

What pharmacology teaches us about the pathophysiology of obsessive-compulsive disorder

O que a farmacologia ensina sobre a fisiopatologia dos transtornos obsessivo-compulsivos

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Abstract Once considered rare and resistant to treatments, obsessive-compulsive disorders (OCD) has now emerged as one the most common psychiatric conditions, with a lifetime prevalence of about 2.5 %, and as a major cause of long-term disability to patients and their families. The treatment of OCD has changed dramatically over the last decade following the introduction of selective serotonin (5-HT) reuptake inhibitors (SSRIs), such as fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, which provide symptom remission in about 60% of the patients. OCD is unique in the response to serotonergic agents and it has been clearly demonstrated that non-serotonergic antidepressants such as desipramine have no effect. The specific response of OCD patients to SSRIs has emphasized the possible role of the main target of these drugs, namely the 5-HT system, in the pathophysiology of the disorder. If the role of 5-HT in OCD is not questionable, future studies should be directed towards the elucidation of the 5-HT receptor subtypes involved, of the second messengers transducing the signal, as well as of the interactions between 5-HT and the other neurotransmitters.

Keywords Obsessive-compulsive disorder. Serotonergic drugs. Serotonin reuptake inhibitors. Psychopharmacology. Serotonin receptors. Signal transduction.

Resumo Antes considerado de ocorrência rara e resistente ao tratamento, o transtorno obsessivo-compulsivo (TOC) é atualmente um dos problemas mais comuns em psiquiatria, com uma prevalência de cerca de 2,5%, e uma das principais causas de incapacidade a longo prazo tanto para pacientes como para suas famílias. Na última década, o tratamento do TOC conheceu mudanças drásticas com a introdução dos inibidores seletivos de captação de serotonina (ISCS), tais como fluoxetina, fluvoxamina, paroxetina, sertralina e citalopram, que proporcionam remissão dos sintomas em cerca de 60% dos pacientes. O TOC responde de forma singular aos agentes serotoninérgicos, mas tal efeito não ocorre quando são usados antidepressivos não-serotoninérgicos, como a desipramina, como foi bem demonstrado. A resposta específica dos pacientes com TOC aos ISCS reforça o possível papel do principal alvo destas drogas, o sistema serotoninérgico, na fisiopatologia deste transtorno. Se o papel da serotonina no TOC é inquestionável, então os futuros estudos devem ser direcionados para o esclarecimento dos subtipos de receptores de serotonina e de mensageiros secundários na transdução do sinal, assim como das interações entre a serotonina e outros neurotransmissores.

Descritores Transtorno obsessivo-compulsivo. Agentes serotoninérgicos. Inibidores da captação de serotonina. Psicofarmacologia. Receptores de serotonina. Transdução de sinal.

Introduction

For more than a decade, the 5-HT hypothesis of obsessive-compulsive disorder (OCD) has constituted a frame of reference for approaching the biology and pathophysiology of this disease. The first observations were those related to the effec-

tiveness of clomipramine, a tricyclic drug that blocks preferentially the 5-HT reuptake, as compared with other tricyclics or placebo. This was subsequently confirmed by the superiority of selective 5-HT reuptake inhibitors (SSRIs), such as fluoxetine, fluvoxamine, paroxetine, sertraline and citalopram.¹⁻⁴ Moreover,

indications of a 5-HT role came also from cerebrospinal fluid (CSF) studies of 5-hydroxyindoleacetic acid (5-HIAA) in OCD, which have shown that a positive response to clomipramine was associated with high CSF 5-HIAA levels,^{5,6} while low levels correlate negatively with the response to clomipramine and positively with OC symptom severity.⁷ Further supporting evidence derived from the exacerbation of OC symptoms with 5-HT agonists have led to the hypothesis of hypersensitivity of postsynaptic 5-HT receptors in OCD, a hypothesis that is still valid.⁸⁻¹⁰

The main target of clomipramine and SSRIs, that is the 5-HT transporter, has been deeply investigated in OCD for its presence in blood platelets. In fact, the active 5-HT uptake in these cells is similar to that present in the brain, as demonstrated by the cloning of the two structures.^{11,12} For some years, ³H-imipramine (³H-IMI) has been mainly used to label it.¹³⁻¹⁵ Insel et al⁵ found no difference in both 5-HT uptake and ³H-IMI binding between healthy controls and OC patients, and Weizman et al¹⁶ and Marazziti et al¹⁷ observed normal 5-HT uptake coupled with a reduced number of ³H-IMI binding sites. Black et al¹⁸ replicated Insel et al's data, and found no changes in ³H-IMI binding, except for a decrease in such binding sites in clomipramine-treated patients, while other studies have shown a decreased number of ³H-IMI binding sites and a decreased affinity for 5-HT uptake,¹⁹ as well as an increased speed of 5-HT uptake, with no change in ³H-IMI binding.²⁰ Subsequently, it has been demonstrated that the more selective ligand ³H-paroxetine (³H-Par) binds to a single site, probably corresponding to the neuronal transporter,^{21,22} and a significant decrease in the number of ³H-Par binding sites, as compared with healthy controls, has been recently reported by two groups.^{23,24}

Serotonin and OCD: the future

A first question to be answered is the meaning to attribute to the reported serotonergic abnormalities: are they the "real causing factors" of the disease or are they caused by it? Are they part of the pathophysiological chain? What is their role in terms of treatment response, i.e., are they state-dependent or "trait" markers? Scattered data suggest that patients showing the most "severe" serotonergic abnormalities are those who respond better to SSRIs and, therefore, link the serotonergic alteration to a positive response to serotonergic drugs.²⁵⁻²⁷

The identification of at least 17 5-HT receptor subtypes²⁸ has led to the question of which subtype or subsystem might be primarily implicated in OCD. The contribution of pharmacological research is fundamental for answering this question. Besides the blockade of the 5-HT transporter, clomipramine enhances the responsiveness of the postsynaptic 5-HT_{1A} receptor and provokes a desensitization of 5-HT_{2C} receptors, while SSRIs cause a decrease in somatodendritic and terminal autoreceptor responsiveness.²⁹ The net increase in 5-HT release provoked by the two actions is particularly evident in the orbitofrontal cortex (an area that appears primarily implicated in

OCD) after a time lag of 8 weeks consistent with the delayed response to these drugs typical of OCD patients, at variance with depression. In addition, high doses of SSRIs are required to elicit this effect, which it is in agreement with the clinical observation that OCD patients need higher doses than depressed patients do. The effect of 5-HT in the orbitofrontal cortex has been linked to 5-HT_{2-like} receptors, since it is reverted by a long-term administration of 5-HT₂ antagonists. Clinical observations support the notion that drugs blocking the 5-HT transporter display anti-obsession properties by increasing the serotonergic transmission. Both metergoline and ritanserin, non-selective 5-HT antagonists, seem to provoke symptoms in drug-remitted patients.^{30,31} The role of 5-HT_{2-like} receptors is supported by preliminary observations of the anti-obsessional effect of psilocybin, an hallucinogen with 2-HT agonist properties,³² and by the clinical use of atypical neuroleptics with a 5-HT_{2/D2} profile, such as risperidone, in resistant OCD.³³ Leckman presented preliminary data showing the effectiveness of another similar compound, ziprasidone, in a group of children and adolescents with Tourette's syndrome and comorbid OCD.

Another useful approach for exploring receptor subtypes is represented by drug-challenge tests. Although the related findings are questionable because no sufficiently selective compounds are currently available, they provide dynamic studies of the receptors and interesting suggestions. The most employed challenge is that with m-chlorophenylpiperazine (m-CP),^{8,9,34} a partial 5-HT agonist with 5-HT_{1A}, 5-HT_{1B/D}, 5-HT_{2C}, 5-HT₂ receptor agonist and 5-HT₂ receptor antagonist properties, which also inhibits 5-HT reuptake and displaces ³H-Par binding to the 5-HT transporter, there is an exacerbation of OC symptoms. On the contrary, MK-212, a 5-HT_{1A} and 5-HT_{2C} receptor agonist, provokes no behavioral effect in OCD.³⁵ The main difference between m-CCP and MK-212 is the fact that the latter shows no affinity for 5-HT_{1B/D} receptors. The possible role of 5-HT_{1B/D} receptors was investigated with the use of sumatriptan, an agonist at this level, but data are still meager and controversial. While Zohar's group³⁶ reported exacerbation of obsessive symptoms, Westenberg's group* did not observe any change in 15 patients, except for a significant increase in growth hormone response. These needs to be further investigated, maybe with 5-HT_{1B/D} receptor agonists with better brain penetrating properties than sumatriptan, which does not pass easily the blood-brain barrier.

To summarize the overall data, they suggest the involvement of the following 5-HT receptor subtypes: 5-HT_{1A} receptors, 5-HT_{2A} receptors, 5-HT_{2C} and 5-HT_{1B/D} receptors. With regard to the 5-HT_{1A} receptor subtype, it is not altered in OCD patients, as demonstrated by the lack of effect of the challenge with ipsapirone, a 5-HT_{1A} receptor agonist,³⁷ and by the lack of clinical efficacy of buspirone,³⁸ so that this drug is no longer recommended in augmentation strategies. The question of the role of the 5-HT_{2A}, 5-HT_{2C} and 5-HT_{1B/D} receptors in OCD is still open and deserves further investigation. However, the potential involvement of other

*Ho Pian KL, Westenberg HGM, van Megen HJGM, Den Boer JA. Sumatriptan (5-HT_{1D} receptor agonist) does not exacerbate symptoms in obsessive-compulsive disorder. Psychopharmacology. In press.

receptor subtypes for which a few or no possibility of exploration exists at the moment cannot be disregarded. In particular to the 5-HT_{5A} and 5-HT₆ subtypes where clomipramine seems to interact, or to 5-HT_{1F} where sumatriptan displays an agonistic activity at the same degree of that exerted at the level of 5-HT_{1D} receptors. With regard to other receptor subtypes, the status of the 5-HT₃ receptors was explored with ondansetron – a drug which display a high affinity at its level, given to 11 OCD patients³⁹ before intravenous administration of m-CPP. The findings of this study, showing that m-CPP provoked exacerbation of OCD symptoms and that pretreatment with ondansetron did not change this response, seem to exclude the involvement of 5-HT₃ receptors in OCD, although further data, in particular comparisons with control groups, are needed.

Given the existence of one or more receptor abnormalities, are these due to a genetic defect, or to an altered expression of the gene products, or to changes in the environment surrounding the receptor? This author's study group is actually focusing on the of 5-HT_{2C} and 5-HT_{5A} subtype expression for the abundance of their mRNA in lymphocytes. The preliminary results of a study that is still in progress suggest an over-expression of the 5-HT_{2C} mRNA in 8 patients with OCD, as compared with controls.

Since a receptor is just the first step of a subsequent cascade of events from a biochemical point of view, currently the interest is focused on the intracellular regulation of the 5-HT transporter and receptors. Some reports have underlined a link between 5-HT reuptake and protein kinase of type C (PKC)⁴⁰ that inhibits the process, and PKA that, on the contrary, exerts a positive influence on 5-HT reuptake.⁴¹ PKC is a class of phosphorylases present at high concentration in the brain.⁴²⁻⁴⁴ Diacylglycerol, derived from the hydrolysis of phosphatidylinositol-4,5-bisphosphate (PIP2), stimulates PKC by increasing its affinity to calcium and membrane phospholipids deriving from receptor-mediated hydrolysis and by promoting its translocation from the cytosol to the particulate fraction.⁴⁵⁻⁴⁷ The effect of the activation of PKC on the 5-HT reuptake was investigated in a group of patients with OCD and compared with a control group. It was observed that the reuptake velocity decreased significantly in both OCD patients and healthy controls, but to a greater degree in OCD patients. This decrease in Vmax of OCD patients was significantly more robust than in healthy controls, indicating that the mechanism is "more ac-

tive" in OCD.* This phenomenon could perhaps be attributed either to a hyperresponsiveness of the 5-HT reuptake system, or to a hyperactivation of PKC in OCD. Such condition might in turn reflect increased endogenous production of diacylglycerol as a result of hyperactive phosphatidylinositol (PI) pathway. A stimulation of the PI pathway in OCD is congruent with data showing a worsening of OCD symptoms following the administration of a 5-HT_{2C} receptor agonist, such as m-CPP;^{8,9} a non-specific 5-HT_{2C} receptor agonist. It is well known that 5-HT_{2C} receptors are linked with a G-protein activating phospholipase C.⁴⁸ However, other receptors are linked with phospholipase C, including 5-HT_{2A}, dopamine and muscarinic receptors. Interestingly, atypical neuroleptics are agonist at 5-HT_{2A} receptor level. Hyperactivity of the PI pathway might provoke an alteration in the normal balance existing between the PI pathway and the cAMP pathway. There is also evidence of the therapeutic effect of inositol, a naturally occurring isomer of glucose that acts as a precursor in the PI pathway in OCD.⁴⁹

Besides the PI pathway, SSRIs and antidepressants have been shown to up-regulate the cyclic adenosine monophosphate (cAMP) response element binding protein (CREB, a transcription factor) cascade, as well as the expression of the brain-derived neurotrophic factor (BDNF).⁵⁰ Interestingly, CREB is a substrate for both PKA and PKC and 5-HT_{2C} agonists seem to influence CREB and BDNF expression.

Conclusions

Throughout the last decade, considerable advances have been made in the understanding of OCD pathogenesis. The availability of research data from a number of sources has helped underline the complexities of the condition. An profusion of evidence in favor of 5-HT system abnormalities has led to the notion that "the best is yet to come",⁵¹ that is, more findings foster new questions. If the successful use of SSRIs has highlighted the key role of the 5-HT transporter, recent developments in the mode of action of these drugs suggest the involvement of different 5-HT receptor subtypes and of second messengers, yet to be identified.

Such findings could enable new treatment possibilities for OCD patients and new therapeutic targets. Thus, compounds acting specifically on 5-HT_{2A} and 5-HT_{2C} receptors, or compounds that inhibit PKC, potentiate PKA or act on various G-protein subunits seem to represent potential antiobsessive drugs.

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