Parkinsonism and Related Disorders xxx (2015) 1–5

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Molecular imaging and neural networks in impulse control disorders in Parkinson's disease

I. Aracil-Bolaños [a, b, c], A.P. Strafella [a, b, c, *]

[a] Morton and Gloria Shulman Movement Disorder Unit & Edmond J. Safra Program in Parkinson Disease, Toronto Western Hospital, UHN, University of Toronto, Ontario, Canada
[b] Research Imaging Centre, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada
[c] Division of Brain, Imaging and Behaviour – Systems Neuroscience, Toronto Western Research Institute, UHN, University of Toronto, Ontario, Canada

ARTICLE INFO

Article history:
Received 24 July 2015
Received in revised form
2 August 2015
Accepted 5 August 2015

Keywords:
Parkinson's disease
Impulse control disorders
Molecular imaging

ABSTRACT

Impulse control disorders (ICDs) may arise in Parkinson's disease (PD) in relation to the use of dopamine agonists (DA). A dysfunction of reward circuits is considered the main underlying mechanism. Neuroimaging has been largely used in this setting to understand the structure of the reward system and its abnormalities brought by exogenous stimulation in PD. Dopaminergic changes, such as increased dopamine release, reduced dopamine transporter activity and other changes, have been shown to be a consistent feature of ICDs in PD. Beyond the striatum, alterations of prefrontal cortical function may also impact an individuals' propensity for impulsivity. Neuroimaging is advancing our knowledge of the mechanisms involved in the development of these behavioral addictions. An increased understanding of these disorders may lead to the discovery of new therapeutic targets, or the identification of risk factors for the development of these disorders.

1. Introduction

Impulse control disorders (ICDs) in Parkinson's disease (PD) offer an unique window into the mechanisms of motivation, reward and addiction in the general population. All these behavioral traits are closely linked to the dopaminergic system. In PD patients, the progressive failure of the dopaminergic network and related motor symptoms (i.e. bradykinesia, rigidity and resting tremor) are treated with replacement therapies such as levodopa or dopamine agonists (DA). Approximately 14% of PD patients treated with DA may develop ICDs [1], however this incidence can be much higher (over 20%) according other reports [2]. Thus, the study of these disorders provides an opportunity for evaluating the impact of dopaminergic degeneration and therapeutic replacement on critical aspects of human behavior.

ICDs are considered behavioral addictions because of their similarities to substance abuse. Both disorders show common features like the experience of withdrawal symptoms and/or the development of tolerance [3]. The most common presentations in PD are pathological gambling, compulsive sexual behavior, compulsive buying and binge eating. Studies assessing possible triggers have found relations with traits such as higher novelty-seeking and impulsivity, but also anxiety and depression [4]. The main predisposing factor, however, has been consistently shown to be the exposure to dopaminergic therapies. It has been observed that drug-naive PD patients show similar proportions of ICDs to healthy subjects [5].

As a result of these observations, an underlying hyperdopaminergic state has been proposed as the cause of ICDs in Parkinson's disease. It is well known that the disease preferentially affects the dorsal (motor) striatum compared to ventral structures [6]. Therefore, dopaminergic treatment of the relatively intact ventral striatum could result in an uncontrolled activation of the reward system. On this regard, it is interesting to note some similarities with the levodopa-induced dyskinesias (LIDs). In a comprehensive review, Voon et al. [7] assessed the overlapping and common biological mechanisms of motor and behavioral complications in PD. They proposed that LIDs and behavioral disorders (i.e. ICDs, punding, and dopamine dysregulation syndrome) may be part of a continuum mediated by similar pathophysiological

* Corresponding author. Toronto Western Hospital and Institute, UHN, CAMH-Research Imaging Centre, University of Toronto, Toronto, Ontario, Canada.
E-mail addresses: antonio.strafella@uhn.ca, antonio.strafella@camh.ca (A.P. Strafella).

http://dx.doi.org/10.1016/j.parkreldis.2015.08.003
1353-8020/

mechanisms acting through different basal ganglia loops. In fact, levodopa treatment may result sometimes in a dopamine dysregulation syndrome, in which patients show an increased appetite for dopaminergic medications and subsequently increase levodopa intake far beyond their prescribed dosage. However, these patients generally do not develop the classic traits of ICDs [8] observed with DA, but concurrent levodopa therapy may increase the incidence of these behavioral complications [2]. While ICDs are generally associated with PD, it is also important to remember that these may occur in other clinical conditions, like restless leg syndrome [9] and hormone replacing therapies in pituitary adenomas [10]. In these instances, DA doses required to develop ICDs were uniformly lower than in PD. Thus, it is hypothesised that the continuous stimulation of DA in a relatively intact reward system may lead to profound consequences in the response to pleasurable stimuli [11].

Research in this field has to account for the complexity of a poorly understood neurobiological system. Molecular imaging is helping to delineate its structure as well as the dynamic interactions between different components involving neurotransmitters, transporters and receptors. ICDs are a dynamic phenomenon where the effects of the neurodegenerative process in PD along with compensatory changes associated with dopamine replacement therapy and genetic vulnerabilities all have to be considered. The unraveling of all these interactions has to be accounted for in this evolving landscape.

In this review, we will describe the neural systems that are being currently targeted and the neurobiological substrate responsible for these findings, trying to outline the future directions in molecular imaging in ICDs.

2. Molecular imaging in ICD

The structural networks underlying impulse control disorders are linked to the so called reward system. Its main components (nucleus accumbens, amygdala, hippocampus, orbitofrontal and anterior cingulate cortices) are all part of the mesocorticolimbic pathway. This system is mainly regulated by dopamine and, in healthy subjects, articulates the salience of external stimuli; a thorough review on its functioning is provided by Probst et al. [12]. In brief, standard pleasurable stimuli (e.g. food, etc.) provoke a tonic dopamine response in the outer shell of the nucleus accumbens, but repeated stimuli shift this response to its core, inducing habituation. In the brainstem, dopamine autoreceptors located in substantia nigra provide an important feedback in order to regulate synaptic dopamine concentrations. As for the top-down control, the orbitofrontal and anterior cingulate cortices are responsible for weighing the importance of the reward and linking it to an appropriate response. Finally, the prefrontal cortex inhibits reward-directed response exerting a balancing effect on the system. With all these elements working correctly, a person is able to successfully adapt their behavior in a dynamic environment. In individuals suffering from addiction, however, substantial changes can occur to these structures. Tonic dopaminergic signals from the midbrain assign increased salience to addictive stimuli and, after repeated exposure, the process is shifted to dorsal striatal and sensorimotor structures, turning the stimulus–pleasure association into a stimulus-action directed towards the addictive input [13]. Finally, top-down control from the cortex seems to be impaired as well, with less activation of the prefrontal cortex.

Molecular imaging in DA-treated PD patients has largely focused on dopamine and its receptors, the autoregulatory mechanisms and the inhibitory inputs from cortical structures. Table 1 summarizes the main observations from different studies and the proposed physiopathological mechanisms. [11C] raclopride is a D2/D3 antagonist radiotracer that selectively binds to these dopaminergic receptors and competes with endogenous dopamine. This radiotracer has provided a wealth of information regarding corticostriatal control of dopamine release and tested the hyper-dopaminergic response in subjects exposed to appetitive stimuli.

Studies in non-PD subjects with ICDs have investigated whether higher dopamine levels were a feature of ICDs. Volkow et al. [14] scanned a group of such patients using [11C] raclopride and found decreased binding compared to controls. In PD, Steeves et al. [15] used a similar approach while exposing PD-ICD patients to a gambling paradigm in which gains and losses were represented. All of the subjects had been previously treated with DA and had developed pathological gambling (PG). In these patients, there was an increased dopamine release in the ventral striatum during the act of gambling compared to non-ICD PD patients. O'Sullivan et al. [16] found a similar decrease in [11C] raclopride binding in response to stimulating cues in PD-ICD patients compared to controls. Finally, a recent study by Wu et al. [17] tried to assess differences between single and multiple ICD patients regarding striatal dopamine release, using [11C] raclopride. No differences were found, but the same pattern of increased striatal dopamine release was observed in single and multiple ICD patients compared to non-ICD PD.

There has been a growing interest in imaging the dopamine D3 receptor because of its relation with mood, motivation and reward. Hypoactivation of this receptor has been linked to anhedonia and depression [18]. Recently, a few PET studies have been using [11C]-(+)-PHNO, a radiotracer that acts as a dopamine agonist and has increased affinity for D3 over D2 receptors. Boileau et al. [19] conducted an investigation contrasting [11C] raclopride distribution with that of [11C]-(+)-PHNO in drug naive PD patients, compared to healthy controls. The study confirmed that the D3 receptor is preferentially ventral-striatum bound, consistent with its proposed limbic role. Using the same radiotracer, a study of PG in the general population provided some interesting observations [20]. In particular, D3 binding in the substantia nigra of PG subjects substantially correlated both with gambling severity and impulsivity trait, but no significant findings were observed in the striatum. Subsequently, Payer et al. [21] studied PD-ICD patients using [11C]-(+)-PHNO and showed that D3 activity was 20% lower in the ventral striatum in these patients compared to PD controls. In sum, these reports suggest that higher levels of endogenous dopamine release and possibly lower D2/D3 receptor density may be a classic feature of behavioral forms of addiction.

The dopamine transporter modulates the availability of dopamine in the synaptic cleft by controlling its clearance. In PD, the dopamine transporter (DAT) is downregulated in order to increase available dopamine in the synapse [22]. In the general population, genetic studies have pointed to a relationship between polymorphisms in the DAT gene and binge eating [23]. In ICD-PD patients, Cilia et al. [24] used a DAT-tracer (123I-FP-CIT) to scan dopamine transporter density. Tracer binding was lower for ICD-PD patients in ventral striatum, indicating a probable functional DAT downregulation. Another possible explanation is that the lower DAT expression may not be a dynamical adjustment, but rather a pre-existing trait that may determine ICD vulnerability. In support of this hypothesis, Vriend et al. [25] tried to weigh DAT expression as a pre-existing condition in ICDs. The authors retrospectively studied a group of drug-naive PD patients and the emergence of ICDs with dopamine replacement therapies. 123I-FP-CIT scans were obtained at baseline, and the DAT binding was compared with the incidence of ICDs in a 31-month follow-up. Interestingly, the group of patients who developed ICDs consistently showed lower DAT density in the ventral striatum.

As already mentioned above, dopamine exerts its influence on a

Please cite this article in press as: I. Aracil-Bolaños, A.P. Strafella, Molecular imaging and neural networks in impulse control disorders in Parkinson's disease, Parkinsonism and Related Disorders (2015), http://dx.doi.org/10.1016/j.parkreldis.2015.08.003