

Opioid analgesic fentanyl may cause autism-like behavior in young mice

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Fentanyl, a mu-opioid receptor agonist, is one of the most commonly used analgesics in hospitals, and may induce long-lasting behavioral and somatosensory impairment in rodents. However, whether the use of

fentanyl is associated with the development of autism is not known. An animal study led by investigators at Massachusetts General Hospital (MGH), Shanghai 10th People's Hospital, and the University of Pennsylvania has shown that fentanyl can induce changes similar to autism-like behaviors in young male and female mice. The findings are published in the *British Journal of Anaesthesia*.

Research by other groups has shown that N-methyl-D-aspartate receptor dysfunction contributes to autism. Variations in *Grin2a* and *Grin2b*, the genes encoding GluN2A and GluN2B subunits of N-methyl-D-aspartate receptor, are associated with autism. In addition, the anterior cingulate cortex of the brain is affected in autism.

In this current study, the research team reports that [fentanyl](#) induces autism-like behaviors in young male and female [mice](#) via activating the [mu-opioid receptor](#) in the anterior cingulate cortex. Further, these fentanyl-induced autism-like behaviors appear partially due to the hypermethylation-mediated reduction of *Grin2b* expression in the anterior cingulate cortex of mice.

"Because the anterior cingulate cortex is a hub for mediating social information, we focused on the expression of *Grin2b* in that area," says Yuan Shen, MD, Ph.D., the paper's senior author and a professor of Psychiatry at Shanghai 10th People's Hospital. "We found fentanyl decreased expression of *Grin2b* in the [anterior cingulate cortex](#). The overexpression of *Grin2b* prevents fentanyl-induced autism-like [behavior](#) in the mice. These findings suggest a potential mechanism to prevent or treat the autism-like behavior," says Shen.

The group conducted experiments using an open field test (in which a mouse can walk inside a box) and an elevated plus-maze (in which a mouse can walk on an elevated platform) to detect the [anxiety](#) and stereotyped behaviors of mice. Using a three-chamber social preference

test (in which a mouse can interact with another mouse), they also assessed potential social deficits. "We used these tests because [impaired social interaction](#), stereotyped behaviors, and anxiety are the key feature of autism-like behaviors in mice," says Zhihao Sheng, co-first author of the paper. Sheng is a graduate student at Shanghai 10th People's Hospital.

"However, the changes of mice in these behavioral tests do not equal autism in humans. These behavioral tests are only used to study the autism-like behaviors in mice because they can demonstrate certain features of behavior changes similar to the manifestation of autism," says Qidong Liu, Ph.D., co-first author and an assistant professor at Shanghai 10th People's Hospital.

Co-senior author Zhongcong Xie, MD, Ph.D., adds, "There is no current evidence that fentanyl is associated with a similar effect in humans and the outcome of the [animal study](#) is not an indication to avoid fentanyl in clinical anesthesia. However, the outcome will promote further research, including clinical investigations, to determine the potential neurobehavioral influence of opioids on brain development." Xie is director of Basic Science Research in the MGH Department of Anesthesia, Critical Care and Pain Medicine and Henry K. Beecher Professor of Anesthesia at Harvard Medical School.

Other authors include Chun Cheng and Mengzhu Li from Shanghai 10th People's Hospital and Shanghai First Maternity and Infant Hospital, W. Andrew Kofke from the University of Pennsylvania, and Jed Barash, a Massachusetts neurologist.

More information: Zhihao Sheng et al, Fentanyl induces autism-like behaviours in mice by hypermethylation of the glutamate receptor gene *Grin2b*, *British Journal of Anaesthesia* (2022). [DOI: 10.1016/j.bja.2022.04.027](#)

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