fos expression following the third priming injection with Quin (1 or 2.5 mg/kg) compared to following SKF, which led to robust striatal Fos expression. Challenge with Quin (0.25 mg/kg) essentially reproduced the categories of AIMs exhibited during priming, with no AIMs in water-primed 6-OHDA rats, mild, non-significant, axial and locomotor AIMs in Quin (1 and 2.5 mg/kg)-primed 6-OHDA rats, and axial, limb, locomotor, and grooming AIMs in Apo- and SKF-primed 6-OHDA rats. These data suggest that the types of AIMs expressed following challenge with Quin depend on the dopamine receptor subtype and dose of dopamine agonist used during priming.

1. Introduction

For Parkinson's disease (PD) patients undergoing pharmacological therapy, treatment with the dopamine precursor L-3,4-dihydroxyphenylalanine (L-dopa) eventually leads to the development of involuntary movements (dyskinesias), which limits its long-term usefulness (Hurley and Jenner, 2006). While the neurochemical bases of dyskinesias are not completely understood, they are thought to result from the effects of chronic dopamine agonist treatment in a dopamine-deprived striatum (Hurley and Jenner, 2006) as well as presynaptic mechanisms leading to elevated synaptic dopamine levels (Carta and Bezard, 2011). Studies of primate models of PD and human PD patients have suggested that two subtypes of dopamine receptors, D1 and D2, are differentially involved in the production of dyskinesias — with dose-dependent variations found in the types and intensities of dyskinesias produced following treatment with L-dopa, D1 or D2 agonists (Adler et al., 1997; Calon et al., 1995, 1999; Pearce et al., 1998; Rascol et al., 2000, 2006; Sethi et al., 1998; Smith et al., 2006).

Since its development several decades ago, the 6-hydroxydopamine (6-OHDA) rat model of PD has served as a valuable means to explore the consequences of dopamine depletion on motor behavior (Ungerstedt and Arbuthnott, 1970). In this model, rats receive a unilateral stereotaxic injection with the neurotoxin 6-OHDA to selectively destroy dopaminergic neurons, resulting in dopamine agonist-mediated motor behavior, in which the animals rotate contralateral to the dopamine-denervated striatum (Carey, 1991). Numerous studies have demonstrated that 6-OHDA rats treated with D1, D2, or D1/D2 dopamine agonists display a behavioral sensitization phenomenon known as "priming" or "reverse tolerance" such that repeated administration of the same dose of dopamine agonist produces contralateral rotational behavior of increasing magnitude (Asin et al., 1995; Carey, 1991; Gancher and Mayer, 1995; Paul et al., 1995; Pinheiro-Carrera et al., 1994; Pollack et al., 1997; Rouillard et al., 1987). As this priming effect is thought to be analogous to the development of dyskinesias in humans with PD (Carey, 1991), there is considerable interest in using 6-OHDA

Abbreviations: 6-OHDA, 6-hydroxydopamine; AIMs, abnormal involuntary movements; Apo, apomorphine; i.p., intraperitoneal; L-Dopa, L-3,4-dihydroxyphenylalanine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson's Disease; SKF, SKF38393; TH, tyrosine hydroxylase; Quin, quinpirole.

* Corresponding author at: Department of Biology, University of Massachusetts-Boston, 100 Morrissey Blvd., Boston, MA 02125, United States. Tel.: +1 617 287 6618; fax: +1 617 287 6650.
E-mail address: alexia.pollack@umb.edu (A.E. Pollack).

0091-3057/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pbb.2013.01.014

rats as a means to explore how to eliminate/minimize the motor side-effects associated with the pharmacologic treatment of PD.

Despite the success of the 6-OHDA rat model, questions have been raised regarding the use of rotational behavior as the sole means of studying dopamine-mediated motor responses and this sensitization phenomenon (Nutt, 1990). This criticism is apt considering the rich repertoire of abnormal motor behaviors displayed by PD patients, such as tremor, rigidity, akinesia, postural instability, and gait disturbance (Nutt, 1990). In response to this criticism, several categories of dopamine agonist-induced abnormal involuntary movements (AIMs) have been described and characterized in 6-OHDA rats (Lee et al., 2000; Lundblad et al., 2002; Winkler et al., 2002). AIMs in 6-OHDA rats were manifested as axial twisting or bending of the spine, limb tremors, purposeless orolingual movements, and repetitive locomotor activity — all directed contralateral to the denervated striatum (Lee et al., 2000; Lundblad et al., 2002; Winkler et al., 2002). AIMs display patterns of sensitization resembling the priming of rotational behavior (Lee et al., 2000; Lundblad et al., 2002; Winkler et al., 2002), and several groups have reported that treatment with D1/D2, D1 and D2 dopamine agonists leads to different intensities and patterns of AIM behaviors in 6-OHDA rats (Carta et al., 2008a; Delfino et al., 2004; Lundblad et al., 2002; Mela et al., 2012; Taylor et al., 2005).

In this study, we examined the occurrence of AIMs in 6-OHDA rats using a priming paradigm we had previously established for assessing behavioral sensitization of D2-mediated rotational behavior (Pollack et al., 1997; Pollack and Thomas, 2010; Pollack and Yates, 1999). A protocol of three priming injections of either D1/D2 agonist apomorphine (Apo, 0.5 mg/kg), D1 agonist SKF38393 (SKF, 10 mg/kg) or D2 agonist quinpirole (Quin, 1 or 2.5 mg/kg), spaced 3–6 days apart, was followed by challenge with a low dose of Quin (0.25 mg/kg) one week later. Our prior results showed that priming with Apo, SKF or Quin permitted challenge with this low, behaviorally ineffective dose of Quin (0.25 mg/kg) to produce robust contralateral rotations (Pollack et al., 1997; Pollack and Thomas, 2010; Pollack and Yates, 1999).

The purpose of the current study was to test whether AIM behaviors, like contralateral rotational behavior, would display sensitization across the three priming injections with D1/D2, D1 or D2 agonists, and to ascertain whether the occurrence of AIMs would be enabled following challenge with a low dose of D2 agonist Quin (0.25 mg/kg), as we have observed for D2-mediated contralateral rotational behaviors. We also sought to determine if the categories and patterns of AIM activity would be expressed differentially according to the receptor subtype selectivity of the dopamine agonist used during priming, and if such patterns of AIM expression would carry over to the low-dose Quin challenge. Lastly, to determine whether any differences in AIMs observed following priming with Quin (1 versus 2.5 mg/kg) were due to activation of D1 receptors by high dose Quin (2.5 mg/kg), separate groups of 6-OHDA rats were primed with D1 or D2 agonists, and striatal Fos-like immunoreactivity was observed 2h following the third priming injection. We reasoned that if high dose Quin (2.5 mg/kg) exerted any stimulatory effect at D1 receptors, then striatal Fos expression would be induced in these animals immediately after the third priming injection, since D1 receptor activation leads to robust striatal Fos expression in 6-OHDA rats (Pollack and Thomas, 2010).

2. Methods

2.1. Subjects and drug treatments

Male, Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA) weighing 270–300 g were anesthetized with ketamine (50 mg/kg, i.p.):xylazine (6 mg/kg, i.p.) (1:1), and pretreated with desmethylimipramine (25 mg/kg, i.p.), to prevent damage to noradrenergic neurons. A stereotaxic injection of 4 μl of a saline solution containing 6-OHDA-HBr (3 mg/ml) and ascorbic acid (2 mg/ml) was administered into the left medial forebrain bundle (coordinates from bregma: −3.7 AP, +1.6 ML, −8.8 DV; Paxinos and Watson, 1986) at a rate of 1 μl/min, as described previously (Pollack et al., 1997). Following surgery, the animals were kept warm until they recovered from anesthesia, and then returned to the animal facility after which no special care was required. The animals were treated according to the University of Massachusetts Policies and Procedures, and the National Institute of Health Guide for Care and Use of Laboratory Animals. All efforts were made to minimize animal suffering and to reduce the number of animals used in experiments.

Beginning three weeks after 6-OHDA injection, the rats were given three priming injections (i.p.), at 3–6 day intervals, with either the following: water (N = 5), D1/D2 agonist apomorphine (Apo; 0.5 mg/kg; N = 5), D1 agonist SKF38393 (SKF; 10 mg/kg; N = 6), or D2 agonist quinpirole (Quin; 1 mg/kg; N = 7 or 2.5 mg/kg; N = 5). Seven days after the third priming injection, 6-OHDA rats were challenged with Quin (0.25 mg/kg).

An additional experiment to measure striatal Fos expression immediately following the third priming injection was conducted using 6-OHDA rats primed with water (N = 3), SKF (10 mg/kg, N = 6), Quin (1 mg/kg; N = 4) or Quin (2.5 mg/kg; N = 5) in the same manner as above, but without subsequent challenge with Quin (0.25 mg/kg). Instead, these animals were perfused with fixative 2 h following the third priming injection in order to stain for striatal Fos-like immunoreactivity as described under Immunohistochemistry. All drugs were obtained from Sigma (St. Louis, MO), and were dissolved in water.

2.2. Assessment of rotational behavior and AIMs

Rotational behavior was recorded using an automated rotometer (AccuScan Instruments Inc., Columbus, OH). The rats were placed in clear cylinders with flat bottoms and tethered to top-mounted sensors, which were connected to a PC running a Rotomax program, which counted 360° contralateral rotations. Following each priming or challenge injection, the number of 360° contralateral rotations was counted in 5-min bins for a total of 90 min (priming) or 110 min (Quin challenge). Rotational data are expressed as the mean (±SEM) total number of 360° contralateral rotations representing activity over the entire 90- (priming) or 110-min (Quin challenge) session. Only 6-OHDA rats, which displayed significant levels of contralateral rotations (≥200 contralateral rotations/90 min) after at least one of the priming injections, were included in the experiment; 79% of 6-OHDA rats tested made this cut-off. Water-primed 6-OHDA rats were assessed for dopamine-depletion by staining post-mortem fixed brain sections for tyrosine hydroxylase (TH) immunoreactivity, as described under Immunohistochemistry.

Scoring of AIMs, by an observer blind to the drug treatments (J.D.D.), occurred concomitantly with the collection of rotational data. Following priming injections, AIMs were scored every 5 min (observation of 1-min), over a total time period of 90 min for priming, and for 110 min for Quin challenge. Categorization of AIMs and criteria for their semi-quantitative measurement were based on previously published methodologies (Lee et al., 2000; Lundblad et al., 2002; Winkler et al., 2002) with the following modifications. First, contralateral grooming behavior was included along with axial, limb, orolingual, and locomotor categories of AIMs. Grooming was scored as AIMs when directed toward the contralateral forepaw, forelimb, hindquarter, or hindpaw. Second, as grooming behavior necessarily includes orolingual movements, and often includes repetitive limb movements, only orolingual activity and dyskinetic limb movements that were unambiguously separated from grooming behavior were scored distinctly as orolingual and limb AIMs, respectively. Finally, axial AIMs were scored while rats were in either bipedal or quadrupedal positions.

The rating scale, adapted from Lee et al. (2000), was used for rating axial, limb, orolingual, locomotor, and grooming AIMs: 0 = behavior absent; 1 = low intensity behavior occurring less than half of the observation time; 2 = intermediate intensity behavior occurring greater than