Neuroscience and Biobehavioral Reviews 37 (2013) 1069–1084

Contents lists available at SciVerse ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review

Neuromodulation in Tourette syndrome: Dopamine and beyond

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ARTICLE INFO

Article history:
Received 29 June 2012
Received in revised form
28 September 2012
Accepted 8 October 2012

Keywords:
Tourette syndrome
Neurochemistry
Dopamine, CSTC

ABSTRACT

Almost since the beginning of research on Tourette syndrome (TS), tics have been linked to a dysfunction of the dopamine (DA) system. At first, this assumption was mainly based on clinical findings of DA antagonists being the most effective drug in treating tics, but in recent years nuclear imaging has enabled a much deeper understanding of DA neurotransmission in TS. Based on the findings of various PET and SPECT studies the first part of the review discusses four hypotheses on DA dysfunctions in TS: (i) DA hyperinnervation, (ii) supersensitive DA receptors, (iii) pre-synaptic DA abnormality and (iv) DA tonic-phasic dysfunction. According to the latter hypothesis, reduced levels of tonic DA in the extracellular space lead to higher concentrations of DA in the axon terminal and an increase of stimulus-dependent DA release. The second part of the review addresses the modulating role of DA in some major clinical features of TS, like the exacerbation with stress or infection and the association with deficient sensorimotor gating.

Contents

1. Introduction

Tourette syndrome (TS) is a chronic tic disorder characterized by the presence of at least one phonic and several motor tics for more than one year with first-onset before the age of 18. Tics are sudden, rapid, non-rhythmic, recurrent and mainly involuntary behaviors. Typically the onset of first tic symptoms is between the age of four and eight years. Symptoms tend to be most severe around the age of 10–14. In most patients, tics improve or fully remit in late adolescence or early adulthood. Tics wax and wane over minutes, hours, weeks, months, and years in frequency, intensity, location and complexity both intra- and inter-individually. The reasons for these fluctuations are still unclear, but modulating effects of different context variables, such as psychosocial stress, anxiety, emotional tension and/or fatigue have been proposed (Lin et al., 2007).

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http://dx.doi.org/10.1016/j.neubiorev.2012.10.004

Table 1
Overview on PET and SPECT ligand studies (based on table in (Rickards, 2009)).

Study	Nuclide	N of TS patients; (Age)	Medication	Result	Author, year
DA receptor ligands					
Summary: Heterogeneous results: Increased as well as decreased receptor binding in TS or no differences between TS and control group reported					
PET	[18F]Dopa-analog of L-DOPA, used to examine presynaptic dopaminergic activity	10 (age range: 18–48)	Majority of patients were medicated	No differences	(Turjanski et al., 1994)
PET	[18F]Dopa	11 (age range: 12–17)	3 treatment-naïve, others medication-free within 6 months before PET	Higher binding in the left striatum	(Ernst et al., 1999)
PET	[11C]Raclopride – D2 and D3 dopamine receptor antagonist	5 (age range: 18–48)	3 Treatment-naïve, 2 medication-free at least 3 months before PET	No differences	(Turjanski et al., 1994)
PET	[11C]Methylspiperone – D2 dopamine receptor antagonist	20 (age range:19–52)	All medication-free within 6 months before PET	Haloperidol pretreatment; Subgroup of four patients with elevated D2 binding (subgroup had higher vocal tic scores)	(Wong et al., 1997)
PET	[11C]Raclopride – presynaptic D2 and D3 dopamine receptor antagonist	7 (age range: 19–50)	2 Treatment-naïve, others medication-free within 6 months before PET	Baseline scans showed no difference; amphetamine challenge led to increased binding	(Singer et al., 2002)
PET	[18F]Fallypride – extrastriatal D2 and D3 dopamine receptors antagonist	6 (age range: 18–45)	Naïve to dopamine receptor-blocking medication	Widespread lower DA binding found	(Gilbert et al., 2006)
PET	[11C]FLB 457 – D2 and D3 dopamine receptor antagonist	8 (age range: 18–48)	All treatment-naïve	Decreased binding potentials bilaterally in cortical and subcortical regions outside the striatum	(Steeves et al., 2010)
PET	[3H] Dopamin	18 (mean age = 16.7)	Majority treatment-naïve or medication-free at least 2 weeks before PET	Lower uptake	(Rabey et al., 1995)
PET	Variety of ligands	14 (mean age = 29)	7 Treatment-naïve, 7 medication-free at least 6 months before PET	Increased DA binding in the left ventral striatum; changes in midbrain 5HT function; amphetamine challenge increased DA release	(Wong et al., 2008)
SPECT	[123I]IBZM – D2 dopamine receptors antagonist	15 (age range: 10–45)	4 Treatment-naïve, 7 medicated, 4 medication-free at least 3 months before SPECT	No difference; Subsample taking D2 blocking medications decreased binding in both the right and left basal ganglia	(George et al., 1994)
SPECT	[123I]IBZM – D2 dopamine receptors antagonist	10, 5 twin pairs (age range: 18–31)	All Medication-free for an extended period before SPECT	Strong "within-pair" concordance; Caudate D2 binding always higher in the more severely affected twin	(Wolf et al., 1996)
SPECT	[123I]IBZM – D2 dopamine receptors antagonist	17 (age range: 9–53)	10 Treatment-naïve, 7 medicated	Reduced binding in medicated patients compared to controls and unmedicated; no difference between unmedicated patients and controls	(Müller-Vahl et al., 2000b)
SPECT	[123I]IBZM – D2 dopamine receptors antagonist	10 (age range: 16–27)	5 Treatment-naïve, 5 medication-free at least 3 months before SPECT	No difference	(Hwang et al., 2008)
Serotonin type 2A (5HT2A) receptor ligand					
PET	[18F]Altanserin – binds to the 5HT2A receptor	20 (age range: 17-49)	10 medication-free at least 9 months before PET, 10 on medication	General up-regulation of 5HT systems; Increased 5HT2A binding in striatum	(Haugbøl et al., 2007)
Dopamine transporter (DAT) ligands					
Summary: Most PET/SPECT on DAT ligands showed higher binding in TS, especially in the striatum					
PET	[11C]MPH – binds to the DAT	33 (age range: 18–58)	Majority treatment-naïve or medication-free for years	No differences	(Albin et al., 2009)
SPECT	[123I]β-CIT – binds to the DAT	5 (age range: 20–40)	1 Treatment-naïve, 4 treatment-free for a mean of 5 years	Higher striatal binding	(Malison et al., 1995)
SPECT	[123I]β-CIT	10 (aged 25–51)	2 Treatment-naïve, 8 medication-free for at least 4 months before SPECT	No difference; Post hoc finding of reduced binding in midbrain and thalamus	(Heinz et al., 1998)
SPECT	[123I]β-CIT	12 (age range: 24–64)	6 Medication-free for at least 5 months, 6 medicated	Higher striatal binding	(Müller-Vahl et al., 2000a)