Dopamine receptor study offers hope for improved treatments with fewer side effects

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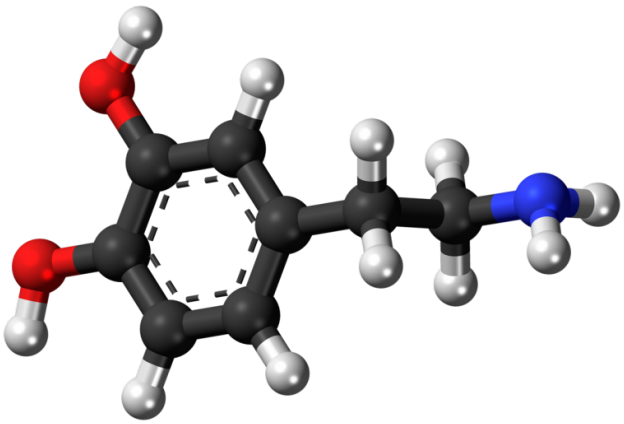

Ball-and-stick model of the dopamine molecule, a neurotransmitter that affects the brain's reward and pleasure centers. Credit: Jynto/Wikipedia

New work from researchers at Columbia University Vagelos College of Physicians and Surgeons sheds light on how dopamine receptors signal within cells, opening the door for more targeted—and more tolerable—therapeutics to treat an array of neuropsychiatric disorders.

The study's findings have been published in the journal *Molecular Psychiatry*.

The central nervous system's dopamine receptors play a critical role in a variety of neural processes, including motor control, learning and memory, and reward. The focus of this study, the dopamine D2 receptor (D2R), is an important target in the treatment of disorders such as schizophrenia and Parkinson's disease. Drugs used to treat these conditions either block or activate these receptors to address dysfunctional receptor signaling. Antipsychotic drugs that target D2Rs, however, can have many unpleasant side effects, including weight gain, involuntary movements, and decreased motivation.

Scientists know that D2Rs send signals through two main pathways within cells—either by activating G proteins or by G-protein independent arrestin-signaling. Recent studies of opioid receptors—targeted for pain relief—suggest that it may be possible to maintain the therapeutic effects while avoiding negative side effects, such as respiratory depression, by selectively activating the G protein signaling pathway. "We asked whether these signaling pathways might also lead to different behavioral effects at the D2R, and whether this might provide a new approach to improved antipsychotic drugs with fewer side effects," says Dr. Jonathan Javitch, Lieber Professor of Experimental Therapeutics in Psychiatry and professor of pharmacology at Columbia University Vagelos College of Physicians and Surgeons.

In order to determine whether the two pathways regulate different behaviors, the researchers examined mice that were engineered to carry a mutated D2R that only facilitated the arrestin pathway. In these mice, the mutant dopamine receptor restored motor function just as the non-mutant form of the receptor does, indicating that arrestin recruitment can enhance motor function on its own. In contrast, motivation was enhanced only by wild-type D2R. "This finding was quite exciting as it indicates that the activational component of motivation that enhances locomotion is regulated by a different intracellular mechanism than the reward driven directional component," says Dr. Christoph Kellendonk, associate professor of pharmacology (in Psychiatry) at Columbia University Vagelos College of Physicians and Surgeons. "For the former, arrestin signaling is sufficient whereas the latter requires activation of G-proteins."

"These results offer the exciting possibility that therapeutic approaches targeting specific D2R-mediated signaling pathways could not only treat

psychosis, but also avoid some of the adverse side effects experienced by patients taking the existing, less targeted medications," says Javitch.

The study is titled "Arrestin recruitment to dopamine D2 receptor mediates locomotion but not incentive motivation."

More information: Prashant Donthamsetti et al, Arrestin recruitment to dopamine D2 receptor mediates locomotion but not incentive motivation, *Molecular Psychiatry* (2018). DOI: 10.1038/s41380-018-0212-4

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