

SERT-ainly Involved in Depression, But When?

The neurotransmitter serotonin is produced by neurons in the raphe nuclei of the brainstem, which send axonal projections broadly to the cerebral cortex, the amygdala, and other brain regions. The modulation of serotonin neurotransmission appears to be involved in both the pathophysiology and the treatment of depression. For example, serotonin-selective reuptake inhibitors (SSRIs), by blocking the reuptake of serotonin into nerve terminals through the serotonin transporter (commonly abbreviated SERT or 5-HTT), reverse the putative deficit of serotonin function in depression. However, the validity of this simple heuristic model is challenged by the variability in the rates of clinical response to pharmacological blockade of the serotonin transporter, suggesting that the exact mechanisms leading to disease and underlying remission are more complex. Here, we briefly review the central role of the serotonin transporter in the normal modulation of serotonin function and the current model of its involvement in the pathophysiology and treatment of depression. We then examine how three reports in this issue of the *Journal* shed new light on this model by partially refining some of its features and suggesting new areas for investigation.

When released from the synaptic vesicles in nerve terminals into the extracellular space, serotonin binds to the numerous types of pre- and postsynaptic serotonin receptors. These receptors in turn activate or repress diverse signal transduction cascades, and thus change the functional status of the targeted neurons, while also inducing long-term structural changes through the regulation of gene expression. The availability, and hence signaling potential, of released serotonin is regulated solely through the action of the serotonin transporter. The serotonin transporter captures serotonin molecules and transports them back into the nerve terminal, making them available for recycling into new synaptic vesicles. Consequently, the strength of serotonin activity at serotonin receptors is inversely proportional to the number of functional serotonin transporter molecules present at the presynaptic membrane. SSRIs and related antidepressant drugs exploit this relationship by blocking the reuptake of serotonin through serotonin transporters, thus increasing serotonin signaling at large. Depending on the brain region and the cellular localization of serotonin transporters, different outcomes may occur. For instance, blocking serotonin transporters in the projection fields of serotonin axons (e.g., in the cerebral cortex or amygdala) increases serotonin levels and signaling at all available serotonin receptors. In contrast, blocking serotonin transporters near serotonin-containing cell bodies (i.e., in the raphe nuclei) leads to increased activation of serotonin 1A (5-HT_{1A}) autoreceptors, which in turn decreases the firing rate of the same serotonin-containing neurons, and thus reduces overall serotonin function. SSRIs rely on the desensitization or inactivation of 5-HT_{1A} autoreceptors to finally increase serotonin output.

The impact of manipulating serotonin transporter activity also differs as a function of the changes in serotonin transporter levels that occur during development. In rodents, serotonin transporter levels peak early in the perinatal period, followed by lower and more stable levels in the adult brain (1). Given the known trophic actions of serotonin in regulating developmental events such as neurogenesis, process outgrowth, and programmed cell death (2), these observations suggest that alterations in serotonin transporter activity early in development may disrupt the formation of neural networks critical for normal adult functions. For example, blockade of serotonin trans-

“The liability for depression in adulthood may result from altered serotonin function... earlier in life.”

porters in rodents during a period corresponding to the third trimester of pregnancy in women induces persistent changes in stress- and fear-related behaviors throughout adulthood (3).

Furthermore, different forms of the gene for the serotonin transporter, which of course are present from conception, can also influence the risk for depression much later in life. In humans the serotonin transporter gene exists in both long and short forms; the short form results in lower levels of serotonin transporter expression, at least in cell lines (4). It is interesting that the presence of the short form of the serotonin transporter gene increases the probability that an individual will develop an episode of major depression when faced with stressful life events, an observation clearly demonstrating an interaction between inheritance and environment (5). However, this finding raises the question, How can the apparent association of lower serotonin transporter levels with an increased risk for depression be reconciled with the clinical observation that reducing serotonin transporter function with SSRIs improves depression? And, in fact, answers to additional questions are needed to address this seeming contradiction. Do these genetic variants actually result in different serotonin transporter levels in the human brain? If so, are these differences present throughout development or only in the adult brain? Does altered serotonin function need to occur during a particular developmental window, and do such changes need to be sustained throughout adulthood, for a depressive syndrome to occur? Can the modulation of serotonin by serotonin transporter blockers alleviate depressive symptoms arising from deficits in serotonin function earlier in life? Reports in this issue of the *Journal* begin to address some of these questions.

In the first of two articles by Parsey et al., the authors report that the serotonin transporter promoter variants do not, in fact, influence serotonin transporter levels in several cortical and subcortical brain areas of healthy or depressed adults, as shown by positron emission tomography. These results imply that in order to increase vulnerability to stressful life events, the serotonin transporter genetic variants must have influenced serotonin transporter levels at an earlier phase of life, perhaps during adolescence or childhood, as suggested by Caspi et al. (5), or even earlier (i.e., late gestation), as suggested by the studies of SSRI administration at a corresponding period in rodents (3).

By shifting the time frame to earlier developmental events, these human and rodent studies may shed light on the apparent discrepancies between the similar biological effects of the short serotonin transporter allele and SSRI treatment (decreased serotonin uptake through either reduced serotonin transporter expression or pharmacological blockade, respectively) and the opposite clinical outcomes (greater risk for depression with the short allele versus therapeutic improvement with SSRIs). Indeed, these observations suggest a modification to the current model of the role of serotonin dysfunction in depression; that is, the liability for depression in adulthood may result from altered serotonin function (due to reduced serotonin transporter levels in carriers of the short allele during a particular developmental window) earlier in life that disrupted the normal maturation of certain neural networks. Once established, these altered neural networks may mediate the increased vulnerability to depression in adulthood, independent of the current state of serotonin function. Furthermore, it may be that the weeks of treatment typically required for the antidepressant efficacy of SSRIs to emerge may reflect not the acute effects on serotonin transporter function but the serotonin-related induction of longer-term changes in neural networks, such as those that are affected by altered serotonin function during development.

Do these findings imply, beyond a role in development, that altered serotonin function is not involved in the pathophysiology of depressive episodes? They do not, suggests the same research group in their second report in this issue of the *Journal*. Indeed, in the same medication-free patients experiencing a major depressive episode, a signif-

icant decrease in serotonin transporter binding was found, regardless of the serotonin transporter genotype of the subject. These results suggest the presence of abnormalities in the serotonin system during a depressive episode, independent of any earlier developmental events related to the serotonin transporter. Understanding the functional consequences of this decreased capacity for serotonin uptake is complicated by the presence of reduced serotonin transporter levels in several different brain areas, where such deficiencies may induce opposite effects on serotonin neurotransmission. For instance, the decreased serotonin transporter binding in the amygdala may correlate with increased activation of this brain area during negative emotional tasks (6). However, a decreased serotonin transporter level in the midbrain raphe nuclei of depressed subjects is expected to reduce serotonin signaling as a result of the increased availability of serotonin to activate presynaptic inhibitory 5-HT_{1A} receptors on the cell bodies of serotonin neurons. Under these conditions, a reduced midbrain serotonin transporter level may directly participate in the decreased serotonergic function that is thought to occur in depression. Patients with such a decrease in midbrain serotonin transporter level may also not respond well to further blockade of serotonin transporters by SSRIs, as the decreased serotonin transporter levels, in essence, already mimic the action of chronic SSRI exposure.

Accordingly, these findings of serotonin transporter down-regulation in depression need to be considered in the context of the results from the large-scale Sequenced Treatment Alternatives to Relieve Depression (STAR*D) clinical trial that is reported in this issue of the *Journal* by Trivedi et al. (also see the editorial by Insel). Indeed, the sobering results from this trial, indicating that the disorders of only about 30% of “real world” patients were considered remitted after a carefully optimized treatment of their depression by serotonin transporter blockade, may be partially due to an already down-regulated serotonin transporter function in some depressed patients. Indeed, given the variability of the measures of serotonin transporter binding density across depressed subjects (the first article by Parsey et al.), it might be expected that only a portion of patients would display optimized therapeutic benefits from a treatment involving serotonin transporter blockade. Knowledge of serotonin transporter binding levels and genotype in depressed subjects who experience response or remission with SSRI treatment, relative to those of nonresponders, will be important to determine in future studies.

Taken together, these findings also highlight the importance of a research focus on the role of the serotonin transporter throughout development and on the identification of the neural networks that are affected by altered serotonin transporter levels. Of course, similar downstream changes in these neural networks could also result from other etiological pathways and represent a “common” mechanism conferring risk for depression in the face of adverse life events. Although early developmental alterations in serotonin transporter function are unlikely to be realistically targeted for the prevention of depression, identifying the molecular, cellular, and circuitry changes that are secondary to altered developmental events related to the serotonin transporter may, in offering a window into the mechanisms leading to an increased risk for depression, reveal new targets for antidepressant drug development.

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