Hypothalamic Circuit Mediates Therapeutic Appetite Suppressive Effect of 5-HT Obesity Medication

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Obesity and its related medical complications are reaching epidemic proportions globally and reflect a substantial unmet clinical need. The medication lorcaserin, a 5-hydroxytryptamine 2C receptor (5-HT2CR) agonist, was recently launched for obesity treatment in the USA. However, the mechanisms underpinning its therapeutic effect have not yet been defined. We chose to take a genetic approach in mouse models to dissect the neurocircuitry underpinning lorcaserin's effects on food intake. We focussed on the key brain region regulating energy intake, the hypothalamus. Specifically, the arcuate nucleus of the hypothalamus (ARC) acts as a gateway for multiple appetitive signals from the brain and periphery to control of feeding behavior through two distinct melanocortin neuronal populations (pro-opiomelanocortin (POMC) and agouti-related protein (AgRP)) (Bell et al., 2005). Within the ventromedial nucleus of the hypothalamus (VMN), brain-derived neurotrophic factor (Bdnf) impacts energy homeostasis. Mouse models of global depletion of Bdnf results in hyperphagic behavior and obesity (Unger et al., 2007), whereas the infusion of Bdnf into the brain significantly reduces food intake (Lapchak et al., 1992).

We observed that preventing Pomc expression in the ARC using the reversible ARC Pomc knockout model abolished lorcaserin's anorectic effects, and that restoration of Pomc expression specifically within 5-HT2CR expressing neurons within the ARC was sufficient to mediate its appetite suppression. Considering that POMC peptides signal at melanocortin4 receptors (Mc4rs) to elicit their effects on feeding, we next observed that Mc4rs are a necessary downstream target for lorcaserin anorexia. Finally, previous reports suggest that Bdnf is a component of the melanocortin energy homeostasis brain circuit. Using viral-Cre mediated selective knock-down of Bdnf within the VMN, we investigated whether VMN Bdnf is necessary for lorcaserin’s anorectic effect. Mice without functional VMN Bdnf did not respond to the anorectic effect of lorcaserin. Thus, our results identify a discrete microcircuit through which lorcaserin elicits its therapeutic effect on reduced food intake. We propose that pharmacologically targeting this circuit through combination drug therapy could yield a more effective obesity treatment, promoting greater weight loss.

Bell et al (2005). Nat Rev Genet. 6(3):221-34.

Unger et al (2007). J Neurosci. 27(52):14265-74.

Lapchak et al (1992). Neuroreport. 3:405–408.