

Serotonin and Mental Disorders: A Concise Review on Molecular Neuroimaging Evidence

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Serotonin is one of the most important neurotransmitters influencing mental health and, thus, is a potential target for pharmacological treatments. Functional neuroimaging techniques, such as positron-emission tomography (PET) and single photon emission computed tomography (SPECT), could provide persuasive evidence for the association between mental disorders and serotonin. In this concise review, we focus on evidence of the links between serotonin and major depressive disorders, as well as other mood disorders, anxiety disorders, schizophrenia, addiction, attention deficit hyperactivity disorder (ADHD), and autism.

KEY WORDS: Serotonin; Mental disorders; Positron-emission tomography; Single photon emission computed tomography.

INTRODUCTION

Serotonin is one of the most important neurotransmitters influencing mental health.¹⁾ Most serotonin is distributed outside of the central nervous system (CNS), and influences a wide range of physiologic processes in many organs.²⁾ However, the 2% of serotonin that is present in the CNS plays a pivotal role in the etiology of many mental disorders. Both receptors and transporters play important roles in synapses. 5-Hydroxytryptamine (5-HT) receptors are activated by the serotonin neurotransmitter, while the 5-HT transporter reuptakes the serotonin neurotransmitter from the synaptic cleft. Altered receptor and/or serotonin transporter (SERT) function may be associated with mental disorders.

The development of selective serotonin reuptake inhibitors (SSRIs) illustrates the importance of the serotonergic system with regard to the treatment of mental disorders. Further, the discovery of the role that the serotonin-transporter-linked polymorphic region (5-HTTLPR) plays in the association between stress and mental health highlights the pervasive influence of the serotonin transporter gene. Meanwhile, noninvasive neuroimaging tech-

niques, such as positron-emission tomography (PET) and single photon emission computed tomography (SPECT), can be used to study regional receptor and transporter concentrations in specific brain areas. These are important tools that can be used to acquire *in vivo* brain images and quantitative measurements with regard to the activities of the serotonergic system.^{3,4)}

Although there are many families of 5-HT receptors, most studies rely on radioligands for 5-HT_{1A} and 5-HT_{2A}. Some of the important radioligands used to study the serotonergic system are shown in Table 1. For instance, [¹¹C]WAY-100635 may be the most important radioligand

Table 1. Important PET and SPECT radioligands for serotonergic targets (5-HT_{1A}, 5-HT_{2A}, and SERT) in humans

Target	Radioligand
5-HT _{1A}	(¹¹ C)WAY-100635
5-HT _{2A}	(¹²³ I)-5-I-R91150 (¹⁸ F)setoperone (¹⁸ F)altanserin (¹⁸ F)deuteroaltanserin (¹¹ C)MDL100907
SERT	Beta-(¹²³ I)CIT (¹²³ I)ADAM (¹¹ C)DASB (¹¹ C)MADAM (¹¹ C)McN5652

PET, positron-emission tomography; SPECT, single photon emission computed tomography; 5-HT, 5-hydroxytryptamine; SERT, serotonin transporter.

Source: Paterson et al.³⁾

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for 5-HT_{1A}; however, there are also other available radioligands. Several radioligands were also developed for 5-HT_{2A}. For SERT, Beta-[¹²³I]CIT is one of the most useful radioligands for the SPECT. However, this radiotracer binds both on SERT and dopamine transporter (DAT). Another important radiotracer for SPECT is [¹²³I]ADAM, which selectively binding on SERT only. [¹¹C]DASB and [¹¹C]MADAM are important radioligands for PET. Evidence from neuroimaging studies may enhance our understanding of the role of serotonin in many mental disorders, and the aim of this essay was thus to provide a concise and updated review of the literature on this topic.

MAIN SUBJECTS

Major Depressive Disorder (MDD)

MDD is one of the most important mental disorders associated with altered serotonergic activity, and several extensive reviews of the literature exist on this topic.⁵⁾ Drevets *et al.*⁶⁾ used PET in conjunction with [¹¹C]WAY-100635, and found that the binding potential of 5-HT_{1A} receptors in the raphe and mesiotemporal cortex of unmedicated subjects with MDD was lower than that in

controls. Similar results were found among medicated and unmedicated MDD subjects in other studies,^{7,8)} as well as among patients with recurrent MDD.⁹⁾ However, not all studies agree on this issue. For example, in another PET study that used the same radioligand, MDD patients using antidepressants had greater 5-HT_{1A} receptor binding potential in the raphe and mesiotemporal cortex than controls and antidepressant-naïve patients with MDD; however, receptor binding potential was not significantly different between drug-naïve MDD patients and controls.¹⁰⁾ All of these earlier studies indicate that serotonin receptors are associated with MDD. The role of serotonin transporters, which influence the level of serotonergic activity, has also been examined in related neuroimaging studies. While it was demonstrated that a lower level of SERT availability in the midbrain is related to MDD,¹¹⁻¹³⁾ several studies presented findings that contradicted this.¹⁴⁻¹⁶⁾ No differences were found in SERT availability between drug-free euthymic patients with MDD and controls.¹⁷⁾ However, our previous study demonstrated that SERT availability in the midbrain was significantly lower in subjects with a first-degree family history of MDD than in healthy subjects.¹⁸⁾ Meanwhile, [¹¹C]McN 5652 studies indicated a lower SERT availability binding

Table 2. The summary of the findings on major depressive disorder (MDD)

Authors (year)	Target	Radioligand	Subject	Regions	Finding
Drevets <i>et al.</i> (1999)	5-HT _{1A}	(¹¹ C)WAY-100635	Unmedicated	RN, mesiotemporal cortex	MDD < controls
Sargent <i>et al.</i> (2000)	5-HT _{1A}	(¹¹ C)WAY-100635	Unmedicated and medicated	Frontal, temporal, and limbic cortex	MDD (medicated and unmedicated) < controls
Hirvonen <i>et al.</i> (2008)	5-HT _{1A}	(¹¹ C)WAY-100635	Unmedicated	AC, AMY, ANG, DLP, ITG, MTG, STG, HIP, INS, MFC, ORB, PC, dorsal RN, SG, VLP	MDD < controls
Parsey <i>et al.</i> (2006)	5-HT _{1A}	(¹¹ C)WAY-100635	Unmedicated	RN, VPFC, MPFC, DLP, AC, CIN, AMY, HIP, PHG, INS, TEM, PAR, OCC	No significant difference
Bhagwagar <i>et al.</i> (2004)	5-HT _{2A}	(¹¹ C)WAY-100636	Recurrent MDD (recovered and antidepressant free)	Temporal, parietal, prefrontal and cingulate cortex	MDD < controls
Malison <i>et al.</i> (1998)	SERT	Beta-(¹²³ I)CIT	Drug-free MDD	Brainstem	MDD < controls
Newberg <i>et al.</i> (2005)	SERT	Beta-(¹²³ I)CIT	Drug-free MDD	Midbrain	MDD < controls
Joensuu <i>et al.</i> (2007)	SERT	(¹²³ I) nor-β-CIT	Unmedicated	Midbrain	MDD < controls
Ahonen <i>et al.</i> (2004)	SERT	(¹²³ I)ADAM	Drug-free MDD	Midbrain	No significant difference
Catafau <i>et al.</i> (2006)	SERT	(¹²³ I)ADAM	Drug-free MDD	Midbrain, thalamus, striatum	No significant difference
Herold <i>et al.</i> (2006)	SERT	(¹²³ I)ADAM	Unmedicated	Midbrain	No significant difference
Hsieh <i>et al.</i> (2010)	SERT	(¹²³ I)ADAM	Drug-free, euthymic MDD	Midbrain	No significant difference
Parsey <i>et al.</i> (2006)	SERT	(¹¹ C)McN5652	Drug-free MDD	AMY, Midbrain	MDD < controls
Reivich <i>et al.</i> (2004)	SERT	(¹¹ C)McN5652	Drug-free MDD	Left frontal cortex, right cingulate cortex	MDD > controls
Cannon <i>et al.</i> (2007)	SERT	(¹¹ C)DASB	Unmedicated	Thalamus, INS, striatum	MDD > controls

RN, raphe nuclei; AC, anterior cingulate cortex; AMY, amygdala; ANG, angular gyrus; DLP, dorsolateral prefrontal cortex; ITG, inferior temporal gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus; HIP, hippocampus; INS, insular cortex; MFC, medial prefrontal cortex; ORB, orbitofrontal cortex; PC, posterior cingulate cortex; SG, supramarginal gyrus; VLP, ventrolateral prefrontal cortex; VPFC, ventral prefrontal cortex; MPFC, medial PFC; DLPFC, dorsolateral PFC; CIN, cingulate cortex; PHG, parahippocampal gyrus; TEM, temporal cortex; PAR, parietal cortex; OCC, occipital cortex.

potential in the amygdala of drug-naïve patients with MDD,¹⁹⁾ and increased SERT availability in the left frontal cortex and right cingulate cortex among drug-free patients.²⁰⁾ Greater SERT availability was reportedly associated with more negative and dysfunctional attitudes among patients with MDD,²¹⁾ and an increase in SERT availability in the thalamus and striatum of patients with MDD was also found in a [¹¹C]DASB study.²²⁾ These findings are shown in Table 2. As serotonergic antidepressants are an important treatment for MDD, PET is also used to probe SSRI occupancy. SERT occupancy is approximately 80% under the effective doses in PET studies using [¹¹C]DASB.^{23,24)}

Other Mood Disorders

Altered serotonergic activity is associated with various other mood disorders. For example, increased SERT binding potential was found among unmedicated subjects with bipolar disorder in a PET study using [¹¹C]DASB,²⁵⁾ and similar findings were also reported in another PET study focused on 5-HT_{1A}.²⁶⁾ However, a decreased level of SERT availability, as assessed by SPECT with [¹²³I] ADAM, was found in medicated subjects with euthymic bipolar I, but not bipolar II.²⁷⁾ We speculate that these findings indicate that SERT availability might not only be a biomarker for bipolar disorder but is also influenced by medication or disease severity. In addition, the biological characteristics of bipolar I and II are different.²⁷⁾ It is also worth noting that altered serotonin activity may be related to the severity of symptoms associated with bipolar disorder.²⁵⁾ We speculate that the mechanism between abnormal serotonergic activity and bipolar disorder may be complex.

Anxiety Disorders

Studies also indicate that serotonergic activity may be associated with anxiety disorders,²⁸⁾ although the evidence remains inconclusive, with some studies reporting that there is no association,²⁹⁾ or only an unclear one.^{30,31)} Meanwhile, reduced SERT³²⁾ and 5-HT_{2A}³³⁾ binding potential was found among drug-naïve subjects with obsessive-compulsive disorder. Kent *et al.*³⁴⁾ reported that occupancy of SERT by paroxetine (a kind of SSRI) was higher in patients with social anxiety disorder. Additionally, other authors found significantly lower 5-HT_{1A} binding potential in several limbic and paralimbic areas.³⁰⁾ Our preliminary small sample study of patients with generalized anxiety disorder showed no significant difference with regard to SERT level compared with a control group

(Yang *et al.*, personal communication).

Schizophrenia

Although it has been proposed that the serotonergic system may interact with the dopaminergic system in ways that may be associated with schizophrenia,^{35,36)} there remains little neuroimaging evidence regarding this issue. There is reportedly no significant decrease in 5-HT receptors or SERT among schizophrenic subjects, based on PET studies using different radiotracers,³⁷⁻⁴⁰⁾ and similar findings were also reported in a SPECT study using [¹²³I] β-CIT.⁴¹⁾ The role of the serotonergic system in the treatment of schizophrenia should be explored further.

Addiction

Although it has been proposed that serotonergic dysfunction may be associated with addictive behaviors,^{42,43)} there is little evidence from neuroimaging studies, and what exists remains inconclusive. Significantly reduced SERT availability in the brainstems of alcoholics was found with SPECT using [¹²³I] β-CIT.⁴⁴⁾ However, another study using the same radiotracer indicated that brainstem SERT availability among smokers was higher than among non-smokers.⁴⁵⁾ Alcoholic nonsmokers reportedly had higher levels of SERT availability in the brainstem and diencephalon than controls.⁴⁶⁾

The serotonergic system might also be also associated with other harmful forms of addiction, although the detailed mechanisms remain to be elucidated. For example, the association between serotonin and heroin use is unclear, although a SPECT study with [¹²³I] β-CIT indicated that the level of SERT availability was similar between heroin users and healthy controls.⁴⁷⁾ One of our studies⁴⁸⁾ indicated that midbrain SERT availability among opioid-dependent patients being treated with low doses of methadone could be lower than that among controls and among former opioid addicts practicing methadone-free abstinence (Fig. 1). On the other hand, another study from our lab indicated that a higher level of SERT availability was associated with a greater likelihood of relapse among former heroin users.⁴⁹⁾ We speculate, therefore, that serotonin may play a number of roles in heroin addiction. For example, both biological (e.g., homeostasis of neuroactivity) and psychological factors (e.g., depressive tendency, personality traits and risk preference) might have joint effects. Altered serotonergic activity may be associated with use of other substances, such as cocaine. An animal study indicated that acute cocaine self-administration may induce higher levels of SERT availability.⁵⁰⁾

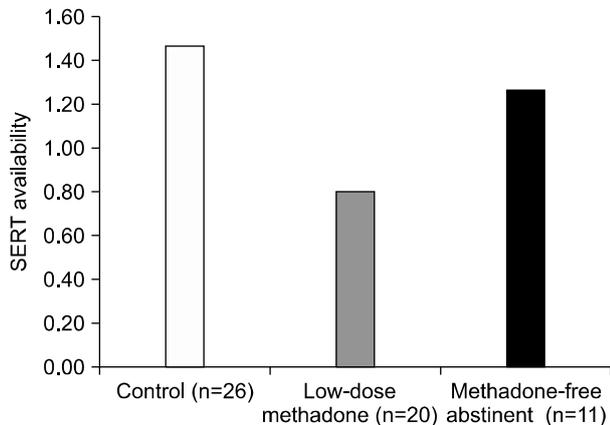


Fig. 1. The serotonin transporter (SERT) availability for heroin users and controls. Reproduced based on Yeh *et al.*⁴⁸⁾

Evidence in humans is scarce. A SPECT study found elevated SERT availability in acutely abstinent patients with cocaine dependency.⁵¹⁾ The association between serotonin and addiction remains to be elucidated.

Attention Deficit Hyperactivity Disorder (ADHD)

It was proposed that serotonin may play a role in ADHD via its interplay with the dopaminergic system.⁵²⁾ Additionally, there was reportedly no difference in SERT availability between treatment-naïve ADHD adults and their controls, while there was a lower level of DAT among ADHD subjects.⁵³⁾ Similar findings were reported in a recent small sample PET study using [¹¹C]MADAM, which indicated that the level of SERT availability was similar between adult patients with ADHD and controls.⁵⁴⁾

Autism

While the mechanisms of autism remain unclear, a lower level of 5-HT_{2A} receptor binding was found among adult men with Asperger's syndrome in a small sample SPECT study.⁵⁵⁾ In a SPECT study using [¹²³I]nor β -CIT, a significantly lower level of SERT availability in the medial frontal cortex was found among children with autism.⁵⁶⁾ More importantly, a PET study reported lower SERT levels throughout the brain in autistic men; reduced SERT level in the anterior/posterior cingulate cortex was associated with poor social cognition.⁵⁷⁾ Although there are few findings on autism in the literature, published work does shed some light on the etiology of this condition.

Other Risks Associated with Mental Problems

Neuroticism is a trait that may be associated with mood

disorders. A PET study reported that a higher SERT binding potential was associated with neuroticism among healthy males.⁵⁸⁾ A higher level of frontolimbic 5-HT_{2A} receptor binding was reportedly associated with neuroticism among subjects with a family history of mood disorders.⁵⁹⁾ However, little is known about the association between serotonin and other personality traits, although a lower SERT level was found among subjects with borderline personality disorder.⁶⁰⁾

The studies mentioned above suggest that a lower level of serotonergic activity might be associated with poor social interaction.^{56,57)} Similarly, our recent study indicated that lower SERT availability was associated with a lower level of perceived social support,⁶¹⁾ which is linked with stress-induced mental illness. In support of this, another of our studies also indicated that perceived stress was associated with SERT availability.⁶²⁾ Furthermore, hypothalamic-pituitary-adrenal (HPA) axis function, as measured by dexamethasone suppression test, was found to be associated with SERT availability in healthy subjects.⁶³⁾

CONCLUSIONS

Serotonin is one of the most important neurotransmitters and, thus, is a potential target for pharmacological treatment. A large body of evidence supports the association between the serotonergic system with MDD and other mood disorders. However, while pharmacological data support the view that serotonin could be related to anxiety disorders, imaging findings remain insufficient and inconclusive. Moreover, the association between serotonin and schizophrenia, which is the most severe psychiatric disorder, has also not been demonstrated by neuroimaging studies. The association between addiction and the serotonergic system could be complex, as the direction of its effects remains unclear. At present, little evidence supports a link between serotonin and ADHD. However, a few studies suggest that altered hyposerotonergic activity might be one of the etiologies of autism. Even in healthy participants, correlations between SERT and stressful life events and stress hormones still exist, and these findings could have implications for clinical practice.

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