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Function of the nucleus of the solitary tract in the therapeutic effect of obesity medication lorcaserin

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Obesity and overweight are leading healthcare issues in developed countries. Despite considerable clinical demand, limited pharmaceutical treatment options are currently available. Amongst those recently developed are the serotonin 2C receptor (5-HT2CR) agonist lorcaserin, glucagon-like peptide-1 receptor (GLP-1R) agonists (e.g. liraglutide) and melanocortin-4 (MC4R) agonists (e.g. setmelanotide). Defining whether these medications target the same or parallel brain circuits to improve obesity is the objective of the present work. 5-HT2CRs, GLP-1Rs, and MC4Rs are distributed throughout the brain including in the key homeostatic region of the nucleus of the solitary tract (NTS)[1,2]. The NTS has a major role in the regulation of food intake and several neuropeptides, including GLP-1 produced by preproglucagon (PPGNTS) neurons, are localized here[3].

Adult male and female mice were used to investigate the therapeutic mechanism of obesity medications lorcaserin. To examine the potential interaction between the serotonin and GLP-1 circuits, neurons within the NTS making GLP-1 were ablated (PPG^{NTS} ablation) or GLP-1 receptors were specifically knocked down within the NTS ($GLP\text{-}1R^{NTS}$ knockdown). All studies were conducted in accordance with The Animals (Scientific Procedures) Act 1986 and the principles of the 3Rs.

Our results demonstrate that 5-HT_{2C}R agonist lorcaserin requires functional PPG^{NTS} neurons to reduce food intake in mice. Lorcaserin significantly reduced cumulative 1–4 hour food intake in control mice but not PPG^{NTS} ablated mice ($F_{(1,26)} = 9.977$, $p = 0.004$). Further analysis of the underlying neurocircuitry shows that approximately one-third of PPG^{NTS} neurons express 5-HT_{2C}Rs ($38.8 \pm 2.8\%$) and display the marker of neuronal activity c-FOS following lorcaserin treatment in mice. We next demonstrate, by knocking down expression of the GLP-1R within the NTS, that GLP-1R NTS neurons are necessary for 5-HT_{2C}R dependent hypophagia. 1–4 hour cumulative food intake was significantly decreased in control mice but not GLP-1R knockdown mice following NTS 5-HT_{2C}R activation ($F_{(2,13)} = 10.22$, $p = 0.002$). We next established that PPG^{NTS} neurons are also partly required for the anorectic effect of MC4R agonist melanotan-II (MT-II). MTII reduced cumulative food intake in both PPG^{NTS} neuron ablated and control mice at 1–4 hours (treatment $F_{(1,11)} = 107.5$, $p<0.0001$). However, PPG_{NTS} neuron ablated mice were resistant to the anorectic effect of MTII 21 hours (treatment $F_{(1,11)} = 4.733$, $p = 0.052$).

These data provide insight into the therapeutic mechanisms of obesity mediations and reveal key brain circuits modulating feeding.

Nutrition in the treatment, management and prevention of disease: nutrition strategies for disease prevention, nutrition in the management and treatment.

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References

1. D'Agostino G, Lyons D, Cristiano C *et al.* (2018) *Cell Metabolism* **28**(4), 533–534.
2. Alhadeff AL, Mergler BD, Zimmer DJ *et al.* (2017) *Neuropsychopharmacology* **42**, 1471–1479.
3. Holt MK, Richards JE, Cook DR *et al.* (2019) *Diabetes* **68**(1), 21–33.