RESEARCH ARTICLE

Enteroendocrine cell types that drive food reward and aversion

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Abstract Animals must learn through experience which foods are nutritious and should be consumed, and which are toxic and should be avoided. Enteroendocrine cells (EECs) are the principal chemosensors in the GI tract, but investigation of their role in behavior has been limited by the difficulty of selectively targeting these cells in vivo. Here, we describe an intersectional genetic approach for manipulating EEC subtypes in behaving mice. We show that multiple EEC subtypes inhibit food intake but have different effects on learning. Conditioned flavor preference is driven by release of cholecystokinin whereas conditioned taste aversion is mediated by serotonin and substance P. These positive and negative valence signals are transmitted by vagal and spinal afferents, respectively. These findings establish a cellular basis for how chemosensing in the gut drives learning about food.

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This study provides insight into the functional diversity of specialized cells in the gut using a combination of transcriptomics, genetics, and behavioral assessment. It demonstrates how select enteroendocrine cell types mediate food reward while others drive aversion.

Introduction

Although the desire to eat is innate, our food choices are driven by learning. Thus, the foods you enjoy today are different from your preferences as a child, in part because you have learned to associate specific flavors with their post-ingestive effects (***Sclafani and Ackroff, 2012***; ***Yamamoto and Ueji, 2011***). This learning process causes nutrient-rich foods to become more rewarding and toxic substances to become aversive and is critical for guiding animals to choose safe and nutritious food sources in the wild (***Myers and Sclafani, 2006***). It also contributes to the motivational pull of energy-dense foods in modern society (***Johnson et al., 1991***; ***Kern et al., 1993***). For these reasons, it is critical to establish where in the body ingested nutrients and toxins are detected to drive learning, and whether these parallel processes of food reward and aversion involve dedicated cell types, signals, and pathways.

One of the first sites of post-ingestive chemosensing is the epithelium of the small intestine, which contains a family of specialized sensory cells known as enteroendocrine cells (EECs) (***Adriaenssens et al., 2018***). EECs exist as multiple subtypes and express receptors and transporters that allow them