Short Report

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Amisulpride-induced acute akathisia in OCD: an example of dysfunctional dopamine–serotonin interactions?

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Abstract

We report about a clinical observation in a well-characterized group of patients with obsessive–compulsive disorder (OCD) during an experimental medicine study in which a single dose of amisulpride (a selective $D_{2/3}$ antagonist) was administered. Almost half of the OCD patients, in particular those with less severe obsessive–compulsive symptoms, experienced acute akathisia in response to the amisulpride challenge. This unexpectedly high incidence of akathisia in the selective serotonin reuptake inhibitor (SSRI)-treated patients with OCD suggests that individual differences in dopamine–serotonin interactions underlie the clinical heterogeneity of OCD, and may thus explain the insufficiency of SSRI monotherapy in those patients not experiencing a satisfactory outcome in symptom reduction. We further speculate about the neuropathology possibly underlying this clinical observation and outline a testable hypothesis for future molecular imaging studies.

Keywords

Akathisia, antipsychotics, dopamine, obsessive–compulsive disorder, serotonin

Introduction

In approximately one-third of patients with obsessive–compulsive disorder (OCD), standard treatment with selective serotonin reuptake inhibitors (SSRIs) fails to bring satisfactory relief of obsessive–compulsive symptoms (Fineberg and Gale, 2005). Atypical antipsychotics can augment the effectiveness of SSRIs in such patients, but the mechanism underlying this synergetic effect is elusive (Fineberg et al., 2006). In an experimental medicine study, we observed an unexpectedly high incidence of episodes of akathisia in patients with OCD following a single dose of the atypical antipsychotic amisulpride in addition to their standard treatment with SSRIs. Akathisia is a movement disorder characterized by inner restlessness and the inability to sit or stand still. It is predominantly evoked by antipsychotic drugs (Poyurovsky, 2010), and has been associated in animal models with reductions in subcortical dopamine levels (Sachdev and Brüne, 2000). However, chronic SSRI treatment can in some cases provoke the development of extrapyramidal syndromes, including akathisia (Chouinard and Sultan, 1992; Koliscak and Makela, 2009). The heightened incidence of akathisia in our SSRI-treated OCD patients following a single dose of amisulpride may provide a clue to a better understanding of OCD neuropathology and give insight into the efficacy of antipsychotic medication in refractory cases of OCD.

Methods and results

As part of an experimental medicine study (NCT00471588) investigating the effects of dopamine $D_{2/3}$ receptor agonist and antagonist drugs in healthy volunteers and patients with addictive and obsessive–compulsive disorders, we studied a group of 22 patients with OCD. These patients were recruited by referral from a specialist NHS clinic for OCD, at the Queen Elizabeth II Hospital, Welwyn Garden City, UK, as well as through media advertisements and via support websites. The study was approved by the Cambridge Research Ethics Committee and all participants provided written informed consent prior to study enrolment.

Out of the 22 patients with OCD, 20 were being successfully treated with SSRIs at conventional doses, while the remaining two had no pre-medication. An experimental challenge with a single dose of amisulpride (400 mg) evoked in eight of the 20 SSRI-treated OCD patients a syndrome of inner restlessness, agitation, accompanied by feelings of anxiety, irritability, panic attacks, or aggression, thus satisfying the subjective criteria for akathisia. Two of these eight patients also reported aggravation of their OCD symptoms. The adverse reactions emerged at a mean of 6.2 h (±2.1 SD)

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after the amisulpride challenge, and persisted for a mean of 25 h (±14.1 SD). The subjective experience was so distressing that four of the eight affected patients withdrew from the study.

Post-hoc analysis showed that those OCD patients experiencing akathisia symptoms (OCD-A) had less severe obsessive–compulsive symptoms on the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) (Goodman et al., 1989) (mean total score: 17.1 ± 6.8 SD) compared with the OCD patients without akathisia (OCD-N) (mean 24.8 ± 6.8 SD) ($F_{1,20} = 6.42$, $p = 0.020$). Prior to drug administration, we had observed differences in performance in a test of probabilistic learning between these two OCD subgroups. The OCD-A patients, as defined post hoc, showed normal task performance, whereas the OCD-N subgroup exhibited over-sensitivity to negative feedback ($F_{1,20} = 5.32$, $p = 0.032$). Similar over-sensitivity to negative feedback in the learning task also occurs in healthy volunteers after SSRI challenge with 30 mg citalopram (Chamberlain et al., 2006), suggesting that there may be pre-existing differences in serotonergic neurotransmission between the OCD-A and OCD-N patients prior to the dopamine agonist challenge. Importantly, the two OCD subgroups did not significantly differ in any other respects, including depressive mood, demographics or personality variables, as shown in Table 1.

Discussion

We speculate that the significantly different response to amisulpride in the OCD subgroups reflects neurobiological differences in the coupling between dopamine and serotonin neurotransmission that are associated with OCD symptom severity. There is growing evidence derived from molecular imaging studies for the occurrence of significant differences in the availability of serotonin transporters (SERT) and dopamine transporters (DAT) in the brains of patients with OCD compared with age-matched healthy volunteers. For example, the availability of SERT binding sites labelled with [^{11}C]-DASB is significantly reduced in medication-free OCD patients, to an extent proportional to the patients' OCD symptom severity (Reimold et al., 2007). SSRIs are the standard treatment for OCD (Bandelow et al., 2008). Prolonged SSRI treatment has been shown to block SERT by 37–50%, and concomitantly increase DAT availability by 16–40%, both in OCD patients (Pogarell et al., 2005) and healthy volunteers (Kugaya et al., 2003). It is likely that the SSRI-induced potentiation of DAT in patients with OCD enhances the reuptake of dopamine in the striatum, thus attenuating dopamine signalling. Corroborating the notion of abnormal dopamine transmission in patients with OCD, it has been reported that $D_{2/3}$ receptor availability in the caudate is

Table 1. Demographic, clinical and baseline personality measures for patients with obsessive–compulsive disorder (OCD) who developed akathisia symptoms following a single dose of 400 mg amisulpride ($n = 8$) and OCD patients who did not experience symptoms of akathisia ($n = 14$)

	OCD patients				
	Without Akathisia	With Akathisia	*F*	df	*p*
Age (years)	37.1 (±8.8)	33.8 (±9.8)	0.70	1.20	0.413
IQ (NART[1])	107.4 (±8.6)	109.5 (±8.5)	0.30	1.20	0.592
Education (years)	11.9 (±1.7)	13.6 (±2.4)	3.82	1.20	0.065
Gender ratio (m: f)	10: 4	2: 6	Fisher's Exact Test		0.074
Depression (BDI-II[2] total score)	18.4 (±10.8)	11.1 (±9.7)	2.50	1.20	0.130
Age of onset OCD (years)	17.6 (±12.0)	18.4 (±8.7)	0.03	1.20	0.870
Duration of OCD (years)	19.6 (±11.2)	15.4 (±8.2)	0.86	1.20	0.365
Symptom severity (YBOCS[3])					
YBOCS Obsession score	12.1 (±3.2)	8.5 (±3.5)	6.21	1.20	0.022
YBOCS Compulsion score	12.6 (±3.8)	8.6 (±3.5)	6.02	1.20	0.023
Probabilistic reversal learning[4]					
Feedback sensitivity (probability)	0.82 (±0.50)	0.35 (±0.39)	5.32	1.20	0.032
Reversal errors (mean)	14.6 (±8.4)	7.9 (±5.9)	4.01	1.20	0.059
Perseverative errors (mean)	2.9 (±2.0)	4.1 (±4.0)	1.02	1.20	0.325
Sustained attention (CANTAB RVIP task)[5]					
Target sensitivity (A')	0.89 (±0.06)	0.92 (±0.05)	1.19	1.20	0.288
Response bias (B'')	0.97 (±0.03)	0.98 (±0.03)	0.45	1.18	0.512
Reaction time (mean, ms)	469 (±114)	488 (±154)	0.11	1.20	0.747
Response Inhibition (Stop-Signal task)[6]					
Reaction time successful Go trials (median, ms)	490.1 (±79.7)	483.8 (±28.1)	0.05	1.19	0.831
Reaction time unsuccessful Stop trials (median)	460.2 (±55.1)	469.3 (±29.3)	0.18	1.19	0.673
Stop-Signal Reaction Time (SSRT; ms)	251.4 (±43.5)	247.3 (±34.5)	0.05	1.19	0.827
Work & Social Adaptation Scale[7] (total score)	21.7 (±8.0)	21.6 (±7.7)	0.001	1.20	0.975

[1]National English Reading Test (Nelson, 1982), [2]Beck Depression Inventory Version 2 (Beck et al., 1996), [3]Yale-Brown Obsessive-Compulsive Scale (Goodman et al., 1989), [4]Probabilistic Reversal Learning Task (Swainson et al., 2000), [5]Rapid Visual Information Processing Task (Sahakian et al., 1988), [6]Stop-Signal Task (Aron et al., 2003), [7]Work and Social Adjustment Scale (Mundt et al., 2002).

reduced by 20% in untreated OCD patients compared with age-matched healthy volunteers (Denys et al., 2004). A single 400 mg dose of sulpiride (an antipsychotic similar to amisulpride) evokes a 40% occupancy of dopamine $D_{2/3}$ receptors in healthy volunteers (Mehta et al., 2008). It is thus plausible that the challenge with a similar dose of amisulpride in our experimental medicine study may have further compromised dopamine signalling, to an extent attaining a symptomatic threshold in those OCD patients who experienced akathisia.

Although the frequency is not as high as with the typical antipsychotics, the prevalence of extrapyramidal side effects caused by atypical antipsychotics is not negligible, and concomitant treatment with SSRIs seem to increase further the risk of these side effects (Chouinard and Sultan, 1992; Kumar and Sachdev, 2009). Akathisia has also been reported as a relatively rare side effect of SSRI monotherapy for depression (Koliscak and Makela, 2009), but was not evident in our OCD patients until the challenge with amisulpride. The synergistically evoked akathisia syndrome occurred in 40% of our SSRI-treated OCD sample, i.e. in the patient subgroup with less severe OCD symptom severity. This suggests that vulnerability to akathisia may emerge from individual differences in the functional coupling of dopamine and serotonin systems. This proposal finds support from observations of the anti-akathisia effects of low doses of mirtazapine, a non-selective $5HT_{2A}$ antagonist which also acts at adrenergic receptors (Poyurovsky et al., 2006). Given the role that serotonin plays in the psychopathology of OCD and the possible serotonin–dopamine imbalance predisposing for akathisia, careful assessment of extrapyramidal side effects is warranted for future pharmacological studies in patients with OCD.

In light of published molecular imaging results, we hypothesize that our patient subgroup with less severe OCD symptoms had greater SERT levels, and thus experienced greater potentiation of serotonin transmission by SSRI treatment than did the patients with more severe OCD symptoms. Insofar as the apparent up-regulation of DAT may conceivably be mediated by serotonin, patients with milder OCD symptoms would then have experienced a greater attenuation of dopamine neurotransmission, which became clinically apparent when challenged with amisulpride (selective $D_{2/3}$ antagonist). This scenario could imply that the benefits of SSRI treatment for OCD are obtained through partial disabling of dopamine transmission rather than by increased serotonin transmission per se. Furthermore, in SSRI-refractory OCD cases, where serotonin–dopamine coupling may be insufficient, the augmentation of SSRIs with antipsychotics may be necessary to sufficiently decrease dopamine neurotransmission and thereby bring about symptom relief. As these patients do not respond to SSRI monotherapy, they would lack the SSRI-induced increase in DAT, and therefore not be at risk of developing akathisia in response to antipsychotics. This suggests a testable hypothesis for explaining the clinical heterogeneity of OCD: de novo OCD patients with higher baseline SERT availability should experience the greatest reduction in DAT availability following SSRI treatment. Elucidation of the basis for the heterogeneous response to treatment would improve our understanding of OCD pathology, while providing the means for more rational treatment of individual patients.

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Conflict of interest

Karen Ersche is supported by the Medical Research Council (MRC). Ulrich Müller, Naomi Fineberg and Trevor Robbins have done consultancy work and/or received research grant support from various pharmaceutical companies, including GlaxoSmithKline. Kevin Craig is now full-time employed by P1vital Ltd. Edward Bullmore is currently part-time employed by GlaxoSmithKline Ltd and part-time by the University of Cambridge. Paul Cumming declares no conflict of interest.

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