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Research Advance

Eating for hunger or pleasure: a Serotonin Model

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Obesity, resulting from an imbalance between energy intake and expenditure, represents a major health crisis to our society, due to its alarmingly high prevalence and comorbidities, including diabetes, cardiovascular diseases, cancer, and COVID-19. Better understanding the neurobiological mechanisms for feeding behavior is essential for developing rational strategies to combat obesity and related comorbidities.

Agouti-related peptide (AgRP) neurons located in the arcuate nucleus of the hypothalamus (ARH) have received perhaps the most attention as a master regulator of feeding behavior. It is well known that AgRP neurons are regulated by multiple hormones that reflect the body's energy storage or nutritional state, e.g., leptin, insulin, ghrelin, and asprosin (Yang and Xu, 2020). AgRP neurons are activated in a calorie-deficient state (Takahashi and Cone, 2005; Yang et al., 2011; Liu et al., 2012), and activations of AgRP neurons can drive eating (Aponte et al., 2011; Krashes et al., 2011). Together, these findings support a physiological feedback pathway that regulates feeding: a calorie-deficient state (e.g. hunger) activates AgRP neurons, which in turn drive eating. However, this 'AgRP model' faces a challenge, as recent *in vivo* recordings revealed that AgRP neurons decrease their activities dramatically within a few seconds after feeding starts, or even without the food actually being consumed (Betley et al., 2015; Chen et al., 2015; Mandelblat-Cerf et al., 2015). This rapid diminishment of AgRP neuron activity (Figure 1A) raises a question regarding how feeding behavior, which usually lasts for minutes to hours, is sustained. Based on our observations reported in a recent *Molecular Psychiatry* article (He et al., 2021), we propose an alternative 'Serotonin Model', which provides physiological feedback signals for feeding control.

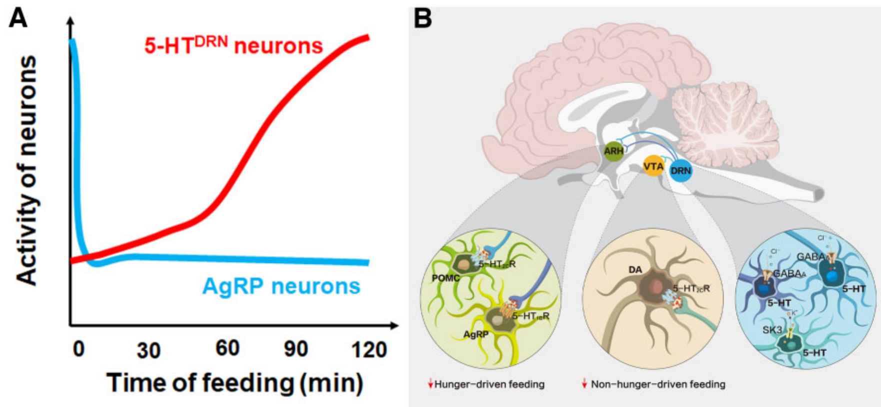

Figure 1 The 'Serotonin Model' illustrates physiological feedback signals to regulate both hunger-driven feeding and non-hunger-driven feeding. (**A**) A schematic illustration of changes in activities of AgRP neurons or 5-HT^{DRN} neurons during feeding. (**B**) A subgroup of 5-HT^{DRN} neurons project to the ARH, inhibiting AgRP neurons via the 5-HT$_{1B}$R and activating POMC neurons via the 5-HT$_{2C}$R, to suppress hunger-driven feeding; another subgroup of 5-HT^{DRN} neurons project to and inhibit DA^{VTA} neurons via the 5-HT$_{2C}$R to suppress non-hunger-driven feeding. The GABA$_A$ receptor and the SK3 potassium channel mediate changes in activities of the ARH-projecting and VTA-projecting 5-HT^{DRN} neurons, respectively, during feeding. 5-HT$_{1B}$R, 5-HT 1B receptor; 5-HT$_{2C}$R, 5-HT 2C receptor; DA, dopamine; DRN, dorsal Raphe nucleus; GABA, γ-aminobutyric acid; POMC, proopiomelanocortin; SK3, small conductance calcium-activated potassium channel 3.

The brain serotonin, a neurotransmitter also known as 5-hydroxytryptamine (5-HT), is mainly synthesized by neurons in the midbrain dorsal Raphe nucleus (DRN). We demonstrated that the activation of these 5-HT^{DRN} neurons can inhibit eating (He et al., 2021). Importantly, using the *in vivo* recordings, we found that 5-HT^{DRN} neurons gradually increase their activities during the 2-h feeding period (Figure 1A). In sharp contrast to the rapid and sustained inhibition of AgRP neurons, the activation of 5-HT^{DRN} neurons occurs in a gradual and slow fashion (He et al., 2021). Importantly, the level of 5-HT^{DRN} neuron activity is correlated to the quantity of food intake (He et al., 2021). Thus, we suggest that 5-HT^{DRN} neurons function as a key component of a negative feedback loop. Low 5-HT^{DRN} neuron activity permits animals to eat; as animals continue eating, 5-HT^{DRN} neurons slowly elevate their activities to eventually terminate the meal.

Feeding can be driven by hunger (a state of nutritional deficit) to ensure survival. Feeding can also be triggered by the hedonic properties of certain foods in the absence of nutritional deficit. Dysregulations of hunger-driven feeding and hedonic feeding both contribute to the development of obesity (Kenny, 2011; Alonso-Alonso et al., 2015). It has been suggested that neurocircuits controlling these two types of feeding behaviors are not completely dissociable (Rossi and Stuber, 2018). Consistent with this notion, we found that 5-HT^{DRN} neurons can regulate a hunger-driven feeding and a non-hunger-driven feeding in animals (He et al., 2021). However, our study further illustrated two largely segregated subgroups of 5-HT^{DRN} neurons: one subgroup send projections to the ARH and specifically inhibit feeding behavior driven by hunger, while the other subgroup of 5-HT^{DRN} neurons project to the ventral tegmental area and reduce the intake of a high palatable diet in the non-hungry state (Figure 1B). Interestingly, these two subgroups of 5-HT^{DRN} neurons both display slow activation during the course of hunger-driven feeding and non-hunger-driven feeding, respectively; however, they use distinct ion channels to achieve these changes (Figure 1B).

In summary, our findings support a 'Serotonin Model' that provides physiological feedback signals to regulate both hunger-driven feeding and non-hunger-driven feeding. We further identified distinct 5-HT^{DRN}-originated neurocircuits and disparate ion channels that can regulate these two types of feeding behaviors. These results provide a necessary framework for the development of a precision medication approach to treat obesity resulting from overeating for hunger or for pleasure.

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