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Molecular and Neural Bases of Nutrition-Based Feeding Decision-Making

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Summary Obesity and life style-related diseases have become major burdens to global health. Not having effective diet therapy that patients can adhere to makes life-style modification difficult. Many diet therapies are developed based on solid scientific evidence in terms of nutrition. However, how to execute such nutritionally-effective diet therapy is not established, nor based on solid science. Current practices are mostly developed by trial-and-error (experience-based), and they do not have solid bases on how eating behavior is regulated. Therefore, one of the major bottlenecks for implementing nutritionally-effective diet therapy is our lack of understanding of the molecular and neural bases of eating behavior. Based on the concept of nutrition, we eat to maintain homeostasis, and therefore, we should be satisfied once the needs are met by the supplies. However, that is only a part of the picture regarding eating. Palatable foods, which stimulate the hedonic system, and the experience-based prediction system work in concert to regulate eating. The information that conveys needs and supplies is multi-modal, each mode working at different timing to modulate each system. Therefore, eating behavior is complex, and the whole picture remains elusive. In particular, how we sense, calculate, and predict the needs and supplies of calories and each macronutrient remains to be understood. In this minireview, the frontiers in our understanding of the mechanism that regulates eating are briefly overviewed, as a summary of the IUNS-ICN symposium entitled "Molecular and neural bases of nutrition-based feeding decision-making."

Key Words appetite, eating behavior, feeding behavior, nutrition, diet selection

Obesity and life style-related diseases have become major burdens to the world. According to the Global Burden of Disease study, these diseases are ranked as 1st, 3rd, 4th, and 7th disease burdens, and their ranking has risen since the prior study in 2010 (*1*). Many efforts have been made to develop medical treatments for such diseases. However, the core of this ongoing problem is that we do not have a thorough understanding of the mechanisms that regulate our lifestyle, especially eating behavior.

Nutrition means that we eat to maintain our homeostasis. Human adults can maintain their body weight within a fairly narrow range over a long period of time, suggesting that nutrition-based homeostatic eating is functional when young. It is commonly believed among the general public and even by some medical practitioners that we start to gain weight when we reach middle age, because our metabolism slows down. That was refuted in a large-scale human metabolic database, which suggested that the basal metabolic rate of humans does not change from their 20s to 60 y old (*2*). Because body weight is defined by the balance between the intake and expenditure of energy, the evidence indicates that we somehow lose control of our eating behavior over time, the mechanisms of which remain elusive.

All motivated behaviors require decision-making, and it uses information as input and output action, if the decision is "go", not "no go". The action generates a new state, which updates information and influences decision (Fig. 1). Eating behavior is complex behavior based on motivation, regulated by multiple inputs and regulatory systems (Fig. 2). Eating consists of the interaction between the eater (animal/human) and food (substance). The former actively seeks and ingests the latter, while the latter influences the former passively to be selected as the target of eating. Therefore, information that represents the needs state of the body, and the information provided by food both play critical roles in regulating eating behavior, each working on different timing and having different meaning toward the eating behavior. Until 2015, nutrition-based feeding was classically regarded as a negative-feedback regulatory system. However, the fact that the activity of the primary center for the homeostatic eating changes before eating based on prediction changed our understanding of feeding behavior (*3*). Once information reaches the brain, it is processed through 3 different systems (homeostatic, hedonic, and predictive), and these systems work in concert to regulate eating. How inter-system interactions are regulated is the on-going hot topic. We now need to understand how we remember our prior eating experiences and refer to them to make a prediction, which is a necessary process for decision-making.

Another ongoing issue is why palatable food, which

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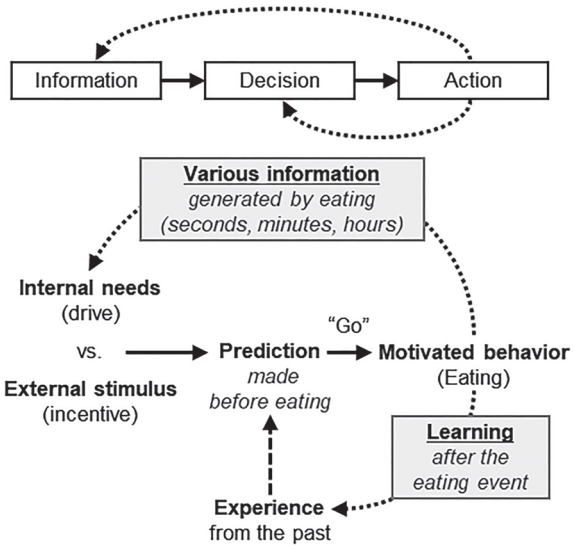

Fig. 1. Decision making processes in motivated behaviors. Decision making is a dynamic cycling process consisting of information, decision, and action. Information that represents internal needs (drive) and external stimuli (incentive) generates motivation to act. The motivated status is referenced to past experience to make prediction on the consequence of the action. If the decision is "go", then the action is taken, and generates a new status. Information representing the new status updates the decision, and once "no go" is decided, the action is terminated. The result of the event promotes learning, and updates the experience, which will influence future prediction.

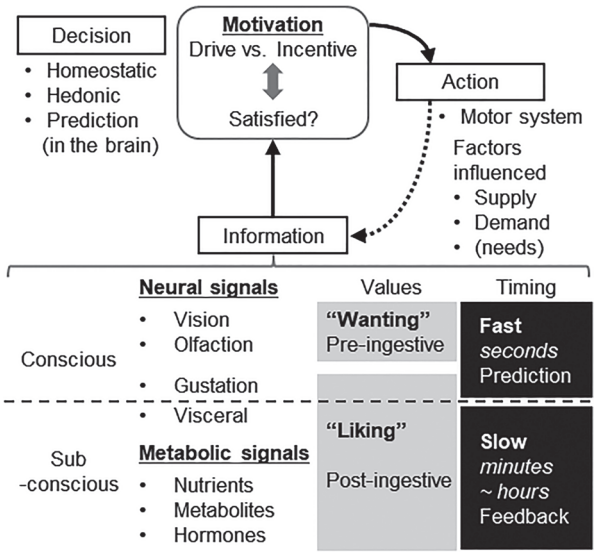

Fig. 2. The systems and information regulating feeding behavior. Information that influences feeding behavior has different properties, values, and times of action. Decision is made through the interaction of homeostatic, hedonic, and prediction systems, and whether desire (need) was satisfied or not is evaluated. Action results in the supply of food and influences the internal state (need/demand).

stimulates the hedonic system, disturbs eating. If we can adjust our eating behavior based on prior experience, why can't we learn and predict the negative health consequence of such food and adjust our behavior? It is well known that palatable foods induce hormone resistances (e.g., leptin and insulin), thereby disturbing homeostatic eating (*4*, *5*). Do they also perturb the prediction system, and if so, how?

Finally, there is an intriguing question of how our body senses calories and macronutrients (*6*). Caloric need is the primary and major driver for eating. The calories stored in our body can be represented by the amount of triglycerides (TG) stored in the adipose tissue. Blood leptin level correlates well with the adipose TG store under healthy conditions, and therefore works as a strong appetite-suppressing hormone. When we try to satisfy our caloric need by supplying food, it becomes a very complex calculation. Calories are the mixture of the macronutrients (protein 4 kcal/g, fat 9 kcal/g, and carbohydrate 4 kcal/g) digested and absorbed, and the timing and the efficiency of digestion and absorption varies tremendously among the foods ingested. Therefore, how we calculate the caloric supply to control our nutrition-based eating remains elusive. Another side of the coin is how we sense the need and supply for each macronutrient. To maintain nutritional homeostasis, our body should also have the system to specifically sense the need and supply of each macronutrient. It has been known for quite some time at the phenotype level that calorie-based appetite and protein-based appetite are different, and animals can sense an imbalance of amino acid in diets (*7*–*9*). However, the mechanisms that regulate each macronutrient are just starting to be understood (*10*–*12*).

As a symposium (1SY8) at the IUNS-ICN entitled "Molecular and neural bases of nutrition-based feeding decision-making", the following 4 speakers will present their recent work.

The first speaker, Dr. Zachary A. Knight, was one of the first investigators to report in 2015 that the activity of AgRP (hunger) neurons and POMC (satiety) neurons change prior to actual food consumption (*3*). Among many aspects of feeding behavior that he investigates, he has reported how mechanical stimuli and nutrient stimuli in the gut control these appetite-regulating neurons (*13*, *14*).

The second speaker, Dr. Ivan E. de Araujo, has investigated how nutrients through the gut modulate the mesolimbic dopamine system and affect feeding. He first showed that the nutritional value of sugar, in the absence of taste receptor signaling, induces dopamine release in the ventral striatum (*15*). He then showed that the high-fat diet suppresses gut-stimulated dopamine release by suppressing the synthesis of the lipid messenger oleoyl ethanolamine (*16*). He also found that the importance of the gut-induced reward pathway is asymmetric, with the activation of the right vagal sensory ganglion pathway being a more effective conditioning signal (*17*).

The third speaker, Dr. Michael J. Krashes, is one of the

first investigators to artificially manipulate the activity of the Agrp (hunger) neuron (*18*). This methodology is powerful, because we can alter the needs state of the animal and assess the effect on behavior to test causality, not just correlation. He utilized this approach to tease out how behavior prioritization occurs (*19*, *20*). He has extended his studies on how high-fat food biases consummatory drives by affecting the hypothalamic and mesolimbic systems (*21*).

The final speaker, Dr. Ken-Ichiro Nakajima, has been studying the interaction between the taste pathway and the homeostatic system. He has elucidated the projection and the tertiary target of hunger-induced taste modification by AgRP neurons (*22*). Simultaneously, he also continues to work on elucidating the taste neural circuits. He identified SatB2 positive neurons in the parabrachial nucleus that encode sweet taste (*23*).

These speakers will present their recent findings and show the audience the frontiers in our understanding of the mechanisms that regulate eating.

Disclosure of state of COI

No conflicts of interest to be declared.

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