Pharmacology of Selective Serotonin Reuptake Inhibitors (SSRIs) in anxiety disorders

MeiKi Wan *

Department of Chemistry, University of California, Los Angeles, 90095, United States of America

* Corresponding Author Email: wanmeiki@outlook.com

Abstract. Selective Serotonin Reuptake Inhibitors (SSRIs) are considered as the first-choice medication for anxiety disorders. However, the exact mechanism of SSRIs' anxiolytic property is still unclear. In addition, the anxiolytic effect of SSRIs is far from perfect as resistance of the SSRIs' effect and other SSRIs-related side-effects are occasionally observed in the process of SSRIs-related anti-anxiety treatments. This study investigates the anxiolytic property of SSRIs, the direct pharmacological effect of SSRIs and the interactions of SSRIs with some of the possible downstream targets. With competitive inhibition of serotonin reuptake by serotonin transporter (SERT) in serotonergic neurons in the brain, SSRIs could lead to an elevation of extracellular/ intrasynaptic level of serotonin in the brain. SSRIs-mediated elevation of serotonin level could further cause the overall activation of serotonin receptors (5-HTRs). Among various 5-HTRs, the activation of 5-HT1A auto receptor and its desensitization after chronic stimulation was found to be some of the key factors are associated to SSRIs-mediated anxiolytic effect by modulating presynaptic activity of serotonergic neurons and optimizing serotonergic signal transduction in the brain. Nonetheless, due to the complexity of 5-HTR system and current limited knowledge about the function of 5-HTRs, it is still difficult to determine the complete mechanism behind SSRIs' anxiolytic effect and further exploration on the working mechanism of 5-HTRs may be required to decipher the anxiolytic nature of SSRIs.

Keywords: Selective Serotonin Reuptake Inhibitor (SSRI), Pharmacology, Anxiety, serotonin receptor (5-HTR).

1. Introduction

According to The Diagnostic and Statistical Manual for Mental Health Disorders-5 (DSM-5), Anxiety disorders are described as a category of disorders that leads to long-term (>6 month) uncontrollable anxiety and feelings of fear which affect the normal functions of patients in daily settings. Generalized anxiety order, social anxiety order, and panic disorder are some of the common disorders which are classified in that category. Including the DSM-5 and recent studies, the increasing global prevalence of anxiety orders is recognized (458 million diagnosed cases globally in 2019, 45.8 million newly diagnosed cases compared to the previous year) [1]. In the current view, despite the developing impact of anxiety disorders, direct and specific pharmacological treatment for anxiety disorders have not been discovered yet. Anti-depressants, especially, selective serotonin reuptake inhibitors (SSRIs) remain as the first-choice medications for anxiety disorder. However, the mechanism behind SSRIs' anit-anxiolytic effect is not completely clear. While.

SSRIs have shown overall positive effects as anxiolytic drugs compared to placebo in placebo-controlled clinical trials (The overall combined effect size, Hedges' g~0.4), the effect of different SSRIs could vary among patients. It is possible that SSRIs can have little or no effect on treating certain patients with anxiety [2]. Besides the uncertainty of treatment effect, the action of SSRIs lacks immediacy (usually 4-6 weeks are needed to reach full potency) and could occasionally lead to adverse side effects (e.g. nausea, gastro-intestinal symptoms, fatigue, sexual dysfunction) [3]. Considering the important role of SSRIs in current anti-anxiety treatments and its limitations, the elucidation of the nature of SSRIs' anxiolytic effect is necessary, and that may also shed light on the pathological property of anxiety disorders and the improvement of related therapeutic strategies.

As SSRIs are mainly recognized as anti-depressants, SSRIs are a series of drugs that are designed based on the "serotonin deficit hypothesis" proposed in the 1960s, which associates depression and other affective disorders to the lowering of serotonin level in the central nervous system (CNS),

especially the brain, of the patient [4]. Thus, the therapeutic effects of SSRIs on psychiatric disorders are often considered as the result of their modulational effect on the serotonergic system. Following the logic above, as the primary target of SSRIs, the serotonergic system and its interaction with SSRIs will be the core of the discussion of SSRIs' pharmacology in anxiety disorders. Thus, in order to investigate the underlying mechanism of SSRIs as anit-anxiolytic agents, this work will explore the pharmacological property of SSRIs by analysing SSRIs' interaction and effects on biological pathways that are targeted directly by SSRIs and potential downstream targets that are related to SSRIs' anxiolytic effect.

2. Inhibition of Serotonin Reuptake by SSRIs

As the decrease in serotonin level in the brain is hypothesized as the cause of affective disorders including anxiety disorders, the pharmacokinetics of SSRIs acts against that effect by suppressing the reuptake of serotonin (5-hydroxytryptamin, 5-HT). In serotonergic neurons, serotonin molecules in the inter-synaptic space are eliminated or re-absorbed by monoamine oxidase or serotonin transporter (SERT). The later one (SERT) is the major molecular target of SSRIs.

Most SSRIs are the competitive inhibitors of SERT. By occupying the active site of SERT, SSRIs could block the reuptake of serotonin by SERT and increase the extracellular serotonin level in theory. Matching the hypothesized pharmacology of SSRIs, SSRIs could contribute to considerable occupancy of SERT under effective dosage (~80% SERT occupancy on average is observed in PET studies on patients of chronic SSRIs treatment) [5]. While the direct measurement of serotonin level in human CNS is hard to achieve, the increase in serotonin level in CNS of animal models and the elevation of blood serotonin level in patients are observed after receiving SSRIs treatment [6,7]. Those evidence indicate that SSRIs could have a significant effect on boosting the serotonin level in CNS by the inhibition of SERT. Considering the direct interaction between SSRIs and SERT, the blockage of serotonin reuptake in serotonergic neurons by SSRIs and the following increase of serotonin level could be viewed as the primary pharmacological effect of SSRIs.

While the inhibition of Serotonin reuptake is recognized as the major pharmacological effect in serotonergic neurons in the CNS, it is often considered that the therapeutic effect of SSRIs is not incurred by this direct process but by the downstream regulation of neurotic function that facilitated by the change in brain chemistry (mainly the elevation of serotonin level). Thus, the investigation of the downstream effect caused by SSRIs is an important focus on the exploration of the anxiolytic property of SSRIs.

3. Activation of Serotonin Receptors via SSRI-mediated Elevation of Serotonin Level

With the elevation of the extracellular and intersynaptic serotonin level caused by SSRI, the immediate effect of this change in chemistry is the rise of the level of the activation of serotonin receptors in serotonergic neurons. Serotonin receptors describe the group of receptors that can receive serotonergic signals and widely exist in serotonergic neurons. Except 5-HT3R (ligand-gated cationic channels), Most of them (from 5-HT1, 2, 4, 5, 6, 7R family) are G-protein coupled receptors and are involved in secondary signalling cascade within serotonergic neurons, which could mediate the regulation of cellular behavior of other neurons, including the release of neural transmitters and modulation of neural dischanges [8]. Owing to their potential to modulate neural activity, those receptors are thought to play key roles in SSRIs-mediated anxiolytic treatment. Among the various types of serotonin receptors, 5-HT1R, 5-HT2R, 5-HT3R, 5-HT4R, 5-HT7R are some of the receptor families that are speculated to have relation to the formation and regulation of anxiolytic behavior [9]. However, most of their precise roles and functions in the serotonergic system are still under mystery. Therefore, to explore the anxiolytic effect of SSRI-medicated amplification of serotonergic signals, the 5-HT1A receptor, which is one of the most studied 5-HT receptor that is known to have

crucial relation to SSRI's antipsychotic effect, will be reviewed in following passages, with the discussion of the possible outcome of the activation the receptor.

3.1. The Function of 5-HT1A Receptor and Its Roles in the Regulation of Serotonergic Signal Transduction Mediated by SSRIs

5-HT1A receptor is a G-protein coupled receptor that couples with the Gi/o protein. It is involved in intracellular pathways of neurons via mainly its negative coupling with adenyl cyclase and its regulation of potassium channels on the cell membrane. The activation of 5-HT1AR will lead to the increase of cAMP level in the cell and the opening of K+ channel, which will cause the cell to hyperpolarize [8,10]. 5-HT1AR could be located mainly in the limbic and cortical region of the brain both presynaptically and postsynaptically. Besides the its presence as autoreceptor that play roles in the negative feedback of the activity of serotonergic neuron, 5-HT1AR also exists as heteroreceptor on the postsynaptic terminals of serotonergic neurons and other non-serotonergic neurons, regulating the activity of the neurons that receive the projection of serotonergic neurons.

Theoretically, the SSRI-mediated elevation of extracellular serotonin level will lead to the overall activation of 5-HT1AR. However, interestingly, the acute stimulation of 5-HT1A autoreceptor will suppress the synthesis and the sequent release of serotonin by the presynaptic terminal of serotonergic neurons, which seemingly to certain extent counteracts the effect of SSRI on serotonin level [11]. Opposite to the acute activation of 5-HT1A autoreceptor, chronic stimulation of the receptor will desensitize it. In view of current studies which investigate the interaction of SSRIs and 5-HTR, the desensitization of 5-HT1A autoreceptor after chronic activation are identified as one of the features and the key factor that contribute to the anxiolytic effect of chronic SSRI treatment [12]; The anxiolytic property of the desensitization of 5-HT1A autoreceptor is probably related to its role in the regulation of presynaptic activity and the modulation of the homeostasis of between the release and reuptake of serotonin in serotonergic neurons.

3.2. Clinical Relevance of 5-HT1A Receptor in Anxiety Disorders and SSRI-mediated Anxiolytic Effects

In the patients with anxiety disorders, high SERT expression and low 5-HT1AR activity are often observed [13,14]. Those changes in protein activity will lead to abnormal patterns of function of the serotonergic system. The rational speculation of the effect of these changes in SERT and 5-HT1AR is that they may increase the rate of 5-HT reuptake by SERT and also the synthesis of serotonin of the presynaptic terminal of serotonergic neurons (lower 5-HT1A autoreceptor stimulation will cause 5-HT synthesis to decrease). The increase in 5-HT reuptake and decrease in synthesis (and release) will result in a lower level of serotonin for the postsynaptic activation of 5-HTR, which could be the representation of one of the expected pathological characters of anxiety disorders: decreased efficiency of serotonergic signal transduction. In order to restore the function of the serotonergic system, establishment of a new homeostasis of serotonin's release and reuptake (to increase the amount of serotonin available for signal transduction) by the blockage of SERT and desensitization of 5-HT1A autoreceptor will be a viable strategy, which could be achieved by chronic SSRI administration.

In the preliminary (acute) stage of SSRI administration, SSRI-mediated blockade of SERT will lower the rate of serotonin reuptake, which elevates extracellular serotonin level without increasing the rate of 5-HT synthesis/release of serotonergic neurons. With the increase of extracellular serotonin, the level of 5-HT1A autoreceptor activation will as well increase. The higher 5-HT1A autoreceptor activation will activate the negative feedback cycle of 5-HT synthesis/release, which, to a content counteracts the elevation of extracellular 5-HT. Under chronic SSRI administration, although the elevation of 5-HT in the acute stage would partially be eliminated by the activation of 5-HT1A autoreceptor, 5-HT1A autoreceptor will eventually be desensitized by the elevated 5-HT level (compared to the basal level of 5-HT of the patient). The result of above process is likely the establishment of a new 5-HT release-reuptake balance, which would lead to an extracellular 5-HT

level that lies between the basal 5-HT and 5-HT level after acute SSRI treatment (basal 5-HT level<chronic SSRI 5-HT level<acute SSRI 5-HT level), despite the lower rate of 5-HT synthesis/release of the presynaptic terminal of serotonergic neuron. Collectively speaking, the anxiolytic mechanism of chronic SSRI treatment possibly involves its contribution to the restoration of the hyperactive presynaptic serotonergic system and the optimization of 5-HT-related neuronal signal transduction.

Since the desensitization of 5-HT1A autoreceptor requires extra time and occur generally with chronic SSRI administration, the time needed for the desensitization of 5-HT1A autoreceptor could be one of the factors that lead to the delay in effect of SSRIs in the treatment of anxiety disorder [11]. Similar to SSRIs, that delay in effect are also discovered in other anxiolytic agents whose pharmacological mechanism involves the interaction with 5-HT1A receptor (e.g. buspirone, a partial agonist of 5-HT1AR, 2-4 week is needed to reach full effect), which in further implies the importance of desensitization of 5-HT1A autoreceptor in the pharmacological mechanism of SSRIs as anxiolytic agents [9].

4. Potential Downstream Biological Pathways Relative to SSRI-Mediated Effect on Serotonin Receptors

Besides the modulation of the activity of the presynaptic serotonergic system, the activation of 5-HTRs mediated by SSRIs could incur other downstream effects related to the improvement of the phenotypic representation of anxiety disorders. Although the specific effect of 5-HTRs' activation is hard to measure collectively, notably, serotonergic neurons in the brain innervate other non-serotonergic neurons and are involved in the regulation of neuronal function, which is controlled by other neurotransmitter (NT)-related neural circuitry (e.g. 5-HT neurons in raphe nuclei interact with noradrenergic, dopaminergic and possibly GABAergic systems). The interaction between the serotonergic system and other NT-releasing systems likely induces some of the biological processes that aid the alleviation of anxiety-like behavior of the patient, for example, the promotion of adult neurogenesis in the hippocampus and the regulation of hypothalamic-pituitary-adrenal (HPA) axis [15,16]. 5-HTR, especially heteroreceptors, possibly play important roles in the above processes. 5-HT1A heteroreceptor, 5-HT4R and 5-HT7R are some of the 5-HTRs that are speculated to participate in the process of neurogenesis in the hippocampus [17,18]. Their activation or interactions could lead to the upregulation of brain-derived neurotrophic factor (BDNF) and contribute to the neurogenesis in the hippocampus, which could lead to increased neuroplasticity and procognitive effect in the patient with anxiety disorders.

Dysregulation of the function (hyperactivity) of the HPA axis and the resulting hypercortisolism are commonly observed in the patient with anxiety disorders [19]. The hyperactivity of the HPA axis is generally considered to be the result of suppression of hippocampus activity and overactivation of amygdala incurred by the dysregulation of the serotonergic system. By attuning the function of the serotonergic system and the increasing neurogenesis in hippocampus, SSRIs could potentially play important roles in alleviating the anxiety and stress-related response caused by the dysregulation of the HPA axis in anxiety disorders.

5. Conclusion

The pharmacological effect of SSRIs as anxiolytic agents are mainly achieved by the inhibition of serotonin reuptake and the subsequent elevation of serotonin level in the brain. Although the rise of brain serotonin level will lead to the overall activation of 5-HT receptors, the effect of that activation is hard to assess due to the complexity of 5-HTRs functionality. 5-HT1A receptor is considered as one of the key players in SSRI-mediated anxiolytic effect. The desensitization of 5-HT1A autoreceptor could participate in the establishment of new 5-HT homeostasis in serotonergic neurons. With the activation of 5-HT receptors, SSRI-mediated elevation of brain serotonin level may regulate

other downstream biological pathways/processes (e.g. neurogenesis in the hippocampus, regulation of HPA axis) and achieve the alleviating effect of the symptoms of anxiety disorders. In conclusion, even though the direct pharmacological effect of SSRIs (blockage of SERT, elevation of 5-HT level) is relatively apparent, the downstream effects of SSRIs are still not completely understood (especially the function of various 5-HTRs and the effect of their activation). Hence, more explorations may be required to completely decipher the anxiolytic nature of SSRIs. With the revelation of the working mechanism of SSRIs in anxiety disorders, new insights for the pathological nature of anxiety disorders may be discovered and potentially contribute to the innovation of the therapeutic strategy for anxiety disorders.

References

[1] Wang J, Guan X, Tao N. GBD: incidence rates and prevalence of anxiety disorders, depression and schizophrenia in countries with different SDI levels, 1990 – 2021 [J]. Frontiers in Public Health, 2025, 13.

[2] Penninx B W, Pine D S, Holmes E A, et al. anxiety disorders [j]. The Lancet, 2021, 397 (10277): 914 – 927.

[3] Gomez A F, Barthel A L, Hofmann S G. Comparing the efficacy of benzodiazepines and serotonergic anti-depressants for adults with generalized anxiety disorder: a meta-analytic review[J]. Expert Opinion on Pharmacotherapy, 2018, 19 (8): 883 – 894.

[4] Moncrieff J, Cooper R E, Stockmann T, et al. The serotonin theory of depression: a systematic umbrella review of the evidence [J]. Molecular Psychiatry, 2022, 28 (8): 3243 – 3256.

[5] Meyer J H, Wilson A, Sagrati S, et al. Serotonin transporter occupancy of five selective serotonin reuptake inhibitors at different doses: an [11C] DASB Positron emission Tomography study [J]. American Journal of Psychiatry, 2004, 161(5): 826 – 835.

[6] Collins H M, Gullino L S, Ozdemir D, et al. Rebound activation of 5-HT neurons following SSRI discontinuation [J]. Neuropsychopharmacology, 2024, 49 (10): 1580 – 1589.

[7] Saldanha D, Kumar N, Ryali V, et al. Serum serotonin abnormality in depression [J]. Medical Journal Armed Forces India, 2009, 65 (2): 108 – 112.

[8] De Deurwaerdère P, Bharatiya R, Chagraoui A, et al. Constitutive activity of 5-HT receptors: Factual analysis [J]. Neuropharmacology, 2020, 168: 107967.

[9] Żmudzka E, Sałaciak K, Sapa J, et al. Serotonin receptors in depression and anxiety: Insights from animal studies [J]. Life Sciences, 2018, 210: 106 – 124.

[10] Albert P R, Vahid-Ansari F. The 5-HT1A receptor: Signaling to behavior [J]. Biochimie, 2018, 161: 34 – 45.

[11] Vahid-Ansari F, Zhang M, Zahrai A, et al. Overcoming resistance to selective serotonin reuptake inhibitors: targeting serotonin, Serotonin-1A receptors and adult neuroplasticity [J]. Frontiers in Neuroscience, 2019, 13.

[12] Blier P, Ward N M. Is there a role for 5-HT1A agonists in the treatment of depression? [J]. Biological Psychiatry, 2003, 53 (3): 193 – 203.

[13] Frick A, Åhs F, Engman J, et al. Serotonin synthesis and reuptake in social anxiety disorder [J]. JAMA Psychiatry, 2015, 72 (8): 794.

[14] Lanzenberger R R, Mitterhauser M, Spindelegger C, et al. Reduced Serotonin-1A receptor binding in social anxiety disorder [J]. Biological Psychiatry, 2006, 61 (9): 1081 – 1089.

[15] Tafet G E, Nemeroff C B. Pharmacological treatment of anxiety disorders: The role of the HPA axis [J]. Frontiers in Psychiatry, 2020, 11.

[16] Hovorka M, Ewing D, Middlemas D S. Chronic SSRI treatment, but not norepinephrine reuptake inhibitor treatment, increases neurogenesis in juvenile rats[J]. International Journal of Molecular Sciences, 2022, 23 (13): 6919.

[17] Castrén E. Neurotrophins and psychiatric disorders[M]//Handbook of Experimental Pharmacology. 2014: 461 – 479.

[18] Crispino M, Volpicelli F, Perrone-Capano C. Role of the serotonin receptor 7 in brain plasticity: From development to disease [J]. International Journal of Molecular Sciences, 2020, 21 (2): 505.

[19] Nestler E J, Barrot M, DiLeone R J, et al. Neurobiology of Depression[J]. Neuron, 2002, 34 (1): 13 – 25.