Moving the motivation meter

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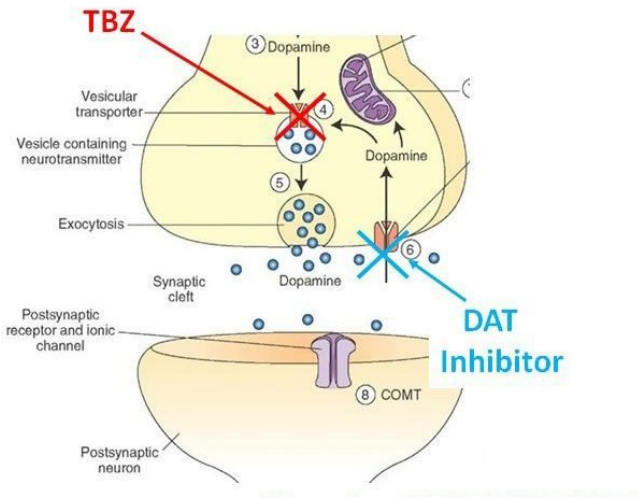

Two brain cells (pale yellow) and the open space between them, called a synapse. The little blue circles are dopamine, a chemical that excites brain cells when it fills the synapse. Some drugs block the supply of dopamine to the synapse (the red X) and this can cause fatigue, lack of motivation and apathy. The blue X shows where other drugs block a protein from cleaning dopamine out of the synapse; this can help restore feelings of motivation to a person. Or a rat. Credit: John Salamone/UConn)

Two novel drugs kickstart motivation in rats suffering from apathy and a lack of oomph, UConn researchers reported at the Society for Neuroscience conference in San Diego on Nov. 5.

Apathy steals the excitement from life. It's a feeling of being fatigued, uninterested, and emotionally flat. People who suffer from apathy find it hard to exert effort, and life can seem tremendously difficult. One of the primary symptoms of depression, it's also a side effect of certain medications. It can also be caused by inflammation from an infection or chronic disease such as multiple sclerosis.

Apathy and lack of motivation are hard to treat. Many medications that help with other symptoms of depression don't help much with them.

But now, UConn behavioral neuroscientist John Salamone and graduate student Renee Rotolo have found that two new drugs can restore normal behavior in rats who lack motivation, pointing the way to potential treatments.

Salamone and Rotolo's rats were not naturally lacking motivation; the researchers induced it with a drug that reduces dopamine signals in the brain. Dopamine affects many things, including mood, motivation, and movement. It works by affecting brain cells when it is released into the synapses (the spaces between the cells). Certain medicines used to treat movement disorders restrict the amount of dopamine available to fill the synapses in the brain. This does calm spastic movements, but it can also cause apathy, fatigue, and low exertion of effort.

Salamone, Rotolo, and other lab members showed that rats given the drug that reduced dopamine were much less likely to work for preferred morsels of food. But when these rats were then given one of the experimental drugs, they regained their motivation to work for the treat.

Both of the experimental drugs Rotolo and Salamone tested stimulate a build up of dopamine in the synapse. They do this by inhibiting the protein that normally clears dopamine away. Other drugs, such as cocaine and amphetamines, work in a similar fashion, but their onset is much faster and the effects more extreme.

"You wouldn't want to give a person with depression cocaine over and over again. They'd crash. These [experimental] drugs provide a long, slow, mild increase in dopamine," which would be much more likely to be therapeutic, Salamone says. They also, hopefully, may have a lower potential for abuse.

One of the new drugs was developed by the British pharmaceutical company Chronos Therapeutics;

the other by an Austrian medicinal chemist Gert Lubec from the Universities of Vienna and Salzburg. Lubec has developed a large family of related drug candidates to increase motivation, all related to modafinil. Modafinil, a drug developed initially to enhance wakefulness, also helps people concentrate on a task and engage with it more. Neuroscientists believe it does this by blocking the inactivation of dopamine from synapses in the brain responsible for attention and focus. Lubec intentionally changed the chemical structure of the drug, which made it even more selective for actions on dopamine.

The next step in the research will be to test these other, related drugs in the series and see if they have similar effects, and identify which one works best to mitigate apathy and fatigue. Salamone's team also intends to test whether the compounds really do have less potential for abuse than more rapidly acting drugs.

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