

Sex-specific brain atlas of GLP-1 reveals why weight-loss drugs may work differently in females and males

Researchers map the peptide behind semaglutide across 25 brain regions in each sex, finding striking differences in appetite and reward circuits.

NEW YORK, NY, UNITED STATES, March 10, 2026 /EINPresswire.com/ -- The drugs have names that sound like small planets: semaglutide, liraglutide, lixisenatide. Collectively they belong to a class of glucagon-like peptide 1 (GLP-1) analogs that has reshaped the treatment of obesity and diabetes so thoroughly that the word "blockbuster" barely covers it. And yet for all the billions of dollars spent, for all the prescriptions written, a fundamental question has lingered like a low hum beneath the clinical noise: where, precisely, does GLP-1 live inside the brain, and does it set up house differently in females and males?

A new peer-reviewed study published in [Brain Medicine \(Genomic Press\)](#) answers both questions with startling clarity. Researchers at the Icahn School of Medicine at Mount Sinai have constructed what is, to their knowledge, the first comprehensive sex-specific atlas of GLP-1 expression in the murine brain at single-transcript resolution, identifying the peptide across 25 distinct brain nuclei, subnuclei, and regions in each sex. The findings, led by Vitaly Ryu, Anisa Gumerova,

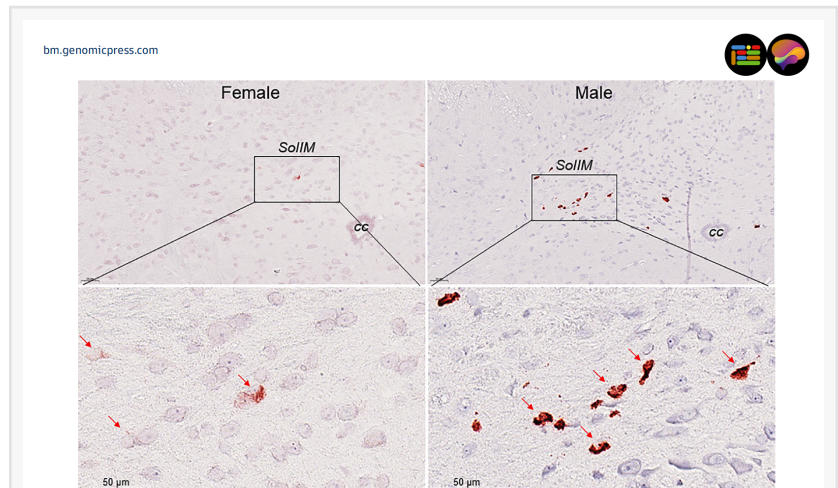


Figure 2. Sex-specific Glp1 density in the medullary NTS. Representative RNAscope micrographs of medullary SolIM subnucleus of the NTS showing Glp1 expression (red arrows) in female and male mice. CC, central canal; NTS, nucleus of the solitary tract; SolIM, nucleus of the solitary tract, intermediate part. Scale bar: 50 μm.

Sex-specific Glp1 density in the olfactory bulb. Representative RNAscope micrographs of olfactory GrO showing Glp1 expression (red arrows) in female and male mice.

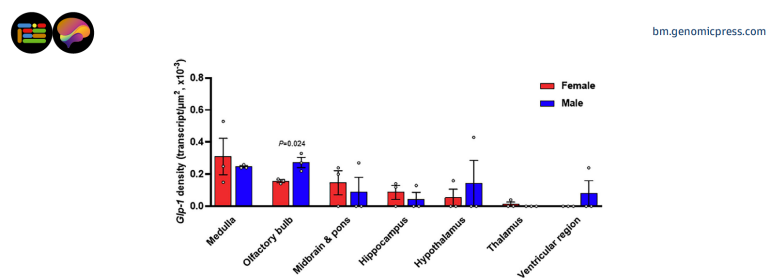


Figure 4. Sex-specific Glp1 density in brain divisions. Glp1 density in main brain regions detected by RNAscope. Notably, female medulla and male olfactory bulb had the highest Glp1 density. In the olfactory bulb, transcript density was markedly greater in males compared to that in females ($P = 0.024$, unpaired Student's t test; Table 1). $N = 3$, values are shown as means $\pm$ SE.

Sex-specific Glp1 density in brain divisions. Glp1 density in main brain regions detected by RNAscope. Notably, female medulla and male olfactory bulb had the highest Glp1 density.

Georgii Pevnev, Tony Yuen, and senior author Mone Zaidi, reveal that the geography of GLP-1 in the brain is not uniform between females and males. It is, in places, dramatically different.

That matters. It matters because obesity and diabetes are common in both women and men, yet certain pathological and clinical features of these conditions exhibit sex-specific differences. It matters because GLP-1 appears to have stronger effects on appetite suppression, glycemic regulation, and body weight loss in females compared with males. And it matters because the psychiatric applications of GLP-1 analogs, including emerging evidence for efficacy in addiction, depression, and other conditions, remain largely unexplored through the lens of sex.

“

GLP-1 analogs, used to treat obesity, are among the most impactful drug classes in decades, yet we have lacked a detailed, sex-specific map of where GLP-1 is expressed in the brain.”

Dr. Mone Zaidi, Institute Director, Icahn School of Medicine at Mount Sinai

counting, and inter-rater reliability was confirmed. Probe specificity was validated by positive staining in the small intestine, pancreas, and medullary nucleus of the solitary tract, with absent staining in the kidney as a negative control.

The result is a compendium unlike anything that existed before.

Within the major brain divisions, the hindbrain revealed differences that run deep. RNAscope detected Glp1 expression in the medulla, olfactory bulb, midbrain and pons, hippocampus, hypothalamus, thalamus, and the ependymal layer of the third ventricle. The medulla and

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RESEARCH ARTICLE

Atlas of GLP-1 expression in the mouse brain: Neuroanatomical basis for metabolic and psychiatric effects

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Recently, glucagon-like peptide 1 (GLP-1) and its new blockbuster class of analogs have emerged as powerful therapeutics to combat obesity and diabetes, with growing evidence for potential efficacy in addiction, depression, and other psychiatric conditions. Although metabolic diseases are common in both women and men, certain pathological and clinical features exhibit sex-specific differences, as do psychiatric disorders. Importantly, as part of a broader network of peptides and hormones regulating ingestive and reward-related behaviors, GLP-1 appears to have stronger effects on appetite suppression, glycemic regulation, and body weight loss in females compared with males—though sex differences in its psychiatric effects remain underexplored. We utilized RNAscope to create a comprehensive atlas of sex-specific (n = 3 per sex) GLP-1 expressing sites in the murine brain. Notably, in the hindbrain, Glp1 densities and total numbers of Glp1-expressing neurons in the raphe obscurus nucleus, ventral and ventrolateral parts of the solitary nucleus were higher in females compared with males. In the olfactory bulb, Glp1 densities were greater in the granular cell layer of males in comparison with females. Collectively, this atlas should serve as a resource to advance our understanding of GLP-1's central functions in both metabolic and psychiatric contexts.

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olfactory bulb harbored the highest total counts of Glp1 in both sexes. But the pattern within the medulla was not symmetrical. In females, the three regions with the highest Glp1 densities in the hindbrain were, in descending order, the raphe obscurus nucleus (ROb), the ventral part of the nucleus of the solitary tract (SolV), and the medial part of the solitary tract (SolM). In males, the highest densities appeared in the central (SolCe), intermediate (SolIM), and medial subnuclei of the solitary tract. Overall, Glp1 densities and total numbers of Glp1-expressing neurons in the ROb, SolV, and ventrolateral part of the solitary tract (SolVL) of females tended to be higher in comparison with males. The numbers of Glp1-expressing neurons were significantly higher in the SolV of females compared with males ($P = 0.034$), with a similar trend in the SolVL ($P = 0.069$).

"What struck us was not just where we found GLP-1 expression, but the degree to which the pattern diverged between females and males in specific hindbrain subnuclei," said Vitaly Ryu, co-first author and lead designer of the experiments. "Several medullary nuclei displayed expression in only one sex, which opens entirely new questions about how GLP-1 circuits operate differently in the female and male brain."

Several medullary nuclei displayed what the authors call sex-biased expression. Glp1 transcripts were detected only in the ambiguus nucleus, tectospinal tract, ventral cochlear nucleus (posterior part), and cuneate nucleus of females, while the dorsomedial spinal trigeminal nucleus, intercalated nucleus of the medulla, paramedian reticular nucleus, SolCe, and spinal trigeminal nucleus (caudal part) showed expression only in males. Two nuclei with the highest Glp1 expression in a single sex were the ambiguus nucleus in females and the SolCe in males. The authors note that the apparent absence of Glp1 expression in one sex may reflect limited power for very low-frequency events, and these findings should be viewed as hypothesis-generating.

Perhaps the most unexpected finding emerged from the olfactory bulb. Glp1 density was significantly greater in the olfactory bulb of males compared with females ($P = 0.024$), driven by markedly higher Glp1 densities in the granular cell layer (GrO) of males ($P = 0.031$). GLP-1-releasing interneurons have previously been located in the olfactory bulb of rats and mice, where they are hypothesized to modulate mitral cell excitability in relation to a post-prandial anorexigenic action.

The observation acquires sharper edges when placed beside recent work showing that food odor induces cephalic phase insulin release in lean and diet-induced obese male mice. Yet females appear to have enhanced olfactory abilities due to the presence and modulatory effects of estrogen via its receptors in the olfactory bulb. The authors suggest a compensatory relationship: given that GLP-1 has strong effects on appetite suppression, glycemic regulation, and body weight loss in females, it seems plausible that lower Glp1 densities in the GrO of females over males are compensated by sufficient and necessary estrogen actions on appetite regulation. Whether the noted higher Glp1 expression in the GrO of males contributes to higher insulin levels compared with females remains to be demonstrated. However, because male but

not female mice develop hyperinsulinemia on high-fat diet, the authors describe it as tempting to speculate that GrO-derived GLP-1 may underlie a sex-specific amplification of olfactory-driven insulin signaling in males.

The study places GLP-1 within a broader network of sexually dimorphic peptide systems regulating ingestive behavior, revealing a web of peptides rather than a solo act. Under unstressed conditions, females have lower levels of orexigenic neuropeptide Y and fewer NPY-expressing neurons in the hypothalamus than males, while females possess more anorexigenic pro-opiomelanocortin (POMC) neurons displaying higher neural activities. Estrogen receptor alpha expressed by POMC neurons suppresses food intake in female but not male mice, pointing to an additional potential interplay between estrogen-driven anorexigenic POMC and GLP-1 mechanisms. Leptin signaling to hypothalamic targets is also sexually dimorphic, and leptin via its receptors stimulates GLP-1 receptor-expressing neurons in the solitary tract, having an additive effect on food intake suppression. The orexigenic gastric hormone ghrelin counterbalances leptin and interacts with GLP-1 through a gating mechanism on vagal neurons. GLP-1 neuronal axon terminals in the ROb lie in close apposition to serotonergic neurons in the parapyramidal region, suggesting projection to brainstem areas implicated in autonomic appetite suppression.

The portrait that emerges is not of a single molecule acting alone. It is a coordinated conversation among multiple peptidergic systems, each inflected by sex.

Though not as plentiful as in the solitary tract or olfactory bulb, the atlas extends well beyond appetite into psychiatric implications and Alzheimer's disease. Glp1 expression was detected in the midbrain and pons (interfascicular nucleus, ventral tegmental area, paranigral nucleus, and interpeduncular fossa), hippocampus (granular layer of the dentate gyrus), hypothalamus (posterior hypothalamic area and lateral hypothalamus), thalamus (dorsal lateral geniculate nucleus), and ependymal layer of the third ventricle. The ventral tegmental area, a brain region central to reward processing, showed Glp1 expression only in females. The lateral hypothalamus, implicated in motivated behavior, showed expression only in males.

"The implications extend well beyond metabolism," said Zaidi. "With growing evidence that GLP-1 analogs may help prevent or treat cognitive decline, and given that we can detect Glp1 transcripts in Alzheimer's-vulnerable regions in the mouse brain, this atlas should help guide future investigations into how GLP-1 acts on neuroinflammation, neuronal degeneration, and memory loss."

The authors are transparent about the boundaries of the work. The relatively small sample size of three animals per sex limits statistical power, particularly for detecting low-abundance or regionally sparse Glp1-expressing cells. Females were not staged for estrous cycle phase, which may contribute to variability within the female group but is unlikely to alter the main qualitative patterns reported. RNAscope identifies Glp1 expression but does not directly assess peptide synthesis, release, or functional engagement; conclusions regarding circuit-level or behavioral

effects remain inferential. The atlas is optimized for detecting moderate-to-high Glp1 expression patterns and has limited statistical power to definitively determine presence or absence in regions characterized by sparse transcript abundance.

This atlas was not built to close a door. It was built to open one. The comprehensive mapping of Glp1 at the single-transcript level in the murine brain lays a foundation for identifying and interrogating new functional GLP-1 circuits in coordination with other peptides that regulate food intake and other behaviors, as well as guiding the development of more precise and effective GLP-1-based therapies. The expression pattern of preproglucagon neurons in the brain is highly conserved between rodents and nonhuman primates, which lends translational weight to the findings.

Somewhere between the raphe obscurus nucleus of a female mouse and the granular cell layer of a male, between the peptide that tells the body to stop eating and the estrogen that modulates how loud that signal gets, lies a piece of the puzzle that clinicians prescribing semaglutide have been assembling by intuition. Now there is an atlas.

The Research Article in Brain Medicine titled "Atlas of GLP-1 expression in the mouse brain: Neuroanatomical basis for metabolic and psychiatric effects," is freely available via Open Access on 10 March 2026 in Brain Medicine at the following link:

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