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Serotoninergic mechanisms in the treatment of obsessive–compulsive disorder

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Obsessive–compulsive disorder (OCD) is a disabling psychiatric condition affecting 1–2% of the community. Although modern drug, behavioral and psychosurgical therapies have improved the prognosis of OCD considerably, approximately 30% of patients remain treatment-refractory. Currently, selective serotonin (5-HT) reuptake inhibitors (SSRIs) are the drug treatments of choice for OCD. Accordingly, this review evaluates the evidence for a role of the serotonin (5-HT) neurochemical system in the treatment and pathophysiology of OCD. However, drug treatment approaches that modify function of interrelated neurochemical systems, such as the dopamine and glutamate systems, are also briefly discussed as they promise to complement and enhance SSRI treatment effects.

Obsessive–compulsive disorder (OCD) is a familial anxiety disorder affecting 1–2% of the general community [1]. Once thought to be quite rare, it is now known to be the fourth most common mental illness, after depression, alcoholism and social anxiety disorder. OCD is a disorder in which the patient's mental state and daily activities are dominated by morbid obsessions or compulsions, or, more typically, a combination of both these. Obsessions are persistent, intrusive and inappropriate thoughts (such as intense contamination fears), impulses or images that are distressing for the patient. Compulsions are repetitive behaviors or mental acts that a person feels driven to perform (e.g. handwashing or checking), that are generally aimed at reducing the distress caused by the obsessions. Recent advances in diagnosis have resulted in the proposal of a dimensional typology comprising several subtypes: obsessions/checking, hoarding, contamination/cleaning and symmetry/ordering [2,3]. These dimensions are hypothesized to have distinct genetic, neurobiological and treatment correlates, and may better account for the clinical heterogeneity seen in OCD. OCD tends to manifest in the teen and early adult years with more than half of all cases having illness onset before 25 years of age. It usually runs a chronic course without treatment. Also, it is complicated by a high rate of psychiatric comorbidity with up to 70% of cases eventually having an additional psychiatric diagnosis, most often depression or another anxiety disorder [4]. In addition, there is a well-described clinical association between OCD and other psychiatric syndromes such as Tourette's syndrome, motor tic disorders and autistic disorders, which have been conceptualized by some experts as OCD spectrum disorders [5]. The pathophysiologic basis of OCD symptoms has not yet been clearly delineated. However, neurochemical dysfunction (with putative abnormalities in serotonin, dopamine (DA) and glutamatergic transmitter systems) in cortico-thalamo-striatal-cortical brain circuits has been implicated in its pathogenesis [6,7].

Advances in antiobsessional therapy over the past two decades have improved the prognosis of this condition considerably. Modern treatment options, including behavioral therapies, drug therapies (selective serotonin reuptake inhibitor (SSRI) with or without an atypical neuroleptic) [8] and psychosurgical interven-

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tions (cingulotomy, deep brain stimulation) [9,10], offer partial symptom relief for many. However, despite these therapeutic advances, 30% of patients remain treatment-refractory [11,12]. With respect to dimensions of OCD psychopathology, the hoarding dimension has been associated with particularly high rates of comorbidity and treatment-refractoriness [2].

In this review, we will outline the evidence suggesting a role for the serotonin (5-HT) neurotransmitter system in the treatment of OCD. We will also briefly mention the therapeutic potential of newer treatment strategies beyond the 5-HT system acting via dopaminergic and glutamatergic mechanisms. Effective treatments strategies are likely to modulate the cortico-thalamic-striatal-cortical circuitry mentioned earlier at different levels thereby re-regulating functioning within multiple neurotransmitter systems (5-HT, DA, glutamate, γ-aminobutyric acid [GABA]).

Drugs targeting the 5-HT transporter

A key piece of evidence implicating the brain 5-HT system in the treatment and possibly the pathophysiology of OCD has been the discovery of the antiobsessional properties of the SSRIs and the serotonin reuptake inhibitor (SRI), clomipramine (see Table 1 for details). By contrast, many other classes of psychotropic medications used for mood and anxiety disorders (e.g. other tricyclic antidepressants, MAO inhibitors, benzodiazepines, mood stabilizers, 5-HT1A partial agonists) do not substantially affect the core symptoms of OCD. The SSRIs potently block the action of the 5-HT transporter (5-HTT) protein, which is responsible for the uptake of intrasynaptic 5-HT released following an action potential, thereby promoting an acute increase in intrasynaptic 5-HT concentrations (Fig. 1). Chronic administration of these agents, via a sequence of neuroadaptive changes, has a net facilitatory effect on 5-HT neurotransmission [13]. Unlike patients with major depression, in whom maintenance of SSRI treatment effects require continued availability of presynaptic 5-HT [14], OCD patients do not experience disruption of SSRI therapeutic effects under conditions of tryptophan/5-HT depletion [15,16], implicating long-term postsynaptic 5-HT receptor changes in therapeutic mechanisms in OCD. Some of these changes, mentioned in more detail later, may account for the later onset of therapeutic action of SSRIs in OCD (up to 12 weeks) compared to major depression (4–6 weeks).

Owing to the selective effectiveness of SRI agents, there has been a focused search for an association between OCD, and the genes coding for the 5-HTT protein and its expression. A 44 bp insertion/deletion polymorphism (5-HTTLPR) has been identified in the promoter region of the 5-HTT gene that regulates 5-HTT protein expression. Efforts to associate allelic variation in the 5-HTTLPR region with OCD have thus far been mixed with some studies [17,18] suggesting increased expression of two copies of the long allele form (l/l) (linked to maximum transcriptional efficiency) of the gene in OCD, and others failing to find this association [19–23]. One group has identified a trend toward increased frequency of the 5-HTTLPR short allele (s) in female OCD patients [24]. Given the clinical heterogeneity of OCD spectrum disorder, further investigation of illness subgroups (e.g. early onset OCD, family history positive patients, dimensional subtypes) and 5-HTT alleles may yet prove rewarding. Preliminary work investigating the interaction of 5-HTTLPR genotype and SSRI treatment response in OCD did not find differing response status among the three

TABLE 1

Antiobsessional agents targeting the 5-HTT protein

Agent	Status as an OCD treatment	$T_{1/2}$ (hours)	Usual dose range for OCD (mg/day)	Relative potency of 5-HT reuptake inhibition [80]	Relative potency of DA reuptake inhibition	Drug–drug interaction potential	Clinical issues
Fluoxetine (Prozac)	Established	24–72 (168–216[a])	40–80	+		+++	Anecdotal data on high-dose admin. >100 mg/day
Sertraline (Zoloft)	Established	24–26	100–200	++	++	+	Potentially more rapid improvement versus fluoxetine [81]. High dose admin. (250–400 mg/day) can improve refractory OCD [82]
Paroxetine (Paxil)	Established	21–24	40–60	++++	+	++	Discontinuation symptoms can be a problem clinically
Fluvoxamine (Luvox)	Established. Most studied for OCD	15–26	100–300	++		+++	Potent CYP-3A4 P450 isoenzyme inhibitor
Citalopram (Celexa)	Established	33–35	40–60	+++		Minimal	IV administration possible [83]
Escitalopram (Lexapro)		30–33	10–30	++++		Minimal	More potent enantiomer of citalopram
Clomipramine (Anafranil)	Established. First FDA-approved medicine for OCD	17–28	150–250	+	+		SEs: anticholinergic, sedation; concern about seizures >250 mg/day. ? Bigger effect size versus SSRIs. Cardiotoxicity in O/D. IV studies – may be a way to hasten treatment in resistant patients [84]. Active desmethyl metabolite is primarily a NE reuptake blocker

[a] Active nor-fluoxetine metabolite.

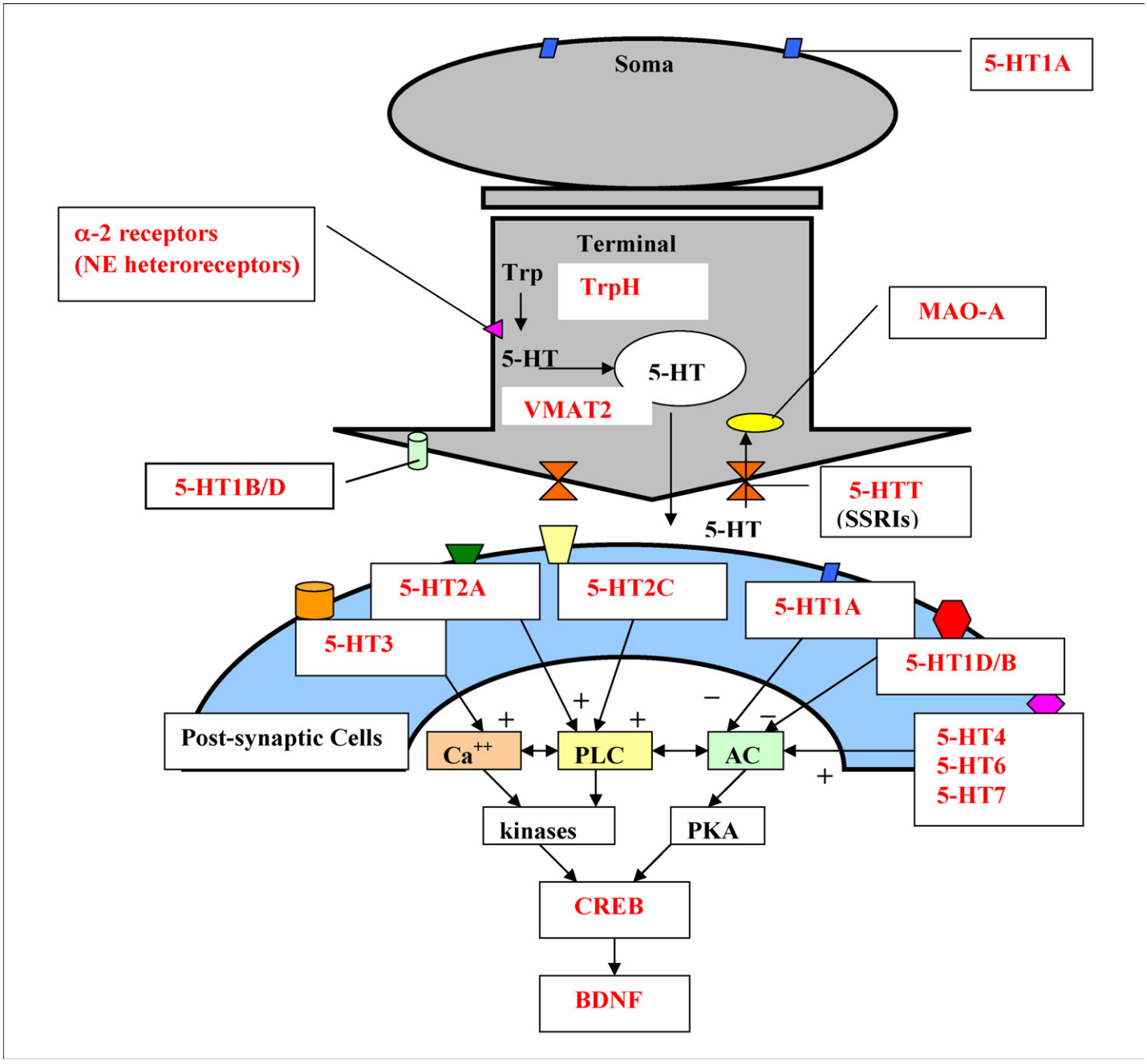

FIGURE 1

A model serotonin synapse, identifying some of the key receptors and other synaptic components that may mediate SSRI therapeutic effects in OCD. Serotonin (5-hydroxytryptamine or 5-HT) is shown from synthesis to synaptic release and then binding to presynaptic and postsynaptic receptors. Tryptophan hydroxylase (TrpH) catalyzes the rate-limiting step in the synthesis of 5-HT from tryptophan (Trp). The vesicular monoamine transporter type-2 (VMAT2) transports 5-HT into presynaptic vesicles. These vesicles then release 5-HT, where 5-HT interacts with postsynaptic receptors including 5-HT1A, 5-HT1B/D, 5-HT2A, 5-HT2C and 5-HT3. 5-HT also binds to somatodendritic (5-HT1A) and terminal (5-HT1B/D) autoreceptors. The serotonin transporter (5-HTT) transports 5-HT from the synaptic space back into the presynaptic neuron. Monoamine oxidase-A (MAO-A) breaks down 5-HT. The SSRIs blocks the 5-HTT, and ultimately increase CREB and BDNF expression in frontal, striatal and limbic brain areas.

different genotypes, when considering total clinical improvement. However, improvement in compulsive behaviors rather than total OCD psychopathology may vary with genotype, with l/s genotype associated with a better response [22]. Another group has also linked l/s genotype to SSRI/SNRI responder status [25]. These results are divergent from the treatment findings in patients with major depression where the l/l genotype confers SSRI responder status [26], and the s/s genotype, nonresponder status. Some have speculated that lessened transcriptional efficiency of the 5-HTTPR in OCD patients could account for the striking delay in onset of SSRI therapeutic effects compared to other conditions such as depression and panic disorder [27]. Other possible explanations for the discrepant findings between OCD and MDD SSRI response status and 5-HTT genotype are differences in the underlying neurobiology of the syndromes as well as their treatment mechanisms. For example, frontal cortical 5-HT mechanisms may be more

involved in OCD treatment responses [28], while hippocampal and hypothalamic 5-HT mechanism may be of greater significance for MDD. The recent discovery of the functional equivalence of the LG allele with the S allele [29,30] is also likely to add refinement to the prediction of SSRI treatment responses and adverse event burden [31] in OCD spectrum disorders, and may lead to reinterpretation of the published literature on this topic. Though promising as a clinical tool, additional work is needed to ascertain whether pretreatment 5-HTT genotyping could routinely inform treatment selection and planning in OCD.

Complementary to the genetic data reviewed, a number of neuroimaging studies have now been conducted attempting to map out the density of the 5-HTT protein in brain regions implicated in OCD, as well as determine brain physiological responses to effective SSRI therapy. There is evidence of abnormal reductions in 5-HTT availability in the thalamus/hypothalamus, midbrain and brainstem of medication-free OCD patients based on single photon emission computed tomography (SPECT) 123-iodine-labeled 2-β-carbomethoxy-3-β-(4-iodophenyl)-tropane (^{123}I β-CIT) imaging assessments [20,32,33]. Other groups have observed findings in the opposite direction in a midbrain–pons region of interest (ROI) utilizing a similar imaging method [34] or no significant change in these ROIs versus control subjects [35], the last group employing a positron emission tomography technique. In a study of OCD patients treated with the SSRI citalopram, there was a 37% reduction in 5-HTT density in the midbrain/pons area following short-term therapy [36], presumably reflecting treatment-related increases in synaptic 5-HT concentrations. A concomitant increase (40%) in dopamine transporter (DAT) availability was also noted in this study, suggesting the potential contribution of functional 5-HT/DA interactions in the mechanisms of antiobsessional therapy. SPECT β-CIT imaging performed on patients after one year of effective citalopram treatment, indicated normalization of 5-HTT availability in the thalamus, midbrain and brainstem. Patients with higher initial levels of thalamic 5-HTT occupancy by the SSRI citalopram tended to have better 12-month treatment outcomes [37]. Although the imaging studies above have been conducted with small samples, overall they support an instrumental role of the 5-HTT in the effective SSRI treatment of OCD. Additionally, these neurochemical findings further emphasize the need for neurocircuitry models to better conceptualize the pathophysiology of OCD, and gain a more complete mechanistic understanding of treatment effects. Research strategies that combine 5-HTT genotyping, neuroimaging approaches and treatment protocols may be especially informative.

Drugs targeting 5-HT receptor subtypes

5-HT2 receptors

The potential involvement of postsynaptic 5-HT2 receptors (Fig. 1) in therapeutic mechanisms in OCD is suggested by clinical observations that psychotropic agents with potent 5-HT2 antagonist properties, such as risperidone [38] and mirtazapine [39], have antiobsessional properties. In addition, some investigators have hypothesized that synergistic treatment effects may occur across a broad range of mood and anxiety syndromes, including OCD, with 5-HT2A antagonist/SSRI combination treatment [40]. This view is partly based on laboratory observations that 5-HT2A receptor stimulation may antagonize behavioral effects produced by activation of other 5-HT receptor subtypes (e.g. 5-HT1A, 5-HT2C). Therapeutic effects of SSRIs in OCD are probably mediated by 5-HT effects at a number of different postsynaptic receptors, and simultaneous 5-HT2A antagonism may enhance these effects. The emerging clinical evidence that atypical antipsychotic drugs, many of which are potent 5-HT2A antagonists, are useful augmenting agents for treatment-resistant OCD, fits to some degree with this theory (Table 2). Based on this treatment literature, it appears that the therapeutic effect of 5-HT2A antagonist/atypical antipsychotic coadministration takes four to six weeks to become established, and is maximally effective with low-dose regimens [28]. The latter observation may be because of 5-HT2A antagonism of receptors in the medial frontal cortex. Higher-dose atypical therapy results in 5-HT2A receptor antagonism in other cortical structures implicated in OCD treatment responses, especially the orbito-frontal cortex, which may actually be countertherapeutic [41]. However, it should be noted that these agents (the atypical antipsychotics) have a complex pharmacological profile that also includes 5-HT2C and D2 receptor antagonism, characteristics that could also relate to treatment response. Furthermore, some of the agents mentioned above, such as risperidone and to a lesser extent, mirtazapine, can block a subpopulation of α-2 adrenoreceptors which are presynaptic heteroreceptors on 5-HT neurons, and which regulate release of 5-HT (Fig. 1). In theory this action would also further enhance other SSRI therapeutic effects such as desensitization of the 5-HT1D terminal autoreceptor [28].

Other investigations have begun to examine the role of the 5-HT2C receptor in OCD. For example, 5-HT2C knock-out mice have been reported to exhibit compulsive behavior (repetitive chewing of non-nutritive substances) [42]. In another animal model of OCD (persistence of rewarded alternation behavior), 5-HT2C receptor agonism, because of either chronic *meta*-chlorophenylpiperazine (*m*-CPP) or chronic fluoxetine administration, was implicated in the observed reductions in compulsive behaviors [43]. In addition, the hallucinogen, psilocybin, a mixed 5-HT2C/2A/1A receptor agonist, has been reported to produce acute reductions in symptomatology in humans with OCD [44]. There is preclinical data that, following eight weeks of SSRI administration, postsynaptic 5-HT2A/C receptors in orbito-frontal cortex projection areas (a brain region implicated in human OCD), remain normosensitive [45]. These intact receptors may be crucial to the mediation of antiobsessional effects of a variety of drugs including SSRIs and hallucinogens [46].

Thus, there is accumulating evidence that agents that are 5-HT2A antagonists (given in low doses) or agents that are 5-HT2C receptor agonists may be useful augmentation therapies for OCD. Drug development efforts aiming to produce agents with both SSRI properties, and these additional 5-HT2 receptor effects, could be particularly beneficial for OCD patients.

The 5-HT1D receptor

Several lines of evidence have implicated the 5-HT1D receptor in the pathogenesis of OCD and compulsive behaviors, thereby stimulating interest in this molecular target as an opportunity for novel therapies. 5-HT1D and possibly 5-HT1B receptors regulate release of 5-HT from the presynaptic terminal, thereby reducing 5-HT neurotransmission (Fig. 1). Therefore, activation of the 5-HT1D receptor by an agonist compound would be expected to worsen

TABLE 2

Dopamine receptor antagonists for OCD

Drug	Status as an OCD treatment	Dose range for OCD (mg/day)	Relative potency of D2 receptor antagonism	Relative potency of 5-HT2A receptor antagonism	Other properties	Clinical issues
Haloperidol	SSRI augmenting agent for refractory OCD. Positive RCT data	1–3	++++	–	–	Four-week trial, in which OCD patients ($n = 34$) on combination (FVX + haloperidol) had a superior response versus FVX + PLAC (39% versus 0% responders) [85]. OCD patients with tics responded especially well
Risperidone	SSRI augmentation in refractory OCD	0.5–3	+++	++	5-HT2C antag. ++	Six-week, RCT 50% of completers were responders ($n = 36$) [38]. Second RCT ($n = 16$) – 40% became responders. Patients respond independent of tic status [86]
Clozapine	Negative, open-label monotherapy trial in refractory OCD	50–200	+	++++	H1 antag. ++++; 5-HT2C antag ++; α_1 antag. ++++; 5-HT1A antag. +	Ten-week trial ($n = 10$) [87]
Olanzapine	Two positive open-label SSRI augmentation trials in refractory patients	2.5–10	++	++	H1 antag. ++++	$n = 10$ patients in open-label study – 16% reduction in Y-BOCS scores [88]. $n = 26$ patients – 68% responders after 12 weeks. Maintained improvement at 12 months [89]
	Negative RCT					RCT × six weeks, $n = 44$ resistant or partially resistant patients following eight weeks of fluoxetine. No btw group differences [90]
Quetiapine	One positive, single-blind, SSRI augmentation RCT	25–300	+	++	5-HT2C antag. ++	64% response rate in refractory patients on SSRI + quetiapine regimen ($n = 27$) [91]
	One positive, open-label, augmentation trial					31% were responders at one of the two treatment sites involved ($n = 30$) [92]
Aripiprazole	Positive monotherapy open trial	10–30	+++	+++	Partial D2 agonist; 5-HT1A partial ag. +++	43% of patients classified as responders $n = 8$; eight-week trial [93]

OCD symptoms, because OCD is a disorder with presumptive chronic deficits in 5-HT functioning [47]. Pharmacologic challenge studies with *m*-CPP, a nonspecific 5-HT agonist (5-HT1D, 5-HT2C, 5-HT1A), have reported symptom exacerbation in OCD patients [48–50], consistent with the above notion. Not all studies, however, have been positive [51]. Furthermore, challenge with oral sumitriptan, a selective 5-HT1D agonist, provoked OCD symptoms in the hands of one group [52], but not others [53]. Another challenging study was conducted with a more potent agent, zolmitriptan, in this class because sumitriptan has poor CNS penetrance. However, this too was negative [54]. A silent polymorphism of the 5-HT1D gene, G861C, has been associated with OCD diagnosis in three of four studies [55–58]. Furthermore, a recent study replicated and extended this result in a group of female eating disorder patients, some of whom met criteria for OCD [59]. Thus, one pathophysiological hypothesis of OCD is that 5-HT1D receptors are supersensitive in this condition, resulting in chronic reductions in synaptic levels of 5-HT. SSRI treatment, then, may work partly via terminal 5-HT1D receptor desensitization, a physiological event which coincides with the delayed onset (8–12 weeks) of therapeutic effects seen in OCD patients [60]. 5-HT1D, and possibly 5-HT1B antagonist compounds (in development) might be expected to hasten the onset of therapeutic action of SSRIs in OCD by rapidly producing a state of 5-HT1D receptor insensitivity.

Other 5-HT receptor subtypes

Other 5-HT receptor subtypes may also be of therapeutic significance for OCD. In the depression treatment literature, considerable attention has been given to augmentation strategies that could hasten antidepressant effects. In theory, 5-HT1A antagonists, such as the β blocker, pindolol, have the capacity to hasten the antidepressant effect of SSRIs by interrupting 5-HT1A somatodendritic autoreceptor inhibition of cell firing that occurs early in treatment. Although this approach has been disappointing in depression, there is some promising controlled data in OCD [61]. Furthermore, the anxiolytic potential of 5-HT3 receptor antagonism has been demonstrated in a number of animal models of anxiety. Although this strategy has met with limited success in clinical trials of some anxiety disorders (GAD, panic), there is modest evidence that ondansetron, a clinically available 5-HT3 antagonist, could be a monotherapy for some OCD patients [62]. Finally, the biological role of some of the more recently identified 5-HT receptors, such as the 5-HT6 receptor, have not been fully elucidated (Fig. 1). However, there is preliminary data that 5-HT6 receptor agonists may reduce compulsive drinking behaviors in one model of OCD [63], possibly via frontal cortical modulation of GABA and glutamate neurons, and thus 5-HT6 antagonists may have an antiobsessional spectrum of action.

Dopamine receptor antagonists/antipsychotics

Although much of the emphasis of pathophysiologic theories of OCD has been on 5-HT, a growing body of evidence supports a role for increased midbrain/basal ganglia dopaminergic (DA) neurotransmission in this disorder [64,65]. Behavioral addiction models of OCD/compulsive behaviors would seem to be a compatible hyperdopaminergic hypothesis. Psychostimulant administration in animals is known to induce stereotypic behaviors, while in humans psychostimulants and other DA agonists (e.g. apomorphine) can provoke OCD symptoms. Also, SPECT β-CIT imaging work has identified an abnormally increased left caudate/putamen region density of DAT in OCD, compatible with dysfunction in the DA system in this condition [66]. Finally, an impressive amount of clinical treatment data is now available on the utility of classical and atypical antipsychotic (D2 receptor antagonists) as adjunctive treatments for OCD (see Table 2 for a comprehensive summary). As mentioned earlier, the atypical antipsychotics have a complex receptor affinity profile. However, the combination of D2 receptor blockade and 5-HT2A antagonism is thought to be central to their therapeutic mechanism in psychotic illnesses, as well as their improved motor side-effect profile over the classical agents. An important clinical observation is that antipsychotic monotherapy is not especially effective in OCD. Rather it is the synergism between the SSRIs and the antipsychotics (especially low-dose administration) that produces optimal therapeutic effects. Case reports suggest that the new generation antipsychotic, perospirone, with a mixture of 5-HT2A antagonism, D2 antagonism and 5-HT1A agonist properties, may be clinically useful for the comorbid MDD/OCD patient [67].

Glutamatergic treatment approaches

More recently a role for glutamatergic hyperactivity in the pathophysiology of OCD has been hypothesized. For example, CSF levels of glutamate are abnormally elevated in unmedicated OCD patients [68]. Also, in pediatric OCD, there are magnetic resonance spectroscopic data documenting abnormally elevated caudate glutamate/glutamine levels in unmedicated patients, which normalize with SSRI/paroxetine treatment [69]. Lack of serotoninergic inhibition of orbito-frontal cortical, thalamic and striatal areas may permit glutamatergic hyperactivity in these areas in OCD [6,70]. By contrast, other brain regions, such as the anterior cingulate cortex, exhibit reductions in glutamatergic activity in both OCD and depression [71]. Alternatively, allelic variation within glutamate transporter genes could account for perturbations in glutamatergic neurotransmission, and is now considered a risk factor for OCD [72]. Also, knock-out of a cytoskeletal protein, SAPAP3, found in the postsynaptic region of glutamatergic cortico-striatal projection neurons, produces excessive grooming behaviors in mice reminiscent of OCD, which are reversed by both fluoxetine administration and restoration of the synaptic protein [73]. Accordingly, psychoactive agents that inhibit/modify glutamatergic function have become important novel treatment options for this condition. Riluzole, an antiglutamatergic drug originally marketed for ALS, has been evaluated in an open-label manner as an augmentation therapy for SSRI-resistant OCD, with improvements observed not only in core OC symptoms but also in associated anxiety and depressive symptoms [74]. Furthermore, case reports suggest that the noncompetitive NMDA/glutamate receptor antagonist, memantine, could also have antiobsessional properties [75,76]. Also, the glutamatergic antagonist/anticonvulsant, topiramate, has been reported in an open-case series to be somewhat therapeutic as an adjunct to ongoing SSRI therapy in patients with refractory OCD [77]. Finally, lamotrigine, an inhibitor of glutamate release, has been tested in an open-label manner in bipolar patients with OCD spectrum symptoms, with equivocal results till date [78,79]. Thus, glutamatergic hyperactivity, which may be a pathophysiological substrate of OCD, can be ameliorated by a number of currently available drugs. In particular resistant cases of OCD, triple therapy with an SSRI/D2 antagonist/and glutamate antagonist may be required to address the simultaneous occurrence of neurochemical dysfunctions in multiple brain regions.

Conclusions

There has been substantial progress in the psychiatric management of OCD in recent years together with a richer appreciation of its significance as a public health problem, as well as its clinical and pathophysiological complexity. SSRI drugs that facilitate 5-HT neurotransmission have been the medical treatments of choice for OCD over the past two to three decades. There is a central role for the 5-HT system in treatment mechanisms in OCD, via its diverse receptors: the 5-HTT protein, 5-HT1A/1D/1B presynaptic and 5-HT2A/2C/3 postsynaptic receptor subtypes. SSRI therapeutic mechanisms in OCD appear to be somewhat distinct from those at work in major depression in that they are not dependent on the short-term availability of 5-HT and its precursors. In the future, novel treatments are likely to be developed that will selectively target some of these elements of the 5-HT system, in addition to the 5-HTT, to either hasten onset of therapeutic effects, and/or promote a more complete treatment response. In addition, other neurochemical systems interacting with 5-HT, such as the DA and glutamatergic systems, have now been implicated in the patho-

physiology and treatment of OCD, and antagonist drugs that modify DA and glutamatergic functioning are now becoming an accepted part of the therapeutic armamentarium. We are on the threshold of a new era of psychiatric therapeutics for OCD spectrum disorders in which multiple medical, behavioral and surgical treatment options targeting these interrelated systems, are likely to advance care with a similar magnitude to the introduction of the SSRIs several decades ago.

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