Dopamine linked to autism symptoms in mouse model study

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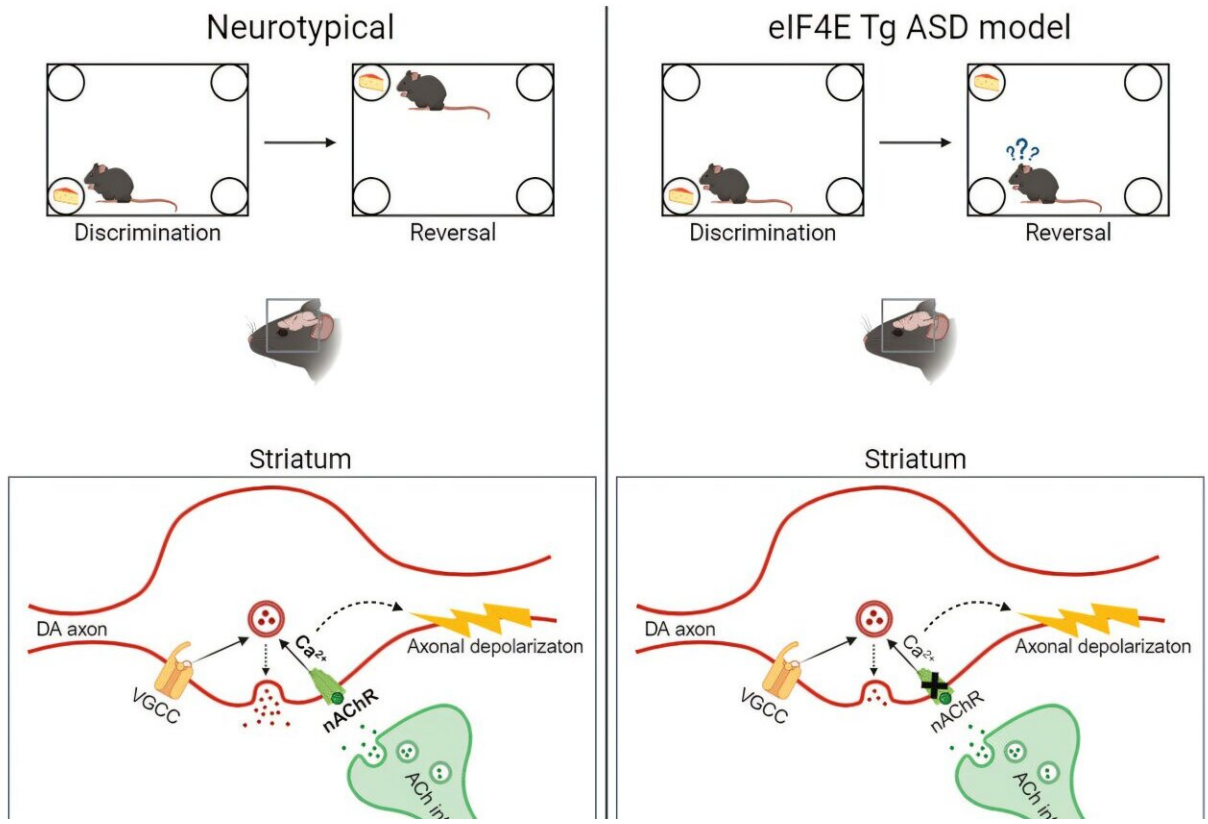

Credit: *Cell Reports* (2024). DOI: 10.1016/j.celrep.2024.114997

Researchers at Karolinska Institutet have uncovered new insights into the mechanisms underlying autism spectrum disorder (ASD). The study, recently published in *Cell Reports*, explores how changes in dopamine

(DA) neurotransmission in the brain contribute to the behavioral symptoms of autism.

Autism is diagnosed based on behaviors that vary greatly among individuals, often overlapping with other conditions, making accurate diagnosis challenging. The study focuses on a mouse model of ASD with elevated levels of eukaryotic initiation factor 4E (eIF4E), a protein that plays a crucial role in the process of translating genetic information into proteins.

"Our study shows that mice with an autism-risk gene, eIF4E, have reduced release of dopamine, a chemical messenger (or neurotransmitter) that is important for motivation, learning and movement," says Emanuela Santini, principal researcher at the department of neuroscience and last author of the article.

Using state-of-the-art techniques like optogenetics, which uses light to control specific brain circuits, the researchers traced the problem to reduced activation of nicotinic receptors by acetylcholine, another neurotransmitter important for decision-making.

The study helps to explain the neurobiological basis for behavioral inflexibility, a common challenge in autism. Understanding how brain circuits and neuronal communication are altered in autism is crucial.

"Our findings reveal that the basal ganglia—a brain circuit regulating adaptive behavior and motor functions—is affected in autism, with disruptions in how dopamine and acetylcholine work together," says Santini.

These findings provide insight into the brain mechanisms behind behavioral inflexibility in autism, potentially aiding future diagnostic approaches.

Comprehensive approach

The researchers used a comprehensive approach, combining genetics, behavioral analysis, synaptic physiology, and imaging techniques. They measured dopamine release in mice with a mutation in the eIF4E gene, which is important for making new proteins. Mutations in this gene have been linked to autism in patients. These mice have autism-like behaviors, such as difficulty adapting to change, repetitive actions, and social challenges, making them a valuable model for studying autism.

"We used optogenetics to understand why dopamine release was reduced in ASD mice. We activated dopamine or acetylcholine neurons and found that dopamine release triggered by acetylcholine neurons was reduced," explains Anders Borgkvist, principal researcher at the same department and co-author of the study.

The team then used imaging techniques to measure acetylcholine levels and calcium influx. Calcium is essential for neurotransmitter release. In the eIF4E mice, acetylcholine binding to dopamine axons was impaired, leading to less calcium influx. Increasing calcium restored dopamine release, showing that the problem lies in nicotinic receptor function.

"Our findings suggest that behavioral inflexibility in autism arises from deficits in the communication between dopamine and acetylcholine in the basal ganglia. We will continue to investigate how this affects other parts of the brain," says Borgkvist.

"This not only enhances our understanding of ASD but also paves the way for innovative therapeutic approaches that could significantly improve the lives of those affected by the disorder," adds Santini.

More information: Josep Carbonell-Roig et al, Dysregulated acetylcholine-mediated dopamine neurotransmission in the eIF4E Tg

mouse model of autism spectrum disorders, *Cell Reports* (2024). DOI: 10.1016/j.celrep.2024.114997