

The Role of Serotonin in the Pathophysiology of Depression: As Important As Ever

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Featured Article: Owens MJ, Nemeroff CB. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. *Clin Chem* 1994;40: 288–95.²

Fifteen years have elapsed since we published this article focusing on the serotonin transporter (SERT)³. Although developed as a review, this report ultimately included original data from a large study of drug-free depressed patients and controls showing that platelet [³H]imipramine binding, the ligand of choice for labeling serotonin transporters, was significantly decreased in depression. We also showed data indicating that the decreased platelet [³H]imipramine binding was specific for major depression. The high number of citations, including numerous citations even in 2009, reflects the ongoing importance of serotonin in depression. Since this report was published, remarkable advances have occurred in our understanding of the molecular neurobiology of serotonergic neurons, and in functional brain imaging studies, which have provided further evidence for a preeminent role for serotonergic circuits in the pathogenesis of major depression and suicide (1). These advances include (a) the development of specific positron-emission tomography ligands for the SERT and their use in detecting alterations in serotonergic circuits in patients with major depression and suicidality, as well as quantifying the magnitude of SERT occupancy associated with antidepressant treatment; (b) functional polymorphism in the promoter region of the gene that codes for SERT [solute carrier family 6 (neurotransmitter transporter, serotonin), member 4 (*SLC6A4*)], which has now been demonstrated to mediate, in part, the well-documented increased vulnerability to depression of adult individuals exposed to child abuse and neglect

early in life; (c) the recognition that members of the selective serotonin reuptake inhibitor (SSRI) class of antidepressants are not, in fact, homogeneous, but differ from each other in a number of important pharmacological properties; and (d) considerable progress in elucidating the molecular substrates of SSRI antidepressant action.

Positron-emission tomography radioligands for the SERT have been developed (2), and some studies (3), but not all, have confirmed previous single-photon emission computed tomography observations (4) and postmortem findings of a reduction in SERT binding density in the raphe nuclei, amygdala, and other brain areas in depressed patients, especially suicidal individuals. The use of these new tools in future studies will clarify the relationship between SERT occupancy and therapeutic response in patients with depression, as well as whether SERT density predicts response/nonresponse to SSRI treatment.

One of the most exciting findings is the importance of SERT polymorphisms in vulnerability to depression, and the interaction of this genetic marker with environmental factors. More specifically, the promoter region of the SERT gene (*SLC6A4*) exhibits a functional polymorphism containing short (s) or long (l) repeats of a base-pair sequence as evidenced by *in vitro* and nonneuronal *in vivo* studies. The presence of the s-allele is associated with a reduction in SERT transcriptional efficiency, with a resulting reduction in SERT mRNA expression and SERT binding density. Caspi et al. (5), in a seminal study, reported that in a New Zealand cohort adult individuals who were exposed to child abuse or neglect during the age range of 3 to 11 years were much more likely to develop major depression if they had the s/s genotype than the l/l genotypes; individuals with the s/l heterozygote were less likely than the s/s group but more likely than the l/l group to develop depression in adulthood after childhood maltreatment. Another important finding has been the demonstration of a pharmacological basis for the observation that some patients fail treatment with 1 SSRI but respond to another. Although all members of the SSRI class inhibit the SERT, thereby blocking presynaptic 5-hydroxytryptamine uptake, the magnitude of the inhibition varies as a function of their potency

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² This article has been cited more than 395 times since publication.

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³ Nonstandard abbreviations: SERT, serotonin transporter; SSRI, selective serotonin reuptake inhibitor; BDNF, brain-derived neurotrophic factor; TrkB, tyrosine kinase, receptor, type 2.

and dose employed. Perhaps more important are potential extraserotonergic effects of the SSRIs. As the dose of sertraline is increased from 50–200 mg, the pharmacological properties of the drug change from an SSRI to a dual 5-hydroxytryptamine and dopamine reuptake blocker. Similarly, as the dose of paroxetine is increased from 20–50 mg, its pharmacological properties change from an SSRI to a dual serotonin/norepinephrine reuptake inhibitor. The clinical significance of these extra actions is not clear at present.

Finally, the molecular mechanism of the SSRIs, namely the train of events set in motion by SERT blockade, ultimately mediates the antidepressant effects of these compounds. One candidate mediator that has garnered considerable attention is brain-derived neurotrophic factor (BDNF) and related molecules. Impairment of BDNF or its receptor [TrkB (tyrosine kinase, receptor, type 2)] appears to block the effects of SSRI antidepressants in rodents. This finding is of particular interest because antidepressants have been reported to increase hippocampal neurogenesis, and BDNF clearly plays a role in this process (6). The relationship between depression, neurogenesis, antidepressants, and BDNF clearly merits additional study.

In 1994 we highlighted the important role of serotonin in the pathophysiology of depression. In 2009 the role of serotonin is as important as ever.

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