Early life stress may cause excess serotonin release resulting in a serotonin deficit

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Studies indicate that the majority of people with mood and anxiety disorders who receive the most commonly prescribed class of antidepressant medications, Selective Serotonin Reuptake Inhibitors or SSRI's, are not helped by these medications. SSRIs are designed to increase serotonin, a neurotransmitter in the brain that is key to maintenance of mood.

Researchers led by Jeremy D. Coplan, MD, professor of psychiatry at SUNY Downstate Medical Center, have published data suggesting an explanation for the longstanding puzzle as to why low serotonin could not be detected in depression without suicidal intent, even though many antidepressant treatments work by increasing serotonin in areas key for mood regulation, such as the hippocampus. The pre-clinical research was published in a recent edition of *Frontiers in Behavioral Neuroscience*.

Dr. Coplan explains, "We have shown that serotonin is too high near the serotonin brain cells, reducing firing of the serotonin nerve cells through a well-documented negative feedback mechanism in the raphe nucleus. The result is that the hippocampus and other critical brain structures needed for mood maintenance do not get enough serotonin. We can see this because the hippocampus is shrunken and the white matter loses integrity. By the time serotonin metabolites are measured in a lumbar spinal tap, the usual way serotonin levels have been measured, the high serotonin has mixed with the low serotonin and you have no difference from people who are healthy."

He continues, "We have hypothesized in an earlier paper that this is a plausible reason why SSRIs may not work in a majority of people, because SSRIs will tend to make the high serotonin even higher in the raphe nucleus. The serotonin neuron may not be able to adapt and restore its firing, inducing a presumed serotonin deficit in terminal fields, evidenced by shrinkage of the hippocampus."

He adds, "We cannot say categorically, in our pre-clinical model, that high serotonin in the raphe nucleus leads to low serotonin in the hippocampus, but studies by J. John Mann, MD, a co-author on the paper, and Victoria Arango, PhD, both of Columbia University Medical Center, have shown that people who committed suicide exhibited high serotonin in the raphe nucleus and low serotonin in another area of the brain critical for mood maintenance, the prefrontal cortex. Additional studies should be performed, especially since better understanding of the serotonin system will significantly improve future treatment options."

In the earlier paper, also in *Frontiers in Behavioral Neuroscience*, Dr. Coplan proposed augmentation therapies in treatment-resistant patients, including stacking one medication upon another in the most difficult cases: "This is what physicians do for hypertension, diabetes, and congestive heart failure," said Dr. Coplan. "But in psychiatry, we sometimes act as if our medications are so effective that we are exempt from how the rest of medicine deals with difficult-to-treat cases."

Other approaches to bypass the high midbrain serotonin impasse, according to Dr. Coplan, are shutting glutamate input into the raphe nucleus, a portion of the brain that controls the release of serotonin, and utilizing drugs that block noradrenergic input into the dorsal raphe.

Dr. Coplan notes that a recent large-scale study showed only a minority of patients do well on SSRIs, and of those, many lose response in a year or two. "There is an epidemic of inadequately treated depression and

psychiatrists are not well trained to deal with this challenge," he observed. "What they often do is change from one antidepressant to another when there is a lack of response. Eventually the patient becomes non-compliant and the patient, rather than the treatment, is blamed for the non-efficacy."

"These two papers provide possible insights as to why our treatments are ineffective and what we should be doing to treat patients effectively," Dr. Coplan said. "Many academic researchers currently do not practice clinically, so they are out of touch with real-life patients and their struggles. In the meantime, suicide rates have not budged in decades."

More information: *Frontiers in Behavioral Neuroscience*, journal.frontiersin.org/Journa … nbeh.2014.00440/full

A related study published by the team of investigators is available at: journal.frontiersin.org/Journa … nbeh.2014.00189/full

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