Neuropharmacology 109 (2016) 69–77

Contents lists available at ScienceDirect

Neuropharmacology

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

Multi-facetted impulsivity following nigral degeneration and dopamine replacement therapy

Michel Engeln [a, b, 1], Solène Ansquer [c, d, e, 1], Emilie Dugast [d, e, f], Erwan Bezard [a, b], David Belin [f, g, h, 2], Pierre-Olivier Fernagut [a, b, *, 2]

[a] Univ. de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, F-33000, Bordeaux, France
[b] CNRS, Institut des Maladies Neurodégénératives, UMR 5293, F-33000, Bordeaux, France
[c] Service de neurologie de l'hôpital de Poitiers, F-86021, Poitiers, France
[d] Université de Poitiers, F-86000, Poitiers, France
[e] CIC INSERM 1402, CHU de Poitiers, Poitiers, France
[f] INSERM U1084 Laboratoire de Neurosciences Experimentales et Cliniques, F-86000, Poitiers, France
[g] Department of Pharmacology, University of Cambridge, CB2 1PD, Cambridge, UK
[h] Behavioural and Clinical Neuroscience Institute of the University of Cambridge, CB2 3ED, Cambridge, UK

ARTICLE INFO

Article history:
Received 17 February 2016
Received in revised form
17 May 2016
Accepted 19 May 2016
Available online 20 May 2016

Keywords:
Parkinson
Impulsivity
Alpha-synuclein
Pramipexole
Substantia nigra

ABSTRACT

Impulse control disorders (ICDs) are debilitating side effects of dopamine replacement therapy (DRT) in Parkinson's disease (PD) that severely affect the quality of life of patients. While DRT, the pattern and extent of neurodegeneration, and prodromic factors of vulnerability (e.g. impulsivity) have all been hypothesized to play a role in the development of ICDs, their respective, and potentially interacting, contributions remain to be established. High impulsive (HI), Intermediate (Int) or low impulsive (LI) rats were identified based on their performance in both a differential reinforcement of low rate of responding (DRL) and a fixed consecutive number (FCN) schedules, that operationalize two independent facets of impulsivity, waiting and action inhibition (motor impulsivity). We investigated whether high impulsivity trait influenced the progressive development of a parkinsonian state induced by viral-mediated over-expression of α-synuclein, and whether impulsivity trait and nigrostriatal neurodegeneration independently or jointly influenced the effects of DRT on impulse control. α-synuclein-induced nigrostriatal neurodegeneration increased both waiting and motor impulsivity. The D2/D3 dopamine receptor agonist pramipexole exacerbated motor impulsivity more than waiting. However, the pramipexole-induced increase in waiting impulsivity observed in both sham and lesioned rats, was more pronounced in HI lesioned rats, which displayed a restricted α-synuclein-induced dopaminergic neurodegeneration. Thus, a PD-like nigrostriatal lesion increases both motor and waiting impulsivity, but its interaction with a pre-existing impulsivity trait, which, at the cellular level, confers resilience to dopaminergic neurodegeneration, worsens the detrimental effects of D2/D3 dopamine receptor agonists on inhibitory control.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized both by degeneration of several neuronal populations, including dopaminergic neurons in the substantia nigra *pars compacta* (SNc), and presence of Lewy bodies, the anatomopathological hallmark containing aggregated α-synuclein. Dopamine replacement therapy (DRT) is the first-line treatment for alleviating the motor symptoms of PD but triggers impulse control disorders (ICDs) in vulnerable individuals (Weintraub et al., 2010). ICDs include behaviors such as pathological gambling, hypersexuality, binge eating or compulsive shopping, which impinge on the quality of life of the patients (Voon et al., 2009). The factors contributing to the development of these debilitating side effects remain poorly known. If dopamine overdose may account for some

* Corresponding author. CNRS UMR 5293, Institute of Neurodegenerative Diseases, Université de Bordeaux, 146 rue Léo Saignat, 33076, Bordeaux cedex, France.
E-mail address: pierre-olivier.fernagut@u-bordeaux.fr (P.-O. Fernagut).
[1] ME and SA contributed equally.
[2] DB and POF contributed equally.

http://dx.doi.org/10.1016/j.neuropharm.2016.05.013

of the deleterious effects of DRT on cognitive processes, dopaminergic depletion and DRT by definition co-exist in all PD patients yet ICDs are only developed by a subset of them (Weintraub et al., 2010), suggesting a role for other factors, such as impulsivity. Indeed, contrasting with the parkinsonian personality usually described as rigid, introverted and slow tempered (Todes and Lees, 1985), novelty seeking, hypomania/extraverted personality, but also impulsivity have been linked to these compulsive behaviors in PD (Dagher and Robbins, 2009; Voon and Fox, 2007; Voon et al., 2011b). PD patients with ICDs display impairments in risk evaluation (Voon et al., 2011a), learning from outcomes (Piray et al., 2014; Voon et al., 2010a) and increased impulsivity (Voon et al., 2010b), alongside alterations of fronto-striatal and cortico-subcortical networks (for review (Tang and Strafella, 2012)).

Impulsivity is a multifaceted construct involving aspects of action inhibition (motor impulsivity) and waiting, both contributing to an inability to withhold prepotent, inappropriate, premature, responses (D'Amour-Horvat and Leyton, 2014; Dalley et al., 2008; Dalley and Roiser, 2012). Motor and waiting impulsivity are related to a dysfunctional dopaminergic modulation of cortico-striatal networks (Antonelli et al., 2013; Basar et al., 2010; D'Amour-Horvat and Leyton, 2014; Jentsch et al., 2014): while drugs enhancing dopamine transmission increase, and dopamine antagonists decrease, motor impulsivity, the opposite modulation is found for waiting impulsivity (reviewed in (D'Amour-Horvat and Leyton, 2014; Dalley et al., 2008; Dalley and Roiser, 2012)). Thus, DRT increasing dopamine signaling may exacerbate motor impulsivity, while dopaminergic cell-loss would decrease dopamine levels and increase waiting impulsivity. Such influences of pharmacological manipulations of dopamine transmission may be biased in PD by the asymmetry in denervation between the relatively spared mesocorticolimbic network and the severely damaged nigrostriatal pathway. Consequently, DRT may induce a dopaminergic overdose of the nucleus accumbens and frontal cortex that may increase impulsivity (Cools et al., 2003; Gotham et al., 1988) in a state-dependent manner (Caprioli et al., 2013).

We hypothesized that baseline individual differences in impulse control may influence the effects of DRT on impulse control after nigrostriatal degeneration. To this end, we performed a longitudinal study investigating the respective, and interacting, contributions of premorbid impulsivity trait, progressive nigrostriatal dopaminergic neurodegeneration and DRT to the development of impulse control deficits in rats with viral-mediated overexpression of α-synuclein. We measured the influence of the bilateral nigrostriatal lesion and DRT on inhibitory control of rats displaying high or low levels of motor and waiting impulsivity as assessed by fixed consecutive number (FCN) and differential reinforcement of low rate of responding (DRL) schedules (Jentsch et al., 2014; Rivalan et al., 2007).

2. Materials and methods

2.1. Subjects

Forty-four male Sprague Dawley rats (Janvier, France, 200–225 g at the beginning of the experiment) were housed in pairs on a reversed 12 h cycle. After 5 days of habituation, they were food restricted to 90% of their free feeding weight during behavioral testing. Water was available *ad libitum*. Experiments were approved by the Institutional Animal Care and Use Committee of Bordeaux (CE50, license # 5012099-A) and performed under the European Union directive (2010/63/EU) on the protection of animals used for scientific purposes.

2.2. Behavioral procedures

Rats were challenged in two different tasks to assess individual ability both to inhibit prepotent responses, or wait (DRL), and maintain ongoing responses (FCN). In the DRL schedule, rats must wait for a specific time prior to responding on a manipulandum to obtain a reward: they have to inhibit a prepotent response. In the FCN schedule, rats must maintain a response on a first manipulandum for a fixed number of times before responding on a second one to obtain a reward. They therefore must not interrupt an ongoing instrumental response. Inabilities to wait in the DRL or to maintain the ongoing response chain in the FCN represent waiting and action impulsivity.

The sequences of training for each task were counter-balanced to avoid any carry-over effect. Results from preliminary experiments demonstrated that the acquisition and performance in the DRL and FCN tasks were not influenced by the nature of the instrumental response. We therefore used lever presses and nosepokes as instrumental responses in the DRL and FCN task, respectively. Experiments were performed in operant chambers (DRL: 29.5 × 32.5 × 23.5 cm; FCN: 24 × 24 × 26 cm, Med Associates, USA) enclosed in sound-attenuating ventilated cubicles. Before being randomly assigned to a FCN-DRL or DRL-FCN group (See Suppl Fig. 1 for experimental design), rats were subjected to one session of magazine training, followed by three successive fixed-ratio 1 schedule sessions (100 lever presses in 45 min) prior to DRL and FCN training (45-min daily sessions).

2.2.1. Differential reinforcement of low rate of responding 20s (DRL-20s)

Operant chambers were equipped with two levers located on the right and left side of a food tray. Above each lever was a white cue light, and a white house-light was on the opposite wall. The procedure was adapted from (Fletcher, 1995). Rats obtained a pellet if at least 5s had elapsed since their previous response on the reinforced lever (DRL-5s). When the subject reached >80% of rewards, the behavioral requirement was incremented to DRL-10s, -15s and -20s. All rats were tested under DRL-20s for 15 days before surgery. Premature responses reset the "waiting period" and were not rewarded. The first response was always reinforced. The following parameters were recorded: number of responses on the active/inactive levers, number of earned reinforcers, efficiency ([number of reinforcers/number of responses] × 100), inter-response time, number of food tray nosepokes, reward collection latency and seeking behavior (number of visits to the magazine/number of earned reinforcers).

2.2.2. Fixed consecutive number schedules 16 (FCN16)

Operant chambers were equipped with a house-light and 2 holes in which rats could make nosepokes at the right and left side of a food tray located on the front wall. The procedure was adapted from (Evenden, 1998; Rivalan et al., 2007). Rats had to respond at least once (FCN1), three (FCN3), six (FCN6), eight (FCN8), twelve (FCN12) or sixteen (FCN16) times on the chain poke followed by a response in the reinforced hole to earn a pellet. Rats reached the following stage if they performed >80% successful trials during the session. Rats were tested under FCN16 over 15 days before surgery. The following parameters were recorded: number of responses on chain/reinforcement pokes, number of earned pellets, number of chains (number of responses on the chain poke before responding on the reinforcement poke), efficiency ([number of reinforcement poke/number of reward earned] × 100) and average chain length.