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Serotonin receptors involved in antidepressant effects

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ABSTRACT

The neurotransmitter serotonin (5-hdroxytryptamine; 5-HT) has been implicated in the pathophysiology and treatment of major depression since the serendipitous discovery of antidepressant drugs in the 1950s. However, despite the generalised use of serotonin-enhancing drugs, such as the selective serotonin reuptake inhibitors (SSRIs) and the dual serotonin and norepinephrine reuptake inhibitors (SNRIs), the exact neurobiological mechanisms involved in the therapeutic action of these drugs are poorly understood. Better knowledge of these mechanisms may help to identify new therapeutic targets and to overcome the two main limitations of current treatments: reduced efficacy and slowness of action. Here I review the preclinical and clinical evidence supporting the involvement of different 5-HT receptors in the therapeutic action of antidepressant drugs. Presynaptic 5-HT_{1A} and 5-HT_{1B} autoreceptors play a major detrimental role in antidepressant treatments, as their activation by the excess of the active (extracellular) 5-HT fraction produced by serotonin transporter (SERT) blockade reduces presynaptic serotonergic function. Conversely, stimulation of postsynaptic 5-HT_{1A} receptors in corticolimbic networks appears beneficial for the antidepressant action. The 5-HT_2 receptor family is also involved as 5-$HT_{2A/2C}$ receptor blockade improves the antidepressant action of SSRIs, and recent data suggest that 5-HT_{2B} receptor activation enhances serotonergic activity. Less is known from the rest of postsynaptic 5-HT receptors. However, 5-HT_3 receptor blockade augments the 5-HT increase evoked by SERT inhibition, and 5-HT_4 receptor activation may have antidepressant effects on its own. Finally, blockade of 5-HT_6 and 5-HT_7 receptors appears also to augment the antidepressant effects of SERT inhibition.

Contents

1. Introduction

Major depressive disorder (MDD) is a severe psychiatric syndrome with high prevalence and socioeconomic impact (Andlin-Sobocki et al., 2005; Kessler et al., 2005; Smith, 2011). Although it is clear that depression results *from*, and can result *in*, changes in the functional neuroanatomy of the brain (Sheline et al., 1996; Duman et al., 1997; Seminowicz et al., 2004; Drevets et al., 2008), the underlying pathophysiology of MDD has not yet been clearly defined. Numerous clinical and preclinical studies indicate that a disturbance in central serotonin (5-hydroxytryptamine; 5-HT) activity is a key factor; however, other monoaminergic neurotransmitters (e.g. norepinephrine -NE- and dopamine -DA) have

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, 5-hydroxytryptamine, serotonin; BDNF, brain-derived neurotrophic factor; CREB, cyclic AMP response element-binding; CNS, central nervous system; DA, dopamine; DHPC, dorsal hippocampus; DR, dorsal raphe nucleus; GABA, γ-aminobutyric acid; LC, locus coeruleus; MDD, major depressive disorder; MnR, median raphe nucleus; mRNA, messenger ribonucleic acid; NE, norepinephrine; NMDA, noncompetitive N-methyl d-aspartate; PET, positron emission tomography; PFC, prefrontal cortex; REM, rapid eye movement; SERT, serotonin transporter; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; STR, dorsal striatum; VHPC, ventral hippocampus; VTA, ventral tegmental area.

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also been implicated (Harro & Oreland, 2001; Nestler et al., 2002; Nestler & Carlezon, 2006). More recently, glutamatergic neurotransmission has been implicated, based on the observation that ketamine (noncompetitive N-methyl D-aspartate—NMDA-receptor antagonist) shows rapid and persistent antidepressant effects (Zarate et al., 2006).

Despite the large body of research focusing on the mechanisms underlying antidepressant efficacy (Blier & de Montigny, 1994; Artigas et al., 1996; Celada et al., 2004; Berton & Nestler, 2006), current antidepressants remain limited—especially in terms of onset of action and overall efficacy (Rush et al., 2006, 2011; Trivedi et al., 2006). The aim of this article is to review our current knowledge of the role of the serotonergic system in depression, including the many serotonergic receptors identified, and how targeting these receptors in novel ways may lead to the development of new antidepressants.

2. The serotonin system in depression

Abnormalities in serotonergic function have been believed to be a common factor in several related mental illnesses since the 1950s (Woolley & Shaw, 1954). Since then, the link between serotonin and depression has been further clarified by clinical studies that have shown that an acute, transient relapse of depressive symptoms can be produced in subjects in remission using the irreversible 5-HT synthesis inhibitor *p*-chlorophenylalanine (Shopsin et al., 1975, 1976) or tryptophan depletion (Delgado et al., 1990; Price et al., 1990) to cause a temporary reduction in central serotonin levels. Overall, these studies show that clinical efficacy of antidepressant drugs depends on presynaptic serotonergic function. Similarly, other studies have shown reduced cerebrospinal fluid concentrations of the serotonin major metabolite—5-hydroxyindoleacetic acid (5-HIAA)—in drug-free depressed patients (Asberg et al., 1976; Roy et al., 1989) as well as reduced concentrations of 5-HT and its main metabolite (5-HIAA) in the postmortem brain tissue of depressed and/or suicidal patients.

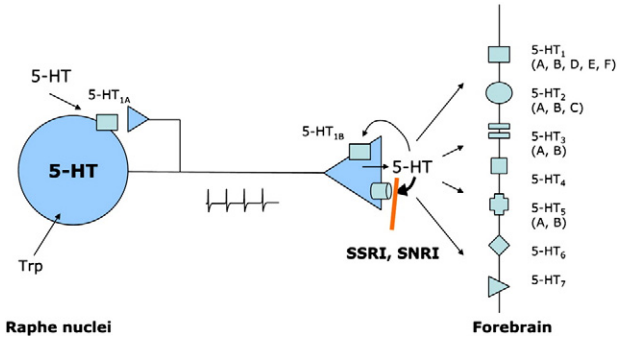
Perhaps the strongest evidence for the role of the serotonergic system in MDD is the efficacy of antidepressants that target the serotonin transporter (SERT)—namely, the selective serotonin reuptake inhibitors (SSRIs) and the dual serotonin and norepinephrine reuptake inhibitors (SNRIs)—which account for more than 90% of the global antidepressant market. A full review of the serotonergic system is beyond the scope of the present article but has been well covered in other comprehensive reviews (Azmitia & Whitaker-Azmitia, 1991; Jacobs & Azmitia, 1992; Smythies, 2005). However, before focusing on the numerous 5-HT receptors, it is important to understand the basic characteristics of the serotonergic system relevant to understanding the effects of antidepressant therapy (Box 1).

First, the serotonergic neurons of the mammalian brain comprise the most extensive and complex neurochemical network in the central nervous system (CNS) after that of glutamate, which makes up the basic wiring of the brain. It has been estimated that the human brain contains about 250 000 5-HT neurons of a total of 10^{11} neurons (Jacobs & Azmitia, 1992). Importantly, whereas serotonergic neurons originate mainly in the brainstem dorsal and median raphe nuclei, their axons arborise over large areas such that they innervate almost every area of the brain with high densities of axonal varicosities. Hence, densities of $>10^6$ nerve terminals/mm^3 have been reported in rat neocortex (Beaudet & Descarries, 1976).

Second, whereas some serotonergic projections form classical chemical synapses, many do not, but instead release 5-HT in a paracrine manner (sometimes termed 'volume transmission'). Thirdly, serotonin neurons are tonically active with a slow (~1 Hz) and regular activity that ceases during rapid eye movement sleep (REM-off neurons), in parallel with noradrenergic neurons of the locus coeruleus (Smythies, 2005). Finally, it is also important to understand that under normal conditions, the activity of serotonergic neurons is tightly controlled via a number of mechanisms including—among others—glutamatergic inputs from forebrain areas such as the prefrontal cortex (Fink et al., 1995; Celada et al., 2001; Martin-Ruiz, et al., 2001a), tonic noradrenergic input from the pontine nuclei (VanderMaelen & Aghajanian, 1983; Peyron et al., 1996; O'Leary et al., 2007), inhibitory γ-aminobutyric acid (GABA)-ergic inputs from local interneurons (Bagdy et al., 2000; Gervasoni et al., 2000; Varga et al., 2001) and dopaminergic input from the midbrain dopaminergic nuclei (Martin-Ruiz et al., 2001b). In addition, the serotonin system is involved in 'self-regulation' of serotonergic activity. Indeed, a key control mechanism of 5-HT neurons is self-inhibition through 5-HT$_{1A}$ autoreceptors, which will be discussed in detail later. Taken together, these basic anatomical and electrophysiological characteristics mean that changes in the activity of serotonergic neurons influence a large population of target neurons in the forebrain.

Considering the complex nature of the serotonergic system and the interplay with other neurochemical systems, numerous mechanisms may play a role in MDD development. Currently, mechanisms suggested include low neuronal production of serotonin or of postsynaptic receptors, reduced excitatory inputs or excessive self-inhibition, reduced 5-HT synthesis and/or tryptophan shortage. Regardless of the exact mechanisms, depression is attributable, at least in part, to abnormal transmission at central 5-HT synapses; therefore, agents that modulate serotonergic transmission in the brain are predicted to be effective antidepressants.

Box 1
Main characteristics of the serotonergic system in mammalian brain



- Low number of neurons: 250.000 5-HT neurons in the human brain (out of a total of 10^{11})
- Extensive arborisation ($>10^6$ nerve terminals/mm^3)
- Innervation of the whole neuraxis
- Control of activity by descending (prefrontal cortex, lateral habenula, hypothalamus, etc.) and ascending (locus coeruleus, spinal cord) inputs to the raphe nuclei
- Slow and regular discharge (pacemaker neurons): strong homeostasis
- Neuronal activity dependent on sleep-wake cycles (REM-off neurons)
- Very sensitive to self-inhibition through activation of 5-HT$_{1A}$ autoreceptors
- Rich neurochemistry: 14 different postsynaptic receptors
- Implication in a large number of physiological functions
- Mutual control with monoaminergic cell groups

3. 5-HT receptors

Following SSRI development, serotonergic targets other than SERT—namely, the 5-HT receptors—have received much research attention.