The Role of Dopamine in Obsessive-Compulsive Disorder: Preclinical and Clinical Evidence

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Obsessive-compulsive disorder (OCD) is a frequent and chronic psychiatric disorder that has been linked closely to the serotonin system mainly because of the antiobsessional efficacy of selective serotonin reuptake inhibitors (SSRIs). A limitation of the serotonin hypothesis of OCD is that a substantial number of the patients with OCD show no significant improvement after an adequate trial with SSRIs. There is substantial evidence that these patients may benefit from addition of antipsychotics to their ongoing SSRI treatment, suggesting that dopamine also might play a role in the pathophysiology of OCD. In this review, the preclinical and clinical evidence on the role of dopamine in OCD is summarized. *(J Clin Psychiatry 2004;65[suppl 14]:11–17)*

Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder characterized by recurrent persistent thoughts (obsessions) and/or repetitive compulsory behaviors (compulsions). Over the past 2 decades, it has been suggested that OCD might be related to the functioning of brain serotonin systems. This hypothesis is based largely on the notion that selective serotonin reuptake inhibitors (SSRIs) possess antiobsessional efficacy.[1–3] There is now growing evidence that the dopamine system may be involved in OCD as well.[4–6] In this article, the preclinical and clinical evidence supporting the role for dopamine in the pathophysiology of OCD will be reviewed. Evidence for the involvement of dopamine in OCD is derived from studies using animal models of OCD and from clinical studies using neurochemical, pharmacologic, genetic, and neuroimaging strategies.

ANIMAL MODELS

Campbell and colleagues[7] have investigated the behavioral consequences of transgenic stimulation of a regional subpopulation of the dopamine neurons that express the dopamine-1 (D_1) receptor in the cortex and amygdala by generating mice that express an intracellular form of cholera toxin. The study suggests that chronic stimulation of these D_1-expressing neurons induces complex compulsive behavior that resembles symptoms of OCD in humans.[8] Although these mice were resistant to behavioral inhibition by a D_1 receptor antagonist and supersensitive to the D_2 receptor antagonist sulpiride,[9] Campbell and colleagues[10,11] suggested that chronic potentiation of cortical and limbic D_1-expressing neurons may cause obsessive-compulsive behaviors.

In another animal model, in which rats are chronically treated with the selective $D_{2/3}$ receptor agonist quinpirole, a ritual-like set of behavioral acts resembling OCD checking behavior was observed.[12–15] Postmortem analyses in these animals revealed increased dopamine tissue levels in the nucleus accumbens and right prefrontal cortex.[16] Joel and Avisar[17] developed a rat model of OCD based on the hypothesis that a deficient response feedback mechanism underlies obsessions and compulsions. Rats undergoing extinction of lever-pressing for food after the attenuation of an external feedback for this behavior exhibit excessive lever-pressing unaccompanied by an attempt to collect a reward, which may be analogous to the excessive and unreasonable behavior seen in OCD. Administration of the D_1 receptor antagonist SCH 23390 reduced the number of compulsive lever-presses without affecting the number of lever-presses followed by an attempt to collect a reward.[18] On the basis of electrophysiologic data, Joel and Doljansky[18] suggested that compulsive lever-pressing depends on a phasic decrease in stimulation of D_1 receptors.[18] These data, using putative animal models of OCD, suggest a role of dopamine,

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in particular of the D_1 and D_2 receptors, in the mechanism underlying compulsive behavior.

DOPAMINE AND METABOLITE CONCENTRATIONS IN HUMANS

Baseline measures of dopamine and its metabolite homovanillic acid (HVA) in psychotropic-naive patients may provide direct evidence for a possible role of dopamine in OCD. Thoren and colleagues[19] assessed HVA in cerebrospinal fluid (CSF) levels before and after 3 weeks of treatment with clomipramine but found no change. Benkelfat and coworkers[20] found no differences between the mean plasma HVA level of 13 medication-free patients with OCD and 29 normal controls. Swedo et al.,[21] examining CSF levels of HVA in 43 children with primary OCD, reported that CSF HVA levels were not significantly related to OCD symptoms and did not correlate with improvement following 5 weeks of treatment with clomipramine. Hollander et al.,[22] on the other hand, observed a significant decrease in plasma HVA in 12 OCD patients relative to 10 controls following fenfluramine treatment, and Zahn et al.[23] showed that CSF metabolites of serotonin and dopamine, but not of norepinephrine, were positively correlated with electrodermal responsivity in a reaction time task in 43 adolescents and children with OCD.

Marazziti et al.[24] measured platelet sulfotransferase activity in 17 drug-free OCD patients and an equal number of healthy controls. Sulfotransferase is an enzyme involved in the catabolism of catecholamines such as dopamine and has similar kinetic characteristics in brain and platelets. Their results showed a higher level of sulfotransferase activity in OCD patients compared with control subjects, suggesting an increased dopaminergic neurotransmission in OCD.

In summary, the neurochemical studies on the role of dopamine metabolites in OCD patients have, by and large, yielded no evidence for an abnormal dopamine function in OCD.

PHARMACOLOGIC CHALLENGE TESTS

Another approach to assessing the functioning of the dopaminergic system is the evaluation of the behavioral and neuroendocrine effects response to administration of indirect (cocaine and amphetamine) or direct (apomorphine [APO] and bromocriptine) dopamine receptor agonists. Cocaine, a dopamine transporter blocker, elevates synaptic dopamine levels and increases the dopamine transporter density.[25] It has been reported that chronic use of cocaine may be associated with stereotyped examining, searching and sorting behaviors, and an exacerbation of obsessive-compulsive symptoms.[26–30] Moreover, cocaine-abusing patients are at increased risk for the later development of OCD.[31] Methylphenidate and amphetamine have been reported to exacerbate or induce[30,32–36] as well as to improve[37–39] OCD symptoms. A limitation of the use of cocaine, methylphenidate, and amphetamine as dopaminergic probes is that they also release serotonin and norepinephrine.

Pitchot et al.[40] assessed the growth hormone (GH) response to 0.5 mg of APO in 8 drug-free OCD patients and 8 healthy male volunteers. No difference in mean GH peak response was found, suggesting that the dopaminergic function was not altered in OCD. In contrast, Brambilla et al.,[41] studying 15 patients with OCD and 15 age/sex-matched controls, found a blunted GH response to APO in OCD patients, hinting at a postsynaptic dopamine receptor subsensitivity. In the same sample, however, cortisol (CORT) responses to stimulation with APO were not different between the 2 groups.[42] Longhurst et al.[43] examined the effects of catecholamine depletion in 6 drug-free patients with the tyrosine hydroxylase inhibitor alpha-methyl-*para*-tyrosine (AMPT) and found no significant changes in obsessive-compulsive symptom severity as compared with placebo. Although bromocriptine, a selective dopamine receptor agonist, has been shown to induce stereotypies in animals, one report describes an improvement of obsessive-compulsive symptoms in OCD patients.[44] Results from pharmacologic challenge studies with dopamine receptor agonists in OCD are as yet inconsistent, but there are indications that obsessive-compulsive symptoms may be related to increased dopamine neurotransmission.

PHARMACOTHERAPY

Indirect evidence for a role of dopamine in OCD comes from treatment studies using pharmacologic agents that modulate the dopaminergic activity in the brain.

Antipsychotics in Monotherapy

Three years after its introduction, chlorpromazine was tested in 75 outpatients with obsessional neurosis and allied disorders in a placebo-controlled trial.[45] A significant response to chlorpromazine as compared with placebo was observed in 27 patients (36%), but it was judged to be disappointing in relieving compulsive symptoms. Ever since, no placebo-controlled trial with a typical antipsychotic drug has been conducted in OCD. Except for some case reports,[46–50] typical antipsychotics in monotherapy are considered to be ineffective in OCD, mainly on grounds of individual clinical experience. McDougle et al.[51] assessed the efficacy of clozapine monotherapy in 12 adults with refractory OCD in a 10-week, open-label trial with clozapine but found no significant change. There have been no placebo-controlled trials with atypical antipsychotics, such as risperidone, olanzapine, quetiapine, or ziprasidone, as monotherapy for OCD.

Table 1. Overview of Addition Trials With Atypical Antipsychotics in Obsessive-Compulsive Disorder

Year of Publication	Author	Design	N	Dose, mg/day	Trial Length, wk	YBOCS Score Decrease, %	Responders, N (%)
Risperidone[a]							
1995	McDougle et al[90]	Open	3	1	1–4	55	3 (100)
1996	Saxena et al[91]	Open	21	0.5–8.0	3	NA	14 (67)
1997	Stein et al[92]	Open	8	1–2	4	22	3 (37)
2000	Pfanner et al[93]	Open	20	1–3	8	31	15 (75)
2000	McDougle et al[94]	Double-blind placebo	20	1–7	6	29	11 (55)
2002	Baxter et al[95]	Double-blind placebo	10	1	9	40	NA
2003	Hollander et al[96]	Double-blind placebo	10	0.5–3.0	8	…	4 (40)
Olanzapine[b]							
1999	Weiss et al[97]	Open	10	1.25–20.00	8	40	7 (70)
2000	Koran et al[98]	Open	10	2.5–10.0	8	16	3 (30)
2000	Bogetto et al[99]	Open	23	5	12	30	NA
2001	Francobandiera[100]	Open	9	2.5–5.0	6	38	6 (66)
2002	Crocq et al[101]	Open	8	5–15	4–74	…	7 (88)
2003	D'Amico et al[102]	Open	21	10	12	26	7 (33)
2004	Bystritsky et al[103]	Double-blind placebo	13	5–20	6	19	6 (46)
2004	Shapira et al[54]	Double-blind placebo	22	5–10	6	± 25	9 (41)
Quetiapine[c]							
2002	Mohr et al[104]	Open	8	50–300	6	21	4 (50)
2002	Atmaca et al[105]	Single-blind placebo	14	50–200	8	56	10 (71)
2002	Denys et al[106]	Open	10	200	8	35	7 (70)
2003	Sevincok and Topuz[55]	Open	8	150	10	27	2 (25)
2004	Denys et al[109]	Double-blind placebo	20	200–300	8	34	8 (40)

[a]For all risperidone studies, total N = 92 and mean YBOCS score decrease = 35%.
[b]For all olanzapine studies, total N = 116 and mean YBOCS score decrease = 27%.
[c]For all quetiapine studies, total N = 60 and mean YBOCS score decrease = 34%.
Abbreviations: NA = not available, YBOCS = Yale-Brown Obsessive-Compulsive Scale.

It is of note that de novo emergence or exacerbation of OCD symptoms during treatment with antipsychotics has been described extensively in patients with psychotic disorders. Lykouras et al.[52] have recently reviewed the reported cases of OCD symptoms induced by atypical antipsychotics.

Antipsychotics in Addition to Selective Serotonin Reuptake Inhibitors

Addition of pimozide and haloperidol to SSRIs proved effective for patients who were refractory to treatment, in particular for patients with comorbid chronic tic disorders or schizotypal personality disorders.[53] Following the successful combination of typical antipsychotics with SSRIs for treatment-refractory patients, there were a number of studies combining atypical antipsychotics with SSRIs (Table 1). Although 2 negative studies have been published,[54,55] risperidone, olanzapine, and quetiapine appear to be efficacious in addition to SSRIs for therapy-refractory patients at low doses within 6 to 8 weeks. Recently, in an open trial, Metin et al.[56] evaluated the efficacy of 325 mg/day of amisulpiride, a selective dopamine $D_{2/3}$ antagonist, to augment the effect of SSRI treatment in 20 patients with treatment-resistant OCD and observed a significant improvement in 95% of the patients.

Mechanism of Action?

It is intriguing that antipsychotics in monotherapy lack efficacy in OCD, while they are capable of inducing de novo OCD symptoms in psychotic disorders and are efficacious in combination with SSRIs in some patients with OCD. It has been proposed that serotonin-2A ($5\text{-}HT_{2A}$) receptor antagonism exacerbates obsessive-compulsive symptoms by increasing the firing rate of the dopamine neurons, whereas D_2 receptor antagonism reduces obsessive-compulsive symptoms through inhibition of the dopamine neurons.[57] Zhang et al.[58,59] have shown in rats that the combination of olanzapine and fluoxetine may increase synergistically extracellular dopamine and noradrenaline levels in the prefrontal cortex, and Denys et al.[60] found that the combination of quetiapine and fluvoxamine may cause a synergistic dopamine increase in the prefrontal cortex and thalamus. Since the combination of antipsychotics and SSRIs does not result in augmented serotonin levels, it is unlikely that an altered serotonergic neurotransmission is underlying the clinical efficacy of this combination. Additional research is warranted to determine whether changes in extracellular dopamine levels may account for the clinical efficacy of the augmentation strategy with atypical antipsychotics in OCD.

NEUROIMAGING

In vivo neuroimaging of dopamine transporters and receptors with positron emission tomography (PET) or single photon emission computer tomography (SPECT) offers another tool with which to probe the dopaminergic function in OCD. Sawle et al.[61] did not find an alteration in

Table 2. Overview of Dopamine-Related Association Studies in Obsessive-Compulsive Disorder (OCD)

Polymorphism	Year of Publication	Author	N	Results
Dopamine Transporter				
40-base-pair repeat in the DAT 1 gene	1998	Billett et al[72]	100 OCD patients and controls	Negative
40-base-pair repeat in the DAT 1 gene	2000	Frisch et al[66]	75 OCD patients and 172 controls	Negative
40-base-pair repeat in the DAT 1 gene	2003	Hemmings et al[67]	71 OCD patients and 129 controls	Negative
D_2 receptor				
Three exons of the DRD2 gene, 4, 5, 6	1994	Novelli et al[71]	45 OCD patients and 26 controls	Negative
Taq-IA	1996	Nicolini et al[69]	66 OCD patients and 54 controls	OCD patients + tics had a higher frequency of Taq I A2 allele (p = .014)
Taq-IA and the serine/cysteine variation	1998	Billett et al[72]	100 OCD patients and controls	Negative
Taq-IA and the serine/cysteine variation	2004	Denys et al[70]	150 OCD patients and 150 controls	Male OCD patients had a higher frequency of Taq I A2 allele (p = .020)
D_3 receptor				
Msc I in the first exon	1994	Catalano et al[68]	97 OCD patients and 97 controls	Negative
Msc I in the first exon	1996	Nicolini et al[69]	67 OCD patients and 54 controls	Negative
Msc I in the first exon	1998	Billett et al[72]	100 OCD patients and controls	Negative
D_4 receptor				
13 base pair deletion in the first exon	1996	Di Bella et al[75]	157 OCD patients and 162 controls	Negative
48-base-pair repeat	1997	Cruz et al[73]	12 OCD patients + tics and 49 patients	OCD patients + tics had a higher prevalence of the 7-fold variant (p = .018)
48-base-pair repeat	1998	Billett et al[72]	100 OCD patients and controls	Negative
48-base-pair repeat	2000	Frisch et al[66]	75 OCD patients and 172 controls	Negative
48-base-pair repeat	2003	Hemmings et al[67]	71 OCD patients and 129 controls	Negative
48-base-pair repeat	2003	Millet et al[74]	55 trios	An absence of transmission of the allele 2 (p = .005)
COMT				
Val-158-Met substitution	1997	Karayiorgou et al[76]	73 OCD patients and 148 controls	Male OCD patients had a higher frequency of LL genotype (p = .0002)
Val-158-Met substitution	1998	Ohara et al[81]	17 OCD patients and 135 controls	Negative
Val-158-Met substitution	1999	Karayiorgou et al[77]	110 nuclear OCD families	Preferential transmission of the L allele in male OCD patients (p = .0057)
Val-158-Met substitution	2000	Schindler et al[80]	72 OCD patients/parent trios	A tendency for association with homozygosity at COMT locus (p = .056)
Val-158-Met substitution	2002	Alsobrook et al[78]	56 OCD patients and 112 parents	Female OCD patients had a higher frequency of LL genotype (p = .049)
Val-158-Met substitution	2001	Niehaus et al[79]	54 OCD patients and 54 controls	OCD patients had a higher frequency of H/L genotype (p = .0017)
C → T transition	2001	Kinnear et al[107]	48 OCD patients and 48 controls	Negative
Val-158-Met substitution	2004	Denys et al[70]	150 OCD patients and 150 controls	Male OCD patients had a higher frequency of L alleles (p = .0035)
Val-158-Met substitution	2003	Erdal et al[82]	59 OCD patients and 114 controls	Negative
Val-158-Met substitution	2004	Meira-Lima et al[108]	79 OCD patients and 202 controls	Negative

Abbreviations: COMT = catechol-O-methyl transferase, DAT = dopamine transporter.

[^{18}F]-6-Fluorodopa uptake into the caudate and putamen in a small (PET) study involving 6 OCD patients with obsessional slowness. A decrease in [^{18}F]-6-Fluorodopa uptake is believed to reflect a reduction in the number of nigrostriatal dopaminergic neurons. Van der Wee et al.[62] found higher binding ratios of [^{123}I] Beta-CIT to the dopamine transporter in the left basal ganglia in 15 drug-naive patients with OCD. Kim et al.[63] found an increased dopamine transporter binding ratio in the right basal ganglia and a tendency toward an increased dopamine transporter binding ratio in the left basal ganglia with [^{123}I] IPT SPECT in 15 OCD patients. Pogarell et al.,[64] on the other hand, did not detect significant differences in striatal dopamine transporter [^{123}I] Beta-CIT binding between 7 patients and 10 controls. Finally, Denys et al.[65] observed a decreased [^{123}I] IBZM binding in the left caudate in 10 OCD patients, suggesting a down-regulated dopamine D_2 receptor. Altogether, these findings indicate that the dopamine system in the basal ganglia could be involved in OCD. Higher dopamine transporter densities in tandem with a down-regulation of the D_2 receptor suggest higher synaptic concentrations of dopamine in the basal ganglia in OCD.

ASSOCIATION STUDIES

A number of candidate gene studies have been conducted in order to elucidate the contribution of the dopamine system in OCD (Table 2). Investigations of the role of the dopamine transporter and D_3 receptor showed no significant association between a particular allele and OCD.[66–69] Except for the TAQ I A2 allele that was found to be associated with OCD patients and tics in male patients,[69,70] no statistically significant differences in allele frequencies or genotype between OCD patients and controls were found with regard to the D_2 receptor.[71,72] Cruz et al.[73] and Millet et al.[74] found an association for the D_4 receptor, but other reports were negative.[66,67,72,75]

The role of catechol-O-methyl transferase (COMT) has been extensively investigated in OCD since COMT is an enzyme that has a crucial role in the elimination of dopamine, and higher dopamine levels may be implicated in OCD. Karayiorgou et al.[76,77] found evidence for an association between the low-activity COMT allele and OCD in male OCD patients in a case-control study and a family-based study, whereas Alsobrook et al.[78] found evidence pointing to an association between the low-activity COMT allele and OCD in female OCD patients. Niehaus et al.[79] reported a preponderance of COMT high/low heterozygotes in an Afrikaner population of 54 OCD patients but did not observe gender differences. Schindler et al.[80] found no association between any particular allele and OCD but found a tendency for an association with homozygosity at the COMT locus. Ohara et al.[81] did not find any association in a small sample of 24 Japanese patients and neither did Erdal et al.[82] in a sample of 59 Turkish patients. In line with the study by Karayiorgou et al.,[77] Denys et al.[70] found a higher frequency of the low-activity COMT in male OCD patients. On the other hand, a recent meta-analysis[83] of the COMT gene in 144 OCD patients and 337 controls showed insufficient evidence to support an association.

A HYPERDOPAMINERGIC STATE?

Despite some inconsistencies, in general, the results from most studies hint at an association between OCD and increased midbrain dopamine neurotransmission. The hypothesis of increased dopamine neurotransmission in the basal ganglia is in agreement with various working hypotheses of the pathophysiology of OCD such as the hyperactive corticostriatal model, the amygdalocentric model, or the model of behavioral addiction in OCD. The corticostriatal working model of OCD suggests an imbalance of the direct versus indirect pathway that produces a hyperactive circuit responsible for the repetitive behaviors seen in OCD.[84,85] Since D_1 preferentially activates the direct and D_2 the indirect pathway, and the density of D_1 receptors in the basal ganglia is higher than the density of D_2 receptors, increased concentrations of dopamine are most likely to result in a dominant D_1-regulated direct circuit and consequently in a hyperactive corticostriatal system.

In the amygdalocentric model, the acquisition and expression of conditioned fear mediated by the amygdala are believed to be actively inhibited by feedback mechanisms from the medial prefrontal cortex.[86] One way to understand OCD is that the normal cortical inhibition of the amygdala is malfunctioning and that the anxiety responses induced by the amygdala therefore become more intrusive and chronic in patients with OCD. Rosenkranz and Grace[87] demonstrated that the response of the amygdala to cortical inhibition is potently affected by alterations of the mesolimbic dopaminergic system. When dopamine is increased, the ability of the prefrontal cortex to suppress the affective responses generated in the amygdala is attenuated.

A number of phenomenological characteristics of OCD such as loss of voluntary control, repetitiveness, compulsiveness, reinforcement of behavior, aberrant habit learning, and uncertainty resemble addictive behavior and may be understood within the conceptual framework of "behavioral addiction."[88] In particular, ritualistic-compulsive actions share similarities with addictive behavior. There is little doubt that midbrain dopamine has positive reinforcing properties, and it is liable that the reinforcing nature of compulsions originates from increased dopamine transmission. Recently, Fiorillo et al.[89] demonstrated that dopamine neurons show increased firing during prolonged periods of uncertainty. Subjective uncertainty is a main feature of pathologic gambling and plays a major role in OCD.

CONCLUSION

To explore these hypotheses, more direct studies of the dopamine function in OCD are needed, in particular, measurements of dopamine and its metabolite and pharmacologic challenge studies with dopaminergic probes during behavioral stimulation. To date, there is sufficient preclinical and clinical evidence that implicates the dopamine system in OCD, but more studies are warranted to understand the function of dopamine in the pathophysiology of OCD.

Drug names: apomorphine (Apokyn), bromocriptine (Parlodel and others), chlorpromazine (Thorazine, Sonazine, and others), clomipramine (Anafranil and others), clozapine (Fazaclo, Clozaril, and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), methylphenidate (Metadate, Ritalin, and others), olanzapine (Zyprexa), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, apomorphine, bromocriptine, chlorpromazine, clozapine, haloperidol, methylphenidate, olanzapine, pimozide, quetiapine, risperidone, and ziprasidone are not approved by the U.S. Food and Drug Administration for the treatment of obsessive-compulsive disorder.

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