Sensing of gut nutrients by the brain

Hunger and food intake are tightly regulated by complex and coordinated gut-brain interactions. While we know some mechanisms through which the gut communicates with the brain, our understanding of how nutrients impact in vivo neural activity is in its infancy. Our previous work demonstrated the ability of nutrients in the gut to rapidly modulate neural activity in a small population of hunger-sensitive, hypothalamic neurons expressing agouti-related protein (AgRP). Fats, sugars, or proteins alone are each capable of inhibiting AgRP neuron activity. How are these nutrients in the gut signaled to the brain to update nutritional status in real time? Because individual macronutrients engage specific receptors in the gut to communicate with the brain, we reasoned that macronutrients may utilize different pathways to reduce activity in AgRP neurons. We therefore explore the relative roles of vagal afferent, spinal afferent, and gut peptide signaling in the regulation of AgRP neuron activity and food intake using fiber photometry to monitor AgRP neuron calcium dynamics as a proxy for neural activity. Our results demonstrate that different gut-brain pathways mediate the effects of fats and sugars on hypothalamic neuron activity. Further focusing on the monosaccharides glucose and fructose, we demonstrate that they too have different effects on AgRP neuron activity, where equicaloric concentrations of oral or gut-delivered fructose are less effective than glucose at inhibiting AgRP neuron activity. Further, the time to maximally inhibit AgRP activity was slower after fructose infusion compared to glucose infusion, raising the possibility that hormonal signaling may mediate the effects of fructose. Indeed, fructose engages gut peptide signaling to inhibit activity in AgRP neurons, and ongoing studies seek to identify the gut-brain mechanisms mediating these effects. Overall, since AgRP neurons drive food intake, understanding the negative regulators of hunger circuits may inform new and effective weight loss strategies.

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Zoom: https://usc.zoom.us/j/94482970549