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Revoking serotonin's auto license

By Tim Fulmer, Senior Writer

Although the majority of marketed antidepressants are designed to boost low levels of the neurotransmitter serotonin in the brain—a well-known cause of depression—only a third of patients actually respond to the first drug they are given. American and French researchers have now identified a receptor on the serotonin-producing neurons themselves that may be at the root of resistance to serotonin-boosting treatments.[1]

Selective serotonin reuptake inhibitors (SSRIs) are first-line therapies in both depression and anxiety. SSRIs prevent uptake of serotonin into presynaptic neurons, thereby increasing extracellular levels of the neurotransmitter and enhancing the activity of serotonin (5-HT_{1A}) receptor (HTR_{1A})-expressing neurons throughout the brain.

But patient responses to SSRIs are highly variable. In addition to resistance to treatment, responders can have a lag of two to three weeks between the start of treatment and clinical improvement.[2,3]

To better understand the mechanisms underlying resistance to SSRIs, a team led by René Hen, professor of psychiatry, neuroscience and pharmacology at **Columbia University**, focused on the presynaptic neurons that synthesize and release serotonin. Previous work by other labs has shown that those presynaptic neurons express *HTR_{1A}*, which helps control the release of serotonin through a negative feedback loop (*see* **Figure 1, "Breaking the feedback loop"**).[4,5]

On those neurons, the receptor is called the 5-HT_{1A} autoreceptor to distinguish it from receptors expressed on neurons that don't produce and release serotonin.

Hen's team hypothesized that the feedback loop dampens the brain's serotonin levels and could be at least partly responsible for resistance and delayed response to SSRIs. If so, antagonizing the autoreceptors could disrupt the feedback loop and improve responsiveness to SSRIs.

Testing that hypothesis first required the group to generate mice that were deficient in the 5-HT_{1A} autoreceptor. After confirming that the animals expressed about 30% less autoreceptor than normal mice, the next step was to study the animals in a variety of behavioral assays.

In a forced swim test, which measures long-term stress responses, the mutant mice showed significantly less despair-related immobility following re-exposure to the stress-triggering environment than normal mice (p=0.0047).

Having established that lower 5-HT_{1A} autoreceptor levels improved mouse tolerance to stress, the next question was whether those lower levels could also improve the animals' responsiveness to SSRIs.

Following 26 days of treatment with Prozac fluoxetine, an SSRI marketed by **Eli Lilly and Co.**, the mutant mice indeed had positive responses to a food-related stress test, whereas normal mice showed no behavioral response when treated with Prozac. Subsequent analysis of brain tissue confirmed that the mutant animals' improved responses to Prozac correlated with increased serotonin levels.

The findings were published in *Neuron*. Hen was corresponding author on the paper and the team included researchers from the **University of Pennsylvania** and the **University Paris-Sud 11**.

"These latest findings converge remarkably well with our own work in humans, which suggests that abnormally high levels of the 5-HT_{1A} autoreceptor at least partly underlie susceptibility to stress," said Ahmad Hariri, professor of psychology and neuroscience at **Duke University**.

Hariri and colleagues have combined genotyping and imaging

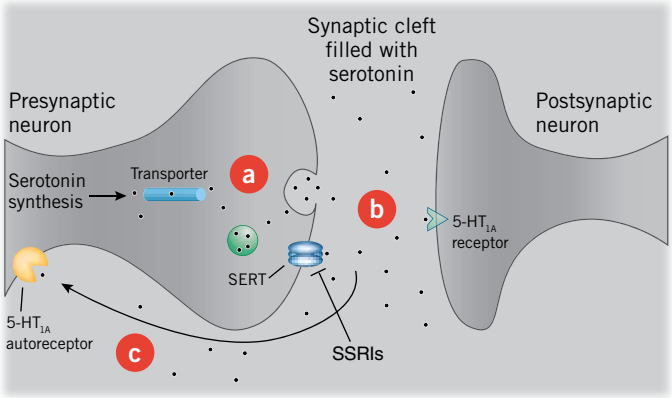

Figure 1. Breaking the feedback loop. A paper published in *Neuron* suggests that preventing a negative feedback loop from acting on serotonergic neurons could improve patient response to antidepressants.

[**a**] Under normal conditions, serotonergic neurons synthesize the neurotransmitter serotonin, packaging the signaling molecule into vesicles and transporting it to the presynaptic membranes of the neuron.

[**b**] Once released into the synapse, serotonin is free to diffuse to the membranes of postsynaptic neurons, in which it binds serotonin receptors and transmits a signal. The serotonin transporter (SERT) on presynaptic neurons takes up serotonin from the synaptic cleft, recycling the neurotransmitter. This regulates its concentration in the synapse, thus modulating the signal.

[**c**] Some of the released serotonin also binds autoreceptors, triggering a feedback loop whereby presynaptic neurons release less serotonin, thus reducing their own signaling.

The new findings suggest that selectively antagonizing serotonin (5-HT_{1A}) autoreceptors could increase serotonergic signaling, which is faulty in various mood disorders such as depression. Moreover, these antagonists could further boost the serotonergic signaling that underlies the antidepressant effects of selective serotonin reuptake inhibitors (SSRIs) that bind SERT.

studies to show that high 5-HT_{1A} autoreceptor levels in humans are associated with low reactivity of the amygdala, a brain region important for helping people deal with stress and threatening stimuli.[6]

In addition, in humans it has been shown that a single mutation in the promoter region of the *5-HT_{1A}* receptor gene can lead to abnormally high levels of autoreceptor expression. Genetics studies have associated this mutation with susceptibility to depression and related mood disorders, as well as with reduced response to antidepressant or antipsychotic treatments.[7]

Treatment angles

Hariri said the therapeutic implications of the *Neuron* paper are clear. "It may be possible to augment the efficacy of SSRIs by combining them with a compound that selectively inhibits the 5-HT_{1A} autoreceptor on serotonin-producing neurons," he told *SciBX*.

Compounds that selectively antagonize the 5-HT_{1A} autoreceptor do not yet exist. Nonetheless, previous clinical studies suggest that more broadly antagonizing the 5-HT_{1A} receptor may indeed increase SSRI action, though in a limited fashion.

Pindolol—a generic 5-HT_{1A} receptor antagonist that targets the receptor on neurons throughout the brain—has been tested in multiple clinical trials as an adjunct for augmenting SSRI efficacy. A meta-analysis of those trials showed that pindolol improved early-stage outcomes of treatment but had no statistically significant effect beyond four weeks.[8,9]

However, according to one researcher, directly antagonizing the receptor may not be necessary.

The knockdown data in the *Neuron* paper suggest that downregulating expression of the 5-HT_{1A} autoreceptor may be more important than blocking the receptor's function with antagonists like pindolol, said Paul Albert, professor of medicine at the **University of Ottawa** and senior scientist at the **Ottawa Hospital Research Institute**.

Thus, an alternative strategy would be to design compounds that decrease levels of the autoreceptor, and Albert has identified potential targets.

"We have identified several transcription factors such as Deaf-1, Hes1, Hes5 and Freud-1 that repress 5-HT_{1A} autoreceptor expression," said Albert. "The idea would be to selectively activate or induce those transcription factors to suppress autoreceptor expression and enhance treatment response."[10,11]

Albert also noted that serotonin-producing neurons "can be regulated by other systems such as dopamine and noradrenaline." Thus, compounds targeting those molecules "could act synergistically with the reduced 5-HT_{1A} autoreceptor levels to mediate antidepressant response," he said.

Hen declined to disclose his next research steps or the IP status of the findings published in *Neuron*.

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