Scientists engineer supersensitive receptor, gain better understanding of dopamine system

14 October 2008

Genetically modifying a receptor found on the neurons that produce the neurotransmitter dopamine has given California Institute of Technology (Caltech) researchers a unique glimpse into the workings of the brain's dopamine system--as well as a new target for treating diseases that result from either too much or too little of this critical neurotransmitter.

Caltech scientists Henry Lester, Bren Professor of Biology, and Ryan Drenan, senior postdoctoral scholar in biology, worked with colleagues from Caltech, the University of Colorado at Boulder, the Rockefeller University, the University of Utah, and the pharmaceutical company Targacept. They genetically modified a type of brain receptor known as an "?6-containing nicotinic acetylcholine receptor" to make it more sensitive to both nicotine and acetylcholine. (Acetylcholine is another of the brain's neurotransmitters.)

The receptor in question is found primarily on neurons that produce the neurotransmitter dopamine. When the receptor is kicked into action by the presence of either nicotine or acetylcholine--two of the keys that fit its biochemical lock--the receptor prompts the neurons on which it sits to begin pumping out dopamine.

While previous studies of this same receptor had shown what happens when you block its function--when you put the brakes on dopamine production--this was the first time anyone was able to look at what happens when you make the receptor more sensitive and thus put the dopamine system into overdrive. "We were able to not only isolate this receptor's function, but also to amplify it," says Drenan, "and that allowed us to see exactly what it and it alone is capable of doing in the brain."

As it turns out, it's capable of doing a lot. Revved up by even low doses of nicotine, these receptors prompt the neurons on which they are clustered to let loose with a flood of dopamine. This flooding was obvious from the behavior of mice carrying the genetically modified receptors: because dopamine plays an important role in movement, the mice became quickly and significantly hyperactive. In fact, the researchers note, low doses of nicotine affect mice with these hypersensitive receptors in much the same way that amphetamines affect "normal" mice. Looking more closely at this phenomenon, the researchers write, "could be useful in understanding the causes of human hyperactivity such as that observed in ADHD."

"This technique also gives researchers the power to activate dopamine neurons selectively," says Lester. "We plan to exploit this opportunity to obtain new knowledge about dopamine neurons' functions."

While these sensitized receptors appear on dopamine neurons throughout the brain, the researchers note that they seem to play an especially critical role in what is called the mesolimbic pathway--one of four pathways that control dopamine production throughout the brain, and the one implicated in the addictive properties of drugs like nicotine.

To this end, Lester's team and their collaborators have already begun to explore the possibilities of targeting these receptors with specific drugs that might work to reduce their sensitivity to nicotine, potentially providing a new line of attack for treating nicotine addiction. In fact, notes Drenan, these same drugs might also one day prove useful in treating other dopamine-related conditions, such as ADHD, Parkinson's disease, and schizophrenia.

"By uncovering the biological role of these receptors, especially with regard to their role in the midbrain dopamine system, we show that they are excellent drug targets," says Drenan.

The paper, "In Vivo Activation of Midbrain Dopamine Neurons via Sensitized, High-Affinity á6* Nicotinic Acetylcholine Receptors," was published in the October 9 issue of the journal *Neuron.*

Source: California Institute of Technology