

 OBESITY

## 5-HT<sub>2A</sub> in GLP1-mediated weight loss

Glucagon-like peptide 1 (GLP1) analogues induce weight loss and hypophagia via the 5-hydroxytryptamine (5-HT; also known as serotonin) receptor 2A (5-HT<sub>2A</sub>), according to new data published in *Diabetes*. Both the GLP1 and 5-HT systems are targets of antiobesity therapeutics, but whether the two systems communicate in the central nervous system was poorly understood, until now.

The investigators utilized immunohistochemical, electrophysiological, neuropharmacological and behavioural techniques to investigate how GLP1-producing neurons interact with the 5-HT system in the brains of rats and transgenic mice. The authors reported that following a central injection of exendin-4 (EX4), a

GLP1 analogue that is used in the clinic, 5-HT turnover in the hypothalamus of rats was increased. Furthermore, EX4 or GLP1 treatment ameliorated the upregulation of 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors in the hypothalamus that was induced by calorie restriction.

The team used EX4 and selective 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> antagonists to assess the role of 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> in the GLP1–5-HT communication system. They found that 5-HT<sub>2A</sub>, but not 5-HT<sub>2C</sub>, was crucial for EX4-induced weight loss and hypophagia. “The 5-HT<sub>2C</sub> receptor, which is believed to be pivotal to the pharmacological effect of the antiobesity drug lorcaserin, is the focus of most antiobesity research,” says Karolina Skibicka, corresponding

author of the study. “The finding that the GLP1 system is utilizing 5-HT<sub>2A</sub> and not 5-HT<sub>2C</sub> could stimulate a shift in research focus.”

The authors stress that their preclinical data need to be investigated further and replicated in the clinical setting before any firm conclusions can be drawn. They do, however, hope that their preliminary data will provide potential avenues for research that could reveal new targets for antiobesity pharmaceuticals or improve current therapies.

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**ORIGINAL ARTICLE** Anderberg, R. H. et al. Glucagon-like peptide-1 and its analogues act in the dorsal raphe and modulate central serotonin to reduce appetite and body weight. *Diabetes* <http://doi.org/10.2337/db16-0755> (2017)