Oral Small-Molecule GLP-1 Drugs Penetrate Deep Into the Brain to Suppress Cravings

NIH-funded research identifies new mechanism of action for next-generation weight-loss drugs.

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A National Institutes of Health (NIH)-funded study has found that an emerging class of GLP-1 weight-loss drugs suppress eating for pleasure, or hedonic feeding, in mice by modulating a reward circuit deep within the brain. This newly charted pathway — separate from previously described mechanisms that broadly affect appetite — could be an avenue by which GLP-1s treat other dysfunctions in reward processing, such as substance use disorder.

In the study [published in Nature], researchers at the University of Virginia specifically investigated small-molecule GLP-1 receptor agonists, such as the Food and Drug Administration (FDA)-approved orforglipron, which can be taken orally and are cheaper to produce than their injectable counterparts.

"As the accessibility of these medications continues to rise and patient uptake increases, it's crucial that we understand the neural mechanisms underlying the effects we're seeing," said Lorenzo Leggio, MD, PhD, clinical director of NIH's National Institute on Drug Abuse (NIDA).

Previous research has extensively explored the effects of larger peptide GLP-1s, such as semaglutide, in the brain, finding that they suppress hunger-driven eating by engaging networks in the hypothalamus and hindbrain. Until now, scientists have had a much less firm grasp on how small-molecule GLP-1 drugs work.

To gain a better understanding, the authors modified the GLP-1 receptors of mice with gene-editing techniques, making them more humanlike.

The team administered orforglipron or another small-molecule drug, danuglipron, and identified brain regions where they induced activity. While the GLP-1s affected familiar territory, they also triggered activity in the central amygdala, a region associated with desire that is deeper in the brain than scientists previously thought GLP-1s could directly reach.

Further experiments showed that, once activated, the central amygdala reduced dopamine

release into key hubs of the brain's reward circuitry during hedonic feeding.

"We've known that GLP-1 drugs suppress feeding behavior driven by energy demand. Now it seems oral small-molecule GLP-1s also dial back eating for pleasure by engaging a brain reward circuit," said co-corresponding author Ali Guler, PhD, a professor of biology at the University of Virginia.

According to scientists, the natural next question is whether these next-generation GLP-1s can also tone down cravings for things other than food. In follow-up studies they hope to dive into their effects on substance use disorder specifically.

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This study was not completed as a clinical trial associated with an application and has not been assessed by FDA for product approval for stated indications.

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