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The genetics of selective serotonin reuptake inhibitors

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ABSTRACT

Selective serotonin reuptake inhibitors (SSRIs) are among the most widely prescribed drugs in psychiatry. Based on the fact that SSRIs increase extracellular monoamine levels in the brain, the monoamine hypothesis of depression was introduced, postulating that depression is associated with too low serotonin, dopamine and noradrenaline levels. However, several lines of evidence indicate that this hypothesis is too simplistic and that depression and the efficacy of SSRIs are dependent on neuroplastic changes mediated by changes in gene expression. Because a coherent view on global gene expression is lacking, we aim to provide an overview of the effects of SSRI treatment on the final targets of 5-HT receptor signal transduction pathways, namely the transcriptional regulation of genes. We address gene polymorphisms in humans that affect SSRI efficacy, as well as in vitro studies employing human-derived cells. We also discuss the molecular targets affected by SSRIs in animal models, both in vivo and in vitro. We conclude that serotonin transporter gene variation in humans affects the efficacy and side-effects of SSRIs, whereas SSRIs generally do not affect serotonin transporter gene expression in animals. Instead, SSRIs alter mRNA levels of genes encoding serotonin receptors, components of non-serotonergic neurotransmitter systems, neurotrophic factors, hypothalamic hormones and inflammatory factors. So far little is known about the epigenetic and age-dependent molecular effects of SSRIs, which might give more insights in the working mechanism(s) of SSRIs.

Contents

Abbreviations: 5-HT, 5-hydroxytryptamine, serotonin; 5-HTT, 5-hydroxytryptamine transporter, serotonin transporter; 5-HTTLPR, 5-hydroxytryptamine transporter-linked polymorphic region; AC, adenylyl cyclase; ACTH, adrenocorticotropic hormone; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; Avp, arginine vasopressin; BDNF, brain-derived neurotrophic factor; CMS, chronic mild stress; COMT, catechol-O-methyltransferase; CREB, cAMP-response element-binding protein; CRF, corticotrophin releasing factor; DA, dopamine; DRN, dorsal raphe nucleus; E(2), estradiol; ES cell, embryonic stem cell; GABA, gamma-aminobutyric acid; Gap-43, growth-associated protein-43; GR, glucocorticoid receptor; GSK3B, glycogen synthase kinase-3beta; HPA-axis, hypothalamus–pituitary–adrenal axis; HTR, hydroxytryptamine receptor; IDO, indoleamine 2,3-dioxygenase; LCLs, lymphoblastoid cell lines; MDD, major depressive disorder; MR, mineralocorticoid receptor; NE, norepinephrine; NMDA, N-methyl-D-aspartic acid; NPY, neuropeptide Y; Oxt, oxytocin; PDE, cAMP-specific phosphodiesterases; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; POMC, proopiomelanocortin; PVN, paraventricular nucleus; REM, rapid eye movement; RNA, ribonucleic acid; siRNA, small interfering ribonucleic acid; SNP, single nucleotide polymorphism; SSRIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant; tPA, plasminogen activator; Tph, L-tryptophan hydroxylase; VEGF, vascular endothelial growth factor.

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1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) are among the most widely prescribed drugs in psychiatry. Besides serving as antidepressants, they are also used in the treatment of anxiety-related disorders (obsessive compulsive disorder, social anxiety, panic disorders) (Bespalov et al., 2010), autism (Williams et al., 2010), eating disorders (Flament et al., 2012), and occasionally posttraumatic stress disorder (Stein et al., 2009). SSRIs increase the extracellular serotonin (5-hydroxytryptamine; 5-HT) levels in the synaptic cleft by blocking the serotonin transporter (5-HTT), a Na^+/Cl^- inward rectifying transporter (Tavoulari et al., 2009) located on presynaptic nerve terminals. This increase in extracellular levels of 5-HT is consistently shown in several brain regions by performing microdialysis followed by high-performance liquid chromatography (Bel & Artigas, 1993; Invernizzi et al., 1995; Kreiss & Lucki, 1995; Wong et al., 1995; Gundlah et al., 1997; Ceglia et al., 2004). The amount of increase can differ between studies, which might be caused by differences in SSRI treatment, brain region or timepoint of measurement. For example, it is shown that acute SSRI treatment results in a transient 5-HT increase, while repeated treatment increases baseline 5-HT levels (Kreiss & Lucki, 1995). There is no evidence that the SSRI-induced increase in extracellular serotonin is caused by blocking the serotonin break down or increasing serotonin synthesis. Due to negative feedback mechanisms caused by activation of inhibitory autoreceptors (discussed below), serotonin synthesis and release is even decreased (Wong et al., 1995). Some SSRIs (fluvoxamine (Luvox), fluoxetine (Prozac)) have varying degrees of selectivity for the 5-HTT, norepinephrine and dopamine transporters, whereas others (e.g. citalopram (Celexa), s-citalopram (Lexapro), paroxetine (Paxil), and sertraline (Zoloft)) have high affinity for the 5-HTT and only weak affinity for the noradrenaline and dopamine transporters (Carrasco & Sandner, 2005). Based on the fact that SSRIs increase extracellular 5-HT levels in the brain, the monoamine hypothesis of depression was introduced, postulating that depression is associated with too low 5-HT (and dopamine and noradrenaline) levels (Schildkraut, 1965). This hypothesis has governed the depression field for several decades. However there is accumulating evidence that this hypothesis is too simplistic. For instance, SSRI treatment results in desensitization of the 5-HT_{1A} autoreceptors and thereby cause an increase in raphe firing (Le Poul et al., 2000). In both animal and clinical studies it has been found that SSRI-5-HT_{1A} antagonist co-administration leads to enhanced antidepressant responses (Artigas et al., 1996; Portella et al., 2011). A recent study has also shown that a 5-HT_{1A} receptor siRNA conjugated to the SSRI citalopram had antidepressant effects in mice (Bortolozzi et al., 2011). These findings suggest that the antidepressant effects of SSRIs at least depend on 5-HT_{1A} receptor function. The process is rather complex and probably goes beyond the serotonin system. For instance, 5-HT_{1A} receptor activation results in a decreased release of glutamate (Drago et al., 2011). The monoamine hypothesis is also not in line with the finding that depletion of the 5-HT precursor tryptophan does not induce depression-like mood symptoms in healthy subjects (Ruhe et al., 2007).

In addition, there are several lines of evidence from rodent studies that in utero or neonatal exposure to SSRIs leads to paradoxical autism-, anxiety- and depression-like symptoms in later life (Olivier et al., 2011a). There is evidence that the 5-HTT expression pattern at early developmental stages is more widespread and it is shown that early life SSRI treatment can affect neurodevelopment (Homberg et al., 2010). Both, more widespread 5-HTT expression and neurodevelopment, can contribute to the paradoxical effects, however the exact mechanisms causing the differences at behavioral level are still not clear.

Furthermore, SSRIs increase risks of "possible suicidal ideation and suicidal behavior" by about 80%, and of "agitation and hostility" by about 130% in children with major depressive disorder (MDD) (Hammad, 2008). Consistent with these observations, animal experimental studies have shown that adolescent SSRI exposure leads to anxiety- and depression-related symptoms (Oh et al., 2009; Homberg et al., 2011). Taken together, a massive amount of data aiming to elucidate the working mechanism(s) of SSRIs has been generated, but simultaneously the findings have raised more questions than they answered. While it is clear that an increase in 5-HT per se does not increase mood state, it is still obscure what mechanisms do contribute to the therapeutic and side effects of SSRIs. Understanding these mechanisms is not only of high interest from a fundamental point of view, but also will lead to improvement of the treatment of disorders characterized by mood disturbances.

To understand SSRI mechanisms it is critical to comprehend 5-HT-mediated signaling. Up to now, 16 different 5-HT receptor subtypes have been identified: $5\text{-HT}_{1A, 1B, 1C, 1D, 1E, 1F}$, $5\text{-HT}_{2A, 2B, 2C}$, $5\text{-HT}_{3A, 3B}$, 5-HT_4, $5\text{-HT}_{5A, 5B}$, 5-HT_6 and 5-HT_7. All of them are G-protein coupled receptors, except for the 5-HT_{3A} and $_{3B}$ receptors which are ligand-gated ion channel receptors (Kriegebaum et al., 2010). The presynaptic 5-HT_{1B} receptor is expressed in rodents and auto-regulates 5-HT release, while the 5-HT_{1D} receptor fulfills this purpose in humans (Kriegebaum et al., 2010). The presynaptic inhibitory 5-HT_{1A} autoreceptor is located in the raphe nuclei and regulates the firing of serotonergic raphe neurons that project to widespread regions in the brain, as well as to the spinal cord. The 5-HT_{1A} and $5\text{-HT}_{1B/D}$ receptors, as all other 5-HT receptors, are also found postsynaptically. Since SSRIs have indirect (increasing serotonin) and direct (SSRI dependent affinity for receptors like 5-HT_2 (Palvimaki et al., 1996) and 5-HT_{1A} (Subhash et al., 2000)) effects on 5-HT receptors, 5-HT receptor agonists/antagonist are widely used to determine via which 5-HT receptor an SSRI effect is caused. Each receptor drives specific intracellular signaling pathways, targeting transcription factors to regulate transcription of multiple genes involved in components of the serotonergic and other neurotransmitter systems as well as in neurotrophic and developmental functions. In addition, 5-HT-receptor linked intracellular signaling pathways may target epigenetic processes like DNA methylation and histone acetylation/methylation (see Section 10). These epigenetic modifications influence the transcriptional machinery, and thereby provide another means by which SSRIs can affect a wide array of central processes. Given the multiple 5-HT receptors and their coupling to various signal transduction pathways and genomic targets (e.g. transcription regulators), which change across developmental stages and in response to external stimuli like stress or pharmacological agents, it may not be surprising that the mechanisms underlying SSRI effects are far more complex than the monoamine hypothesis suggests.

Here we aim to provide an overview of the effects of SSRI treatment on the final targets of 5-HT receptor signal transduction pathways, namely the transcriptional regulation of genes (Table 1). We address gene polymorphisms in humans that affect SSRI efficacy, as well as in vitro studies employing human-derived cells. We also discuss the molecular targets affected by SSRIs in animal models, both in vivo and in vitro (see Box 1 for the (dis)advantages of the biological materials).