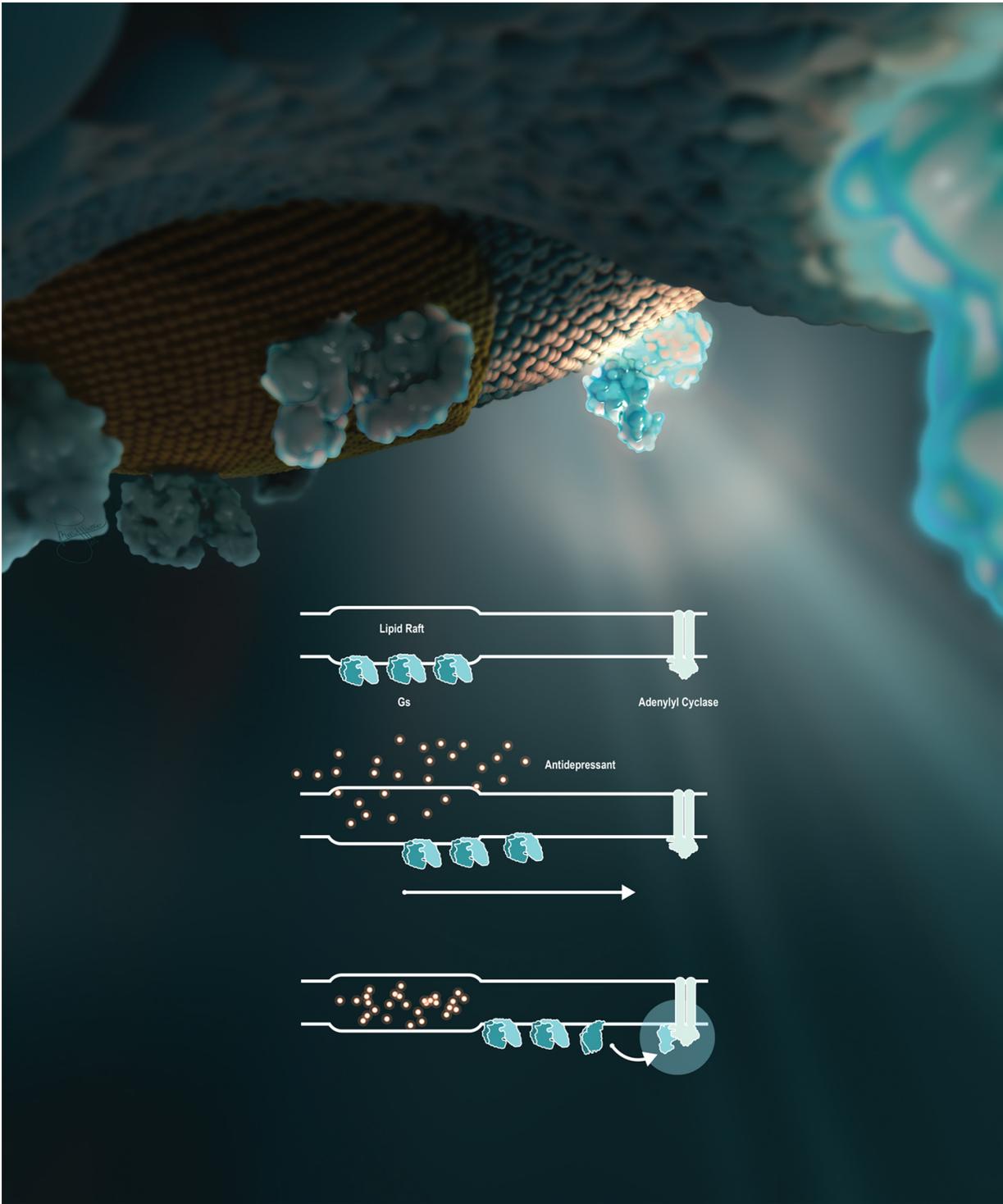


Why do antidepressants take so long to work?

July 28 2016, by Sharon Parmet



Antidepressants move G proteins out of lipid rafts in the cell membrane. Credit: Molly Huttner.

An episode of major depression can be crippling, impairing the ability to sleep, work, or eat. In severe cases, the mood disorder can lead to suicide. But the drugs available to treat depression, which can affect one in six Americans in their lifetime, can take weeks or even months to start working.

Researchers at the University of Illinois at Chicago have discovered one reason the drugs take so long to work, and their finding could help scientists develop faster-acting drugs in the future. The research was published in the *Journal of Biological Chemistry*.

Neuroscientist Mark Rasenick of the UIC College of Medicine and colleagues identified a previously unknown mechanism of action for selective serotonin reuptake inhibitors, or SSRIs, the most commonly prescribed type of antidepressant. Long thought to work by preventing the reabsorption of serotonin back into nerve cells, SSRIs also accumulate in patches of the [cell membrane](#) called lipid rafts, Rasenick observed, and the buildup was associated with diminished levels of an important signal molecule in the rafts.

"It's been a puzzle for quite a long time why SSRI antidepressants can take up to two months to start reducing symptoms, especially because we know that they bind to their targets within minutes," said Rasenick, distinguished professor of physiology and biophysics and psychiatry at UIC. "We thought that maybe these drugs have an alternate binding site that is important in the action of the drugs to reduce depressive symptoms."

Serotonin is thought to be in short supply in people with depression. SSRIs bind to serotonin transporters - structures embedded within nerve-cell membranes that allow serotonin to pass in and out of the [nerve cells](#) as they communicate with one another. SSRIs block the transporter from ferrying serotonin that has been released into the space between neurons

- the synapse - back into the neurons, keeping more of the neurotransmitter available in the synapse, amplifying its effects and reducing symptoms of depression.

Rasenick long suspected that the delayed drug response involved certain signaling molecules in nerve-cell membranes called G proteins.

Previous research by him and colleagues showed that in people with depression, G proteins tended to congregate in lipid rafts, areas of the membrane rich in cholesterol. Stranded on the rafts, the G proteins lacked access to a molecule called cyclic AMP, which they need in order to function. The dampened signaling could be why people with depression are "numb" to their environment, Rasenick reasoned.

In the lab, Rasenick bathed rat glial cells, a type of brain cell, with different SSRIs and located the G proteins within the cell membrane. He found that they accumulated in the lipid rafts over time—and as they did so, G proteins in the rafts decreased.

"The process showed a time-lag consistent with other cellular actions of antidepressants," Rasenick said. "It's likely that this effect on the movement of G proteins out of the lipid rafts towards regions of the cell membrane where they are better able to function is the reason these antidepressants take so long to work."

The finding, he said, suggests how these drugs could be improved.

"Determining the exact binding site could contribute to the design of novel antidepressants that speed the migration of G proteins out of the [lipid rafts](#), so that the antidepressant effects might start to be felt sooner."

Rasenick already knows a little about the lipid raft binding site. When he

doused rat neurons with an SSRI called escitalopram and a molecule that was its mirror image, only the right-handed form bound to the lipid raft.

"This very minor change in the molecule prevents it from binding, so that helps narrow down some of the characteristics of the [binding site](#)," Rasenick said.

More information: Samuel J. Erb et al, Antidepressants Accumulate in Lipid Rafts Independent of Monoamine Transporters to Modulate Redistribution of the G protein, $G\alpha$, *Journal of Biological Chemistry* (2016). [DOI: 10.1074/jbc.M116.727263](https://doi.org/10.1074/jbc.M116.727263)

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