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REVIEW

Interplay between the key proteins of serotonin system in SSRI antidepressants efficacy

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ABSTRACT

Introduction: Selective serotonin reuptake inhibitors (SSRIs) are the most effective and most used antidepressant drugs. Acting by inhibiting serotonin (5-HT) transporter, SSRIs display a typical 3–4-week delay in their therapeutic effects, with nearly 40% of depressed patients remaining treatment-resistant. Recent evidence suggests complex interplay between 5-HT receptors and key proteins of 5-HT metabolism in molecular mechanisms of such delay and resistance to SSRIs.

Area covered: This paper concentrates on the interplay between 5-HT receptors in the delay of therapeutic effect of SSRIs, and the interaction between tryptophan hydroxylase 2 and 5-HT transporter in the SSRI resistance. Specifically, it discusses: (1) the data on the association between antidepressant drug efficacy and genetically defined characteristics of key proteins in the 5-HT signaling (TPH2, MAOA, SERT and 5-HT_{1A} receptor), (2) the effect of dimerization of 5-HT_7 and 5-HT_{1A} receptors on the internalization and functioning of 5-HT_{1A} presynaptic receptors, (3) the role of *Tph2* deficiency in the resistance to SSRIs treatment. We shift the emphasis from individual proteins to their interactions in explaining antidepressant action of SSRI.

Expert opinion: These interactions should be considered when developing more effective antidepressant drugs as well as for predicting and improving the efficacy of antidepressant therapies.

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SSRI resistance; 5-HT; tryptophan hydroxylase 2; 5-HT transporter; 5-HT1A receptor; 5-HT7 receptor; gene polymorphism; gene knockout

1. Introduction

Depressive disorders are among the leading causes of mental disability in industrial countries [1–4] with about 12% of men and 21% of women having a life-time risk of depression [5,6]. Depression is associated with increased risk of suicide [7] and is highly comorbid with other mental disorders [8–10]. Antidepressant drugs occupy leading position in the global drug market [11]. Selective serotonin (5-HT) reuptake inhibitors (SSRIs), such as fluoxetine, citalopram, and paroxetine, are the most commonly used antidepressant drugs [12–19]. SSRIs were also found to be efficacious drugs for several anxiety disorders [20] and obsessive-compulsive disorder (OCD) [21]. However, two main problems are recognized concerning efficacy of SSRIs action. First, prolonged (2–4-week) delay in the onset of their therapeutic action [22]. Second, about 40% of patients with depressive, anxiety disorders and OCD remains refractory to the treatment [23–26]. Thus, the understanding of the molecular mechanism of action and efficacy of SSRIs becomes an important biomedical problem.

Recent studies indicate the growing recognition of multiple genetic, neuronal, and endocrine factors in resistance to antidepressants [24,25,27]. Therefore, the search for biomarkers associated with sensitivity to antidepressant drugs may help select optimal antidepressant for therapy and predict its therapeutic effect.

Two powerful genetic tools for studying the genetics of antidepressant drugs efficacy include genome-wide association studies (GWAS) and the candidate genes approach. GWAS has been applied in several large-scale psychopharmacological projects, including the Genome-Based Therapeutic Drugs for Depression (GENDEP), the Munich Antidepressant Response Signature (MARS), and the Sequenced Treatment Alternatives to Relieve Depression (STAR*D). These studies examined over 1,200,000 genetic markers (single-nucleotide polymorphisms, SNPs) [28,29] but failed to identify reliable predictors of antidepressants treatment outcome, although they did present modest direct evidence that common genetic variation contributes to individual differences in response to antidepressant drugs treatment [30].

Widely accepted, the 5-HT hypothesis of depression links the risk of depression to deficiency of 5-HT neurotransmission in the brain [31,32]. The main argument for this hypothesis is that most clinically effective antidepressant drugs increase 5-HT neurotransmission in the brain by blocking 5-HT degradation or

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Article highlights

- Understanding of the molecular mechanisms underlying the delay of therapeutic effect and resistance to SSRIs treatment is important biomedical problems.
- Recent evidence suggests a key role of complex interplay between the key proteins of 5-HT metabolism and reception in the molecular mechanisms of the therapeutic delay and resistance to SSRIs.
- Dimerization of 5-HT1A and 5-HT7 on the presynaptic membrane of 5-HT neurons decreases functional activity of 5-HT1A autoreceptor, attenuates the feedback inhibition of 5-HT secretion and can decrease delay of therapeutic effect of SSRIs.
- Interplay between 5-HT transporter and key enzyme of 5-HT synthesis, tryptophan hydroxylase 2, defines the level of 5-HT in the brain. Prolonged blockade of transporter with SSRIs decreases the brain 5-HT concentration in individuals with genetically defined low tryptophan hydroxylase 2 activity. Tph2 gene polymorphism attenuates the effect of SSRIs treatment.

reuptake, which elevates 5-HT levels in the synaptic cleft [13,14,33]. All genes encoding the enzymes of 5-HT metabolism, 5-HT transporter (5-HTT) and 5-HT receptors are considered as candidate genes associated with antidepressants efficacy. However, clinical data linking antidepressant drugs efficacy with polymorphisms in these genes remain conflicting [34–37].

A probable cause for these discrepancies can be that the commonly used genetic approaches are generally targeting only individual genes, rather than an interaction between two or more biomarkers. At the same time, mounting evidence suggests complex interplay between key enzymes, receptors and 5-HTT in modulating functional activity of central 5-HT system [38,39]. Here, we discuss the interplay between several key proteins of the 5-HT system (including enzymes of 5-HT synthesis and metabolism, as well as 5-HTT and 5-HT receptors) in sensitivity and resistance to SSRIs, and in the delay of their therapeutic action.

2. Central 5-HT system and SSRIs

The brain 5-HT system is one of the most expansive neurotransmitter systems. The cell bodies of 5-HT neurons are localized in the midbrain, while their terminals innervate all brain regions (except some areas of the cerebellum), with every cortical neuron receiving about 200 serotonergic contacts [40,41]. 5-HT is synthesized from the essential amino acid L-tryptophan by two brain enzymes, tryptophan hydroxylase 2 (TPH2) and aromatic L-amino acid decarboxylase (AAAD) (Figure 1). While AAAD is the widespread and nonspecific enzyme [42], TPH2 is the rate-limiting and the only specific enzyme of 5-HT synthesis and metabolism in the brain (with TPH1 playing a similar role in the periphery) [43,44]. An irreversible TPH1/TPH2 inhibitor, p-chlorophenylalanine [45,46], and TPH2 gene knockout [47–49] dramatically reduce 5-HT concentration in the brain. Synthesized 5-HT is stored in synaptic vesicles, transported to presynaptic terminals, and released in the synaptic cleft. The 5-HT secretion is regulated by the feedback mechanism including presynaptic 5-HT_{1A} and 5-HT_{1B} autoreceptors on the cell body of 5-HT neuron [50–52]. The secreted 5-HT interacts with 14 types of currently known 5-HT receptors with four different mechanisms of signal transduction [50,53].

Released 5-HT is removed from the synaptic cleft by the plasma membrane 5-HT transporter (5-HTT), which takes it into the presynaptic 5-HT neurons [54–56], where the neurotransmitter can either storage in the vesicles or be oxidized to 5-hydroxyindoleacetic acid (5-HIAA) by the monoamine oxidase A (MAOA) [57,58] (Figure 1). Therefore, 5-HTT, TPH2, presynaptic 5-HT_{1A} receptors, 5-HTT and MAOA regulate 5-HT concentration and 5-HT signaling in the brain. Moreover, 5-HTT and MAOA and are the molecular targets for the majority of antidepressant drugs.

3. Delay of the therapeutic effect of SSRIs treatment

Although SSRIs inhibit 5-HTT in minutes, their therapeutic effect usually appears several weeks later. Principal role of presynaptic 5-HT_{1A} autoreceptors desensitization in such delayed SSRI therapeutic effect has been widely recognized [59–62] (Figure 2). The 5-HT_{1A} receptor, which is located both pre- and postsynaptically, is an important regulator of neuronal development, plasticity [63,64], and 5-HT signaling [50]. The 5-HT_{1A} receptor has also been implicated in various physiological functions [65] and pathogenesis of depression, anxiety, suicide, and schizophrenia [66–70].

Activation of 5-HT_{1A} autoreceptors by endogenous 5-HT attenuates 5-HT neuronal firing rate, as well as 5-HT release, thereby providing an effective feedback mechanism to control 5-HT concentration in the synaptic cleft. Analysis of *postmortem* brains of depressed subjects revealed upregulation of 5-HT_{1A} autoreceptors in the raphe area, with no changes in postsynaptic 5-HT_{1A} receptors [71]. Chronic antidepressant treatment downregulates the 5-HT autoreceptors and suppresses the negative feedback mechanism in the regulation of 5-HT system (Figure 2). Therefore, a key element responsible for the onset of SSRI therapeutic action is progressive desensitization of 5-HT_{1A} autoreceptors, and the time course taken for this process determines the delay of antidepressant treatment effect [59–61]. The problem, however, is the unexplained selective desensitization by chronic SSRI treatment of 5-HT_{1A} autoreceptors, but not postsynaptic 5-HT_{1A} receptors.

There were three hypothetical mechanisms of 5-HT_{1A} receptor downregulation: (1) the internalization of 5-HT_{1A} receptors, (2) reversible violation of the conjugation between the receptor and the G_i-protein, or (3) destruction of 5-HT_{1A} receptors. Recently, a novel molecular mechanism of the downregulation of 5-HT_{1A} receptor activity has been discovered. It was shown that 5-HT_{1A} receptor, as other G-coupled receptors, could form homodimer with another 5-HT_{1A} molecule as well as heterodimer with other kinds of 5-HT receptor molecule [72,73]. Importantly, heterodimerization of 5-HT_{1A} and 5-HT_7 receptors changed functional activity of 5-HT_{1A} receptors [74].

4. Possible role of 5-HT_{1A} and 5-HT_7 receptors heterodimerization in anxiety and depression

The 5-HT_7 receptor, one of the least studied members of the 5-HT receptor is coupled to G_s-protein and activates adenylyl cyclase [75–77]. The brain 5-HT_7 receptors are mostly expressed in the limbic structures and raphe nuclei [78]. Highly co-localized 5-HT_{1A} and 5-HT_7 receptors can form heterodimers, and this heterodimerization facilitates the internalization and reduces functional activity of 5-HT_{1A} receptors [74,79]. Functional analysis of dimerization between 5-HT_{1A} and 5-HT_7 receptors reveals that hetero-oligomers decrease 5-HT_{1A} receptor-mediated activation

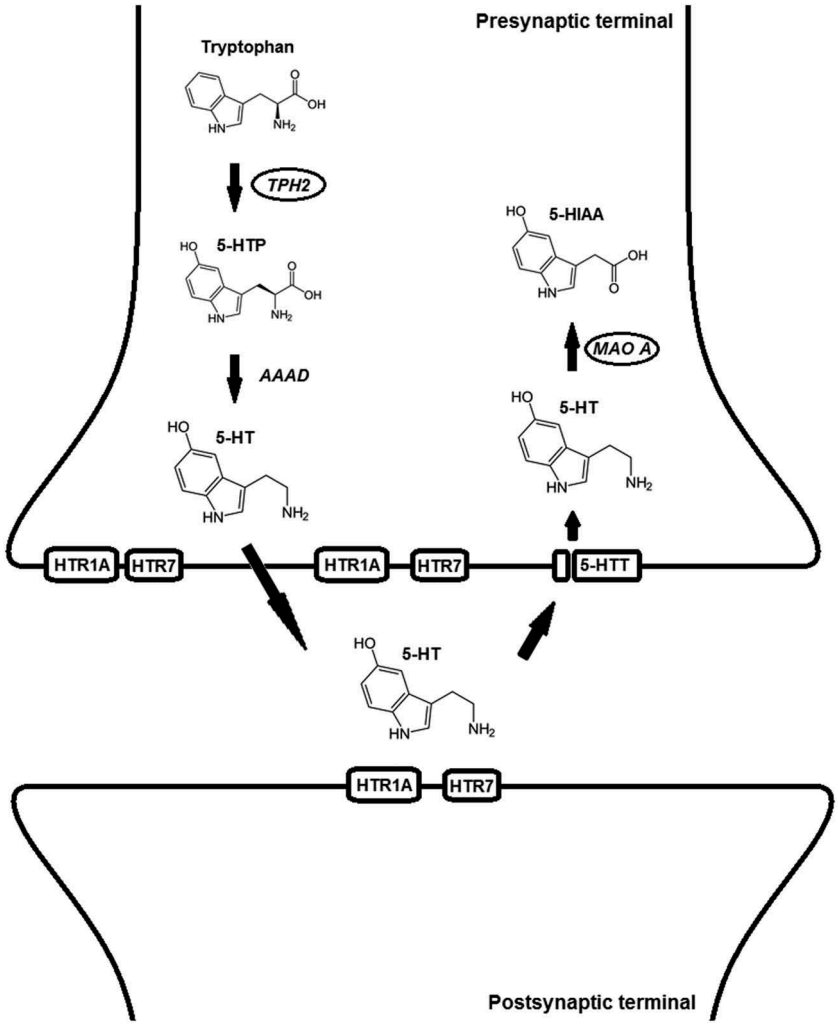

Figure 1. Summary of the 5-HT synthesis, turnover and metabolism in the brain. In the presynaptic neuron, tryptophan hydroxylase 2 (TPH2) hydroxylates L-tryptophan to 5-hydroxytryptophan (5-HTP), followed by decarboxylation of 5-HTP by L-aromatic amino acids decarboxylase (AAAD) to 5-HT. The synthesized 5-HT is deposited in synaptic vesicles, which are transported to the neuron endings. After depolarization 5-HT is released into the synaptic cleft. The presynaptic 5-HT1A and 5-HT7 autoreceptors are interact to regulate the 5-HT secretion. The secreted 5-HT interacts with numerous postsynaptic 5-HT receptors. 5-HT transporter (5-HTT) reuptake 5-HT into presynaptic neuron where the neurotransmitter is redeposited in vesicles or oxidized to the final product of 5-HT metabolism in the brain, 5-hydroxyindoleacetic acid (5-HIAA), by monoamine oxidase A (MAOA).

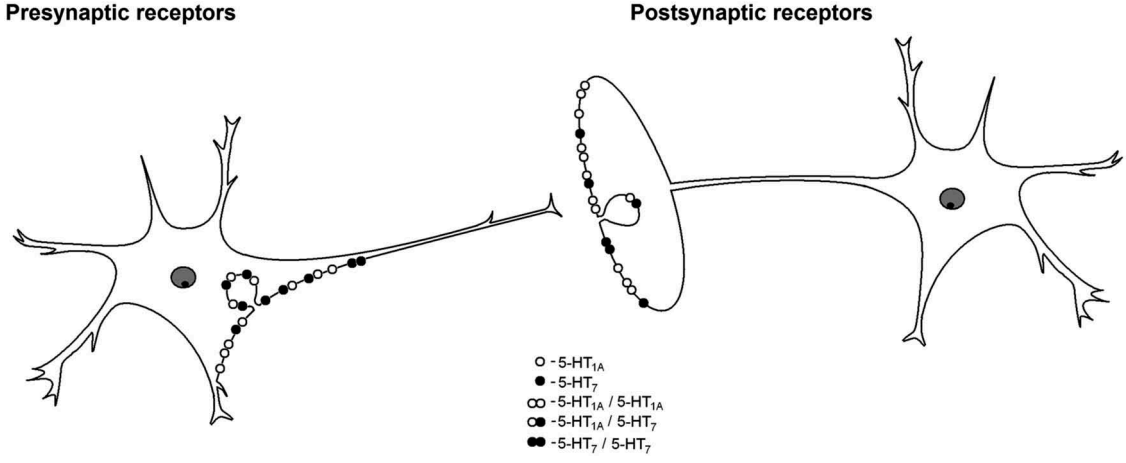

Figure 2. The proposed model of the involvement of presynaptic 5-HT_{1A} autoreceptors and the 5-HT_{1A}/5-HT_7 receptors interaction in the mechanism of the delay of therapeutic effects of SSRIs. The increase of 5-HT in the synaptic cleft induced by an acute SSRI administration inhibits 5-HT release from the presynaptic endings via the 5-HT_{1A} receptor-dependent feedback mechanism. Chronic SSRI treatment desensitizes 5-HT_{1A} autoreceptors. The 5-HT_{1A}/5-HT_7 dimerization decreases functional activity and facilitates the SSRI-induced desensitization of the presynaptic 5-HT_{1A} autoreceptors. The SSRI-induced 5-HT_{1A} receptor desensitization restores the 5-HT release in the synaptic cleft and thereby results in antidepressant therapeutic effect (From Naumenko et al. 2014 [39]).

of G_i-protein without affecting 5-HT_7 receptor-mediated activation of G_s-protein.

Different concentration of 5-HT_{1A}/5-HT_7 heterodimers in 5-HT presynaptic autoreceptors versus postsynaptic receptors can potentially explain not only the difference in desensitization of pre- versus postsynaptic 5-HT_{1A} receptors, but also suggests that the balanced ratio of homo- and heterodimerization in pre- and postsynaptic neurons may be critically involved in sensitivity to SSRIs treatment. Moreover, differences in relative concentration of 5-HT_{1A}/5-HT_7 heterodimers in the raphe nuclei and hippocampus may explain regional differences in the coupling of 5-HT_{1A} receptor to G-proteins and, subsequently, distinct responses to chronic antidepressants treatment [39] (Figure 2).

In adult brain, the density of 5-HT_7 receptors in the midbrain raphe nuclei area (with prevailed presynaptic 5-HT_{1A} receptors) is higher than in the hippocampus and other brain regions with prevailed postsynaptic 5-HT_{1A} receptors. Therefore, high 5-HT_{1A}/5-HT_7 heterodimerization and subsequent functional desensitization of 5-HT_{1A} receptors in the midbrain can decrease the inhibitory effect of presynaptic 5-HT_{1A} receptors on the brain 5-HT system functioning. This possibility [39], based on 5-HT_{1A}/5-HT_7 receptors dimerization, adds the 5-HT_7 receptors to the list of potentially important players in the mechanism of autoregulation of the brain 5-HT system and, albeit necessitating additional investigation, may provide novel explanation for regional difference in 5-HT_{1A} receptors response and delayed clinical effect of SSRIs.

5. Resistance to SSRIs

Several comprehensive recent reviews on possible mechanisms of resistance to antidepressant therapy [see 24, 25] may benefit from more mechanistic, factor-specific molecular analyses. Here, we discuss selected factors relevant to the known mechanisms of antidepressant drugs action.

Hereditary resistance to SSRIs treatment has long been linked to mutations in genes encoding 5-HT_{1A} receptor, MAOA, 5-HTT, and TPH2. However, clinical data linking SSRIs efficacy with polymorphism in these genes remain conflicting [34–37].

Mice are a valuable tool for reverse genetics and a useful model for testing antidepressant drugs [80]. In clinical study, antidepressants efficacy is usually evaluated as an improvement in depressive score of the patients. What are animal equivalents of such depressive score? Any animal model for testing antidepressants must meet three main criteria of validity [81,82], including face, predictive, and construct validity. The predictive validity remains the main criterion for experimental antidepressant drugs screening, and several rodent models do possess high predictive validity. For example, the forced swim and tail suspension tests are the simplest, commonly used assays with a nearly 95% predictive validity for clinically effective SSRIs [81,83,84].

At present, there are several knockout, knockin, and congenic mouse lines to study the association the genes encoding 5-HT_{1A} receptor, MAOA, 5-HTT, TPH2 with SSRIs efficacy (Table 1).

MAOA is the main enzyme of 5-HT catabolism. MAO inhibitors increase the neurotransmitter concentration in the brain and produce a therapeutic effect in some depressive patients. The *Maoa* gene deficient mice (Tg8) with increased 5-HT levels and decreased 5-HIAA/5-HT ratio [87,88] is a promising model to study the association between hereditary MAOA deficiency and SSRIs efficacy. MAOA deficiency increases the effect of SSRIs on 5-HT neurotransmission. Indeed, SSRI citalopram produces more intensive 5-HT release in MAOA deficient Tg8 than in wild-type C3H mice [89]. Regretfully, the effect of SSRIs on the depressive-like behavior of Tg8 mice was not studied.

Since presynaptic 5-HT_{1A} autoreceptors attenuate 5-HT release and their blockade may accelerate SSRIs action [52,124], their role in genetics of antidepressant response can be reasonably expected. The 5-HT_{1A} receptor-deficient mice were generated on three genetic backgrounds – 129/SvJ [93], Swiss [91], and C57BL/6J [92]. The 5-HT_{1A} receptor knockout does not affect the levels of 5-HT and 5-HIAA in the brain [93–96], but reduces immobility time in the tail suspension test [101]. Moreover, the suppression of 5-HT_{1A} receptor mRNA by the selective siRNA

Table 1. Genetically modified mouse strains used to study the effects of MAOA, 5-HT_{1A} receptor, SERT, and TPH2 deficiency on behavior and antidepressants efficacy.

Human gene and prototype	Mouse model	Control genotype (background)	Anxiety and depressive-like behavior, 5-HT system
MAOA knockout [85], 1.2 kb upstream VNTR, 3-repeats allele [86]	Maoa$^{-/-}$ mice (Tg8)	C3H [87]	Increased 5-HT and decreased 5-HIAA levels in the brain in young [87] and adult [88] mice. Increased spontaneous 5-HT release [89] and elevated anxiety in the light/dark test [90].
HTR1A	Htr1a$^{-/-}$ mice	Swiss [91] C57BL/6J [92] 129/SvJ [93]	No or 50% reduction of 5-HT_{1A} receptors level in Htr1a$^{+/-}$ and Htr1a$^{\pm}$ mice, respectively [91–93]. Unaltered metabolism or release of 5-HT in the brain of Htr1a$^{-/-}$ mice [93–96]. Increased anxiety in the open field, plus-maze, zero-maze, or novel object tests [91–93,97–99]. Antidepressant-like effect in the forced swim [101,102] and tail suspension [92,100,101] tests.
SLC6A4, 5-HTTLPR [102,103]	Slc6a4$^{-/-}$ and Slc6a4$^{+/-}$ mice	C57BL/6J [104]	No or 50% reduction of SERT in the brain of Slc6a4$^{-/-}$ or Slc6a4$^{+/-}$ mice, respectively [104,105]. Increased 5-HT level in the synaptic cleft in the brain of Slc6a4$^{-/-}$ mice [106,107]. Increased anxiety in the plus-maze [103] and the open field [108] tests. Conflicting depressive-like phenotypes in the forced swim and tail suspension tests [109], unaltered sucrose preference [110].
TPH2	Tph2$^{-/-}$ mice	C57BL/6 [47–49]	Reduced 5-HT level in the brain (<8% of the wild-type mice) [47–49]. Decreased anxiety in the elevated plus- [111,112], novelty-suppressed feeding and dark/light box [112,114] tests. Decreased [48] or increased [112] depressive-like immobility in the forced swim test.
TPH2, **R441H** [115]	**R439H** mice	C57BL/6 [116]	80% reduction of TPH2 activity and 5-HT level, increased anxiety-related behavior in the dark/light box, decreased depressive-like immobility in the tail suspension test [116,117].
TPH2, G6493A [118]	C1473G, **P447R** B6-1473G/B6-1473C	C57BL/6 [119–121]	50% reduction of TPH2 activity in the brain [120,122,123] but unaltered 5-HT and 5-HIAA levels [121]. B6-1473G mice show lower immobility in the forced swim test vs. the B6-1473C mice [120].

administration produces marked antidepressant-like effects in the forced swim and tail sustention tests [125,126] (Table 1). At the same time, 5-HT_{1A} receptor deficiency in 5-HT_{1A} receptor gene (*Htr1a* gene) knockout mice [94–96] or induced by siRNA administration [126] markedly increased the 5-HT extracellular concentration evoked by SSRIs treatment.

With a minor nonspecific contribution from dopamine and norepinephrine transporters, 5-HTT selectively reuptakes 5-HT from the synaptic cleft into the 5-HT neurons, thereby controlling extracellular 5-HT level and restoring intraneuronal pool of this neurotransmitter. SSRIs block 5-HTT and increase 5-HT concentration in the synaptic cleft. Among numerous mutations in the human 5-HTT gene (*Slc6a4)*, two common mutations in the promoter and the second intron are the most studied. The STin2 polymorphism in the second intron of 5-HTT gene includes 10 or 12 repeats of 17 bp sequence [127]. The 5-HTTLPR polymorphism in the promoter region includes mainly 14 (short) or 16 (long) repeats of 22 bp [102,128]. The short alleles of these polymorphisms reduce the *SLC6A4* gene expression *in vitro* compared with the long alleles [102,129]. However, the clinical data on association of these polymorphisms with SSRI efficacy are rather conflicting [37].

Since 5-HTT is the primary target for SSRIs, mice with genetic ablation of 5-HTT gene (*Slc6a4*$^{-/-}$) show blunted response to these drugs [103,109]. Vital and fertile, these mice are devoid of functional 5-HTT, and therefore cannot reuptake the majority of 5-HT [104], except for trace amounts of 5-HT still nonspecifically uptaken by other monoamine transporters. 5-HTT expression and 5-HT reuptake in the brain of heterozygous *Slc6a4*$^{+/-}$ mice are about 50% of the wild type values [104,105], strikingly paralleling human carriers of the S/S genotype of 5-HTTLPR polymorphism [103]. The basal concentrations of extracellular 5-HT were markedly increased in the cortex, striatum [107], and substantia nigra [106] in the *Slc6a4*$^{-/-}$ mice.

Homozygous 5-HTT-deficient mice show numerous behavior alterations compared with their wild-type and heterozygous counterparts (Table 1). The *Slc6a4*$^{-/-}$ mice of three genotypes on the C57BL/6J genetic background do not differ in the depressive-like immobility time in the tail suspension and forced swim tests, but the *Slc6a4*$^{-/-}$ mice with the 129/S6 genetic background show decreased tail suspension and increased forced swim immobility [109]. Acute administration of SSRI, fluoxetine, does not alter the *Slc6a4*$^{-/-}$ mouse immobility, but produces overt antidepressant effects in both control *Slc6a4*$^{+/+}$ and *Slc6a4*$^{+/-}$ mice [103,109], collectively negating the clear link between genetic deficits in 5-HTT function and SSRI efficacy.

TPH2 is the key enzyme of 5-HT synthesis in the brain and, therefore, its gene may be a likely candidate gene for SSRIs resistance. There are three currently available mouse models of genetically defined TPH2 deficiency: (1) several TPH2 gene knockout strains [47–49,114], (2) the R439H knockin strain [116], and (3) 'natural' C1473G polymorphism [122,123]. The TPH2 knockout markedly reduces 5-HT level in the mouse brain without altering 5-HT neuron formation and migration [47–49], but causes delayed development and early postnatal growth retardation [49,130]. The R439H knockin is a homologous model of human R441H polymorphism, resulting in 80% reduction of the mouse TPH2 activity as well as 5-HT and 5-HIAA levels in the brain [116]. C1473G polymorphism in the TPH2 gene results in about 50% reduction of the enzyme activity in the brain [119,120,122,123]. Recently, the G allele has been transferred from the Balb/c [121] or CC57BR [119,120] to the C57BL/6 genetic background, and two congenic strains (B6-1473C and B6-1473G mice) with high and low TPH2 activity have been generated. While these strains show about 50% difference in the rate of 5-HT synthesis, they do not differ in 5-HT and 5-HIAA levels in the brain [121,131,132].

The link between depressive-like behavior and TPH2 deficiency in mice is unclear, as some studies report a mild antidepressant effect of TPH2 gene knockout [48] and C1473G polymorphism [120], while others shows increased depressive-like immobility in the forced swim test, without altering the tail suspension test behaviors [112]. At the same time, the R439H knockin mice are more immobile (and, therefore, more depressive) in the tail suspension test [116,117].

In contrast, experimental data linking TPH2 deficiency and antidepressant-like response to SSRIs are more consistent. For example, citalopram [133] and paroxetine [134] decrease depressive-like immobility in the forced swim test in C57BL/6 and 129/Sv strains homozygous for 1473C allele (high TPH2 activity) but failed to produce antidepressant-like effect in mice homozygous for 1473G allele (Balb/c and DBA2 strains with low TPH2 activity). A TPH2 inhibitor, pCPA, reduced antidepressant-like effect of citalopram in C57BL/6 and 129/Sv mice, whereas boosting 5-HT synthesis with L-tryptophan restores lowered antidepressant-like response to citalopram in Balb/c and DBA2 mice [133]. Both citalopram and paroxetine reduced immobility in the forced swim test in B6-1473C mice with high TPH2 activity, but not in B6-1473G mice with low TPH2 activity [135] (Figure 3), however, showing no difference between the B6-1473C and B6-1473G congenic mice in the effect of citalopram in the tail suspension test [121].

As already mentioned, all clinically effective SSRIs produce therapeutic (antidepressant) effects only after several weeks of treatment. Chronic treatment with fluoxetine or paroxetine reduced brain 5-HT level in the R439H knockin mice to 1–3%, while in their wild-type counterparts this reduction was less pronounced [136] (Figure 4). Figure 5 outlines possible mechanism of this 5-HT level reduction. 5-HTT returns 5-HT from the synaptic cleft to the presynaptic serotonergic neuron for further neurotransmitter reutilization. The 5-HTT blockade by SSRIs prevents this 5-HT reuptake, thus resulting in 5-HT loss from the presynaptic pools. High TPH2 activity can compensate this 5-HT loss, and be sufficient to maintain normal 5-HT level in the brain, In contrast, low activity of mutant TPH2 does not minimize the 5-HT loss, causing a dramatic reduction of 5-HT levels in the brain in R439H mice [136]. Thus, SSRIs can produce negative effect on nervous system and behavior instead of expected positive therapeutic effects [136].

Finally, the application of MAOA, 5-HT_{1A} receptor, 5-HTT, or TPH2-deficient mice clarified the role of interaction between the corresponding proteins and efficacy of SSRIs. The MAOA

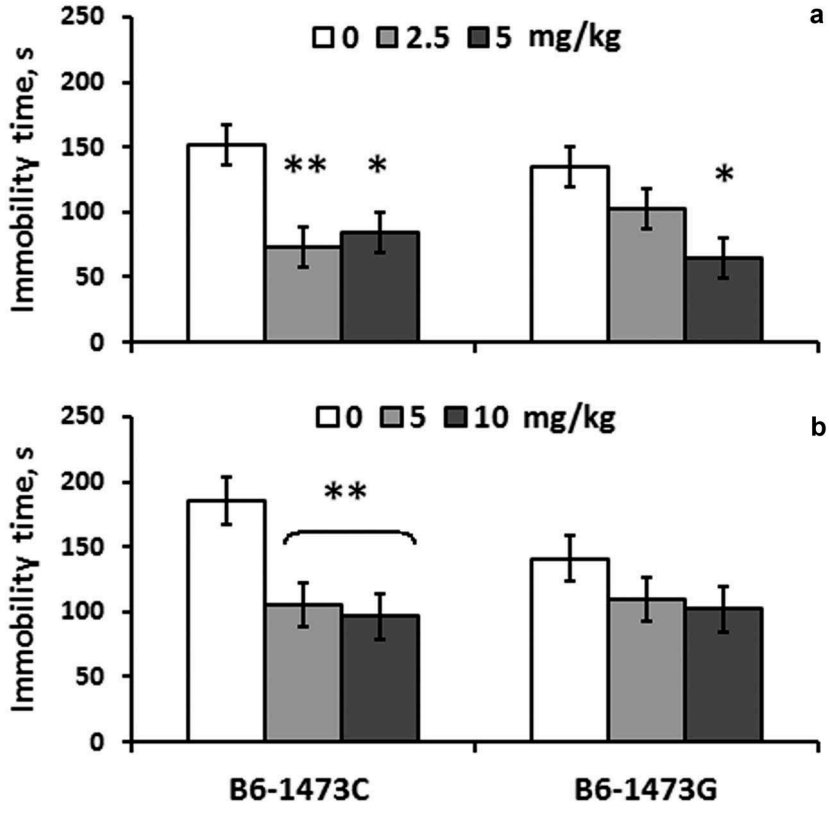

Figure 3. Effect of acute. administration of citalopram (2.5 and 5.0 mg/kg) (a) and paroxetine (5.0 and 10.0 mg/kg) (b) on immobility time of the B6-1473C (high TPH2 activity) and B6-1473G (low TPH2 activity) mice in the forced swim test. Note that both SSRIs significantly reduced immobility in B6-1473C, but not in B6-1473G mice, * $p < 0.05$ vs vehicle-treated control group (from Kulikov et al. 2011 [135]).

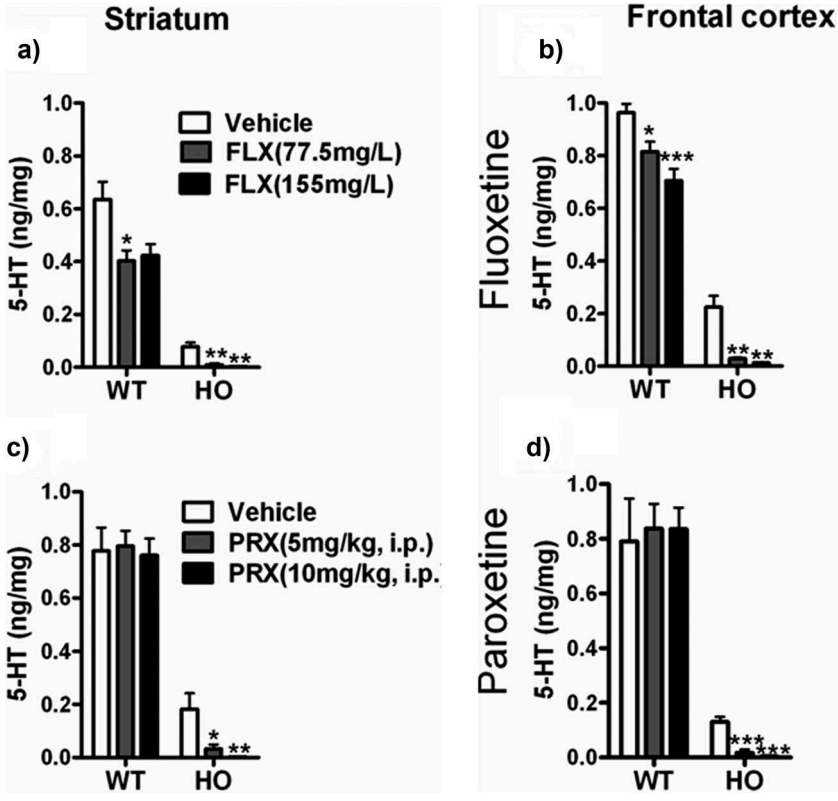

Figure 4. Effects of chronic fluoxetine (FLX) and paroxetine (PRX) treatment on 5-HT levels in the *Tph2KI* mutant (HO) and wild-type mice (WT). Levels of 5-HT in HO R439H *Tph2* mice, which are normally 20% of wild-type baseline levels, are depleted further and to a greater extent than in wild-type mice by chronic fluoxetine treatment in the drinking water for 6 weeks. 5-HT levels for FLX are shown in the striatum (a) and the frontal cortex (b). Similar to FLX in drinking water, chronic i.p. PRX treatment depleted the 5-HT levels to a greater extent in HO R439H Tph2 mice in the striatum (c) and the frontal cortex (d). Data are expressed as ng/mg wet tissue weight and presented as mean ± SEM *, **, ***, $p < 0.05$, 0.01, 0.001 vs vehicle [from 136].

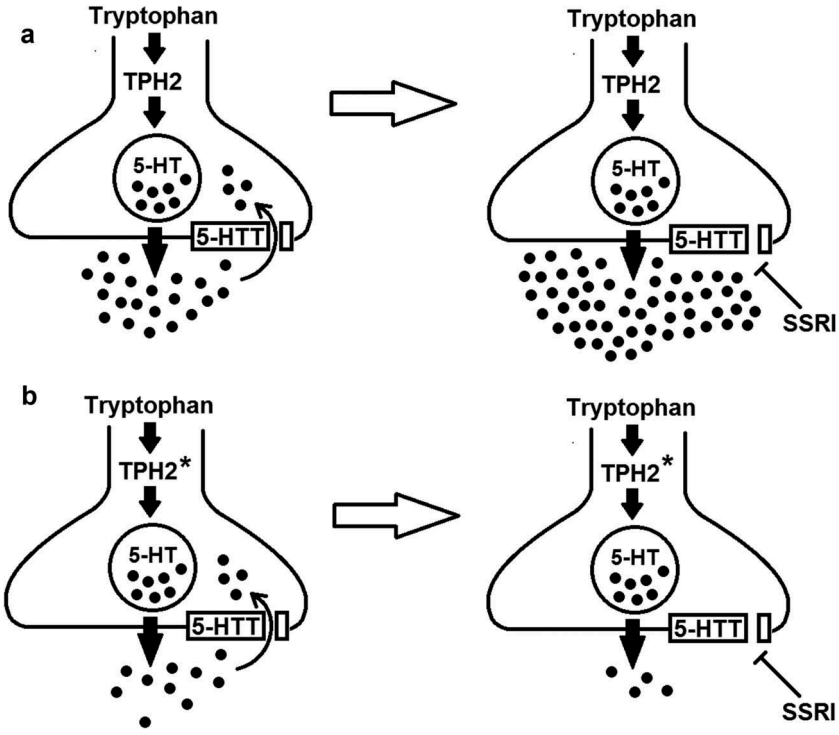

Figure 5. A possible mechanism of the interplay between 5-HT transporter (5-HTT) and tryptophan hydroxylase 2 (TPH2) in the mechanism of SSRI resistance. (a) 5-HTT brings back to the presynaptic neuron a major portion of 5-HT secreted in the synaptic cleft. SSRI inhibits the 5-HTT that result in increased extracellular 5-HT level but also in decreased intraneuronal stores of 5-HT. High TPH2 activity is sufficient to compensate the inevitable loss of 5-HT in the neuron during SSRI treatment. (b) Low TPH2 (TPH2*) activity together with normal 5-HTT-mediated reuptake can maintain a steady-state (albeit lower) 5-HT level in the presynaptic neuron. At the same time, low TPH2* activity itself is insufficient to maintain steady intraneuronal 5-HT level when 5-HTT is inhibited with SSRI. Therefore, a chronic SSRI treatment results in dramatic loss of 5-HT in the brain of individuals with low TPH2 activity.

deficiency enhanced SSRI effects on extracellular 5-HT, whereas the *Htr1a* gene knockout evoked a pronounced antidepressant-like action even without any additional SSRIs treatment. Studies using *Slc6a4*$^{+/-}$ mice with 50% *Slc6a4* gene expression show that these heterozygous mice have unimpaired sensitivity to SSRIs. Taken together, these data suggest that *Maoa, Htr1a, Slc6a4* deficient mouse models do not confirm essential role of these genes in mechanisms of SSRI resistance, and may require shifting research focus to the role of the TPH2 and 5-HTT interaction in antidepressant responses in both mouse models and human populations.

6. Expert opinion

Overall, novel insights into the role of 5-HT receptors and the recently identified role of genetically defined activity of TPH2 seems to explain two main challenges related to SSRIs antidepressant efficacy – the delay of the onset of their therapeutic effect, and the high percentage of depressive patients that remain insensitive/resistant to SSRIs.

Progressive desensitization of 5-HT_{1A} autoreceptors and the time taken by this process may determine the delay of antidepressant treatment [52,59–61]. The selectivity of such desensitization only presynaptic 5-HT_{1A} receptors can be explained by recent data on the role of 5-HT_{1A} receptor dimerization in the internalization and functional activity of 5-HT_{1A} and 5-HT_7 receptors. The dimerization of 5-HT_{1A}/5-HT_7 receptors facilitates internalization and reduces functional activity of 5-HT_{1A} receptors [74,79]. Notably, the density of 5-HT_7 receptors is higher in the midbrain raphe nuclei (with prevalent presynaptic 5-HT_{1A} receptors) than in brain regions with predominantly postsynaptic 5-HT_{1A} receptor localization. Thus, the 5-HT_{1A}/5-HT_7 dimerization decreases the functional activity of presynaptic 5-HT_{1A} autoreceptors and makes them less effective as 5-HT autoinhibitors, thereby promoting antidepressant response [39].

Modulation of receptor signaling by 5-HT_{1A}/5-HT_7 heterodimerization, including enhanced 5-HT_{1A} receptor internalization, is also likely to play a role in CNS pathophysiology, and may also be of clinical interest, since both receptors are important targets for depression and anxiety therapy.

In addition to 5-HT_{1A}, compounds acting on other 5-HT receptors can also lead to new therapies. Notably, agonists of 5-HT_4 receptors exert a rapid antidepressant effect in rodents after a 3 days treatment [137]. These effects in rats were accompanied by a desensitization of 5-HT_{1A} presynaptic and sensitization of postsynaptic 5-HT_{1A} receptors in hippocampus, thus suggesting the interplay between 5-HT_4 and 5-HT_{1A} receptors in the effect of antidepressants.

Numerous clinical observations of the association between the SSRIs efficacy and the genetically defined characteristics of key proteins in 5-HT signaling (TPH2, MAOA, 5-HT_{1A} receptor, and 5-HTT) remain contradictory and complicate our understanding of the SSRIs resistance. During the last decades, multiple transgenic, knockout and mutant mouse strains have been generated, offering another opportunity to test the effect of individual genes and proteins on antidepressant drug efficacy [80].

Preclinical studies using the 'reverse genetics' (from gene to traits) approach and mutant mouse strains also failed to

confirm the association between MAOA, 5-HTT, and 5-HT_{1A} receptor deficiency and resistance to SSRIs treatment, since their ablation produced antidepressant-like or no effects on SSRIs action. In contrast, 5-HT_7 receptor deficiency may attenuate the 5-HT downregulation induced by presynaptic 5-HT_{1A} receptors and, therefore, increase the therapeutic delay or produce the antidepressant resistance.

At the same time, experimental data consistently show essential role of TPH2 deficiency in the efficacy of SSRIs treatment. The observation that chronic SSRI treatment further reduces 5-HT levels in mice with decreased TPH2 activity may indicate a probable TPH2-mediated mechanism of antidepressant resistance [136]. The effect of interplay between 5-HTT and TPH2 on SSRIs resistance is also in line with proposed drug target × drug sensitivity predictor interplay [27], as 5-HTT is the target for SSRIs while TPH2 acts as a predictor for their clinical effects. Finally, this interplay may also be clinically relevant for 'personalizing' pharmacotherapy, since SSRI therapy could not be recommended for depressive patients with reduced TPH2 activity (where other treatments, such as MAOA inhibitors or 5-HT precursor 5-hydroxytryptophan, may be more effective).

These considerations also highlight the need to explore mutations reducing TPH2 activity. Such functional mutations are rare, and alone cannot explain the high (20–40%) percent of SSRI-resistant patients. To address this question, one may consider a target sequencing of the TPH2 gene in patients with SSRI-resistant depression in order to find new rare mutation(s) that decrease TPH2 activity. Other approaches may focus on common mutations with moderate negative effects on TPH2 activity. One of such mutations is the G6493A polymorphism (SNP rs1389493) with 6493A allele found in about 18% of Caucasian populations [118].

In summary, this review proposes shifting the research focus from individual genes and proteins to their interactions in explaining the mechanism of action of SSRIs antidepressants. These interactions should be considered when developing antidepressant drugs as well as for predicting and improving of the efficacy of existing antidepressant therapies.

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Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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