The Metabolic Mechanism of Satiety Signal and Adiposity Signal on Food Intake Regulation

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Abstract: Obesity rates rose sharply in past 40 years, owing to the availability of appetizing food and work-related sedentary habits. Obesity is caused by a long-term positive energy balance, but by reducing food intake significant weight loss can be achieved. Food intake is simultaneously regulated by biochemical signals (homeostasis) and social factors (non-homeostasis). As two important homeostasis factors, satiety and adiposity signals have been well studied, but it is relatively fragmented. Therefore, this study looks at satiety and adiposity signals to understand the metabolic mechanism of human food related metabolic pathways from the perspective of homeostasis factor. Satiety and adiposity signals are critical for reducing obesity, because they play such a large role in appetite control to reduce food intake. This research analyses literature about satiety and adiposity signals, such as references related to CCK, GLP-1, ghrelin, leptin and insulin, and combines the research of exogenous injection satiety and adiposity signals for calorie restriction to better illustrate the metabolic pathways of these hormones.Through the analysis of these factors, it is concluded that satiety and adiposity signals are expressed on two neuron pathways via NTS and ARC to synergeticly control food intake by regulating appetite, but it seems that the method of injecting exogenous hormones to treat obesity is currently difficult to achieve.

1 INTRODUCTION

In the past 40 years, the global obesity level exorbitantly rose by three times, according to WHO report, the percentage of overweight and obesity for 18 years old and elder adults was 39% and 13% in 2016, respectively (Website: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight). Obesity is characterized as having a BMI of 30kg/m2 or above and it has become one of the most important global public health issues which affects human well-being and lifetime. Thus, it is very important to find an effective way to lose weight.

Increasing activities and dietary restriction are the only two methods that have been proved effective in improving obesity from the energy balance view. Comparing these two methods, dietary restriction is a more effective way for weight loss than moderate energy expenditure without calorie restriction (Swift, McGee, Earnest, Carlisle, Nygard, Johannsen 2018; Varady 2011).

Food consumption is coordinately regulated by homeostasis and non-homeostasis factors. Non-homeostasis factors include all external social factors, such as food availability, eating patterns, food delectability and previous experience, so it is unpredictable and hard to control for improving obesity. However, homeostasis factors play an important role in controlling food intake by biochemical signals (hormones) and understanding the fundamentals of food intake control is critical to understanding the etiology of eating disorders and obesity. Homeostasis factors have been extensively explored in human physiology to assist people in understanding the cause of obesity and develop therapeutic targets to cure obesity.

Depending on energy requirements, the physiological regulation of calorie intake is exerted on the meal's conclusion through a subtle modification of meal size and sensation of fullness. Thus, satiety and adiposity signal as the homeostasis factors are important in appetite regulation because the amount of food consumed in each meal is mostly determined by the gut secreted hormones (satiety

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signal) and adipose related hormones (adiposity signal) (Brunerová, Anděl 2013), lots of exogenous injection of satiety and adiposity signal has been put forward to reinforce specific neurons by changing hormone level for treating obesity. And it's important to combs out the metabolic mechanism of satiety and adiposity signals to let more people know the mechanism in a clearer way.

However, there is relatively few article that combs out these two signals and their effect in human's brain, thus, this study aims to evaluate the impacts of two key hormonal signals (adiposity signal and obesity signal) in the metabolic pathways on food intake and discuss the feasibility for administration of the exogenous key hormonal signals for weight loss. Through this paper, relevant researchers can get a clear idea of the internal mechanisms of obesity. And for those who are relatively fat, knowing the related concepts and mechanism about dietary restriction will also help them lose weight and find a healthier life style in a more scientific way.

2 FOOD IN TAKE RELATED METABOLIC PATHWAY

As homeostasis regulation, key hormone signals control dietary calorie intake via meal size, satiety, and feeding interval, these controlling are based on the action of these hormones to the brain to regulate food intake, such as cephalic insulin (Ahrén, Holst 2001). To understand the effect of these hormones, it is essential to understand their metabolic pathways. As two important food intake related hormones, satiety and adiposity signals regulate appetite through reaching the signal integration site, the arcuate nucleus of the hypothalamus (ARC) and the nucleus tractus solitarius (NTS).

Hypothalamus as the body's most important brain tissue to regulate of food intake has several regions, as shown in Fig.1, the lateral hypothalamus and ventromedial nucleus are associated with hunger and satiety, which has been proved in animal experiments. As the main region for integrating food intake related signals to controlling food intake in hypothalamus, ARC is close to the third ventricle. ARC is engaged in two well-studied interconnected neural pathways that are crucial for controlling food intake. The effects of the two neuronal groups on food intake are diametrically opposed, where the synergy of pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) are responsible for satiety to reduce

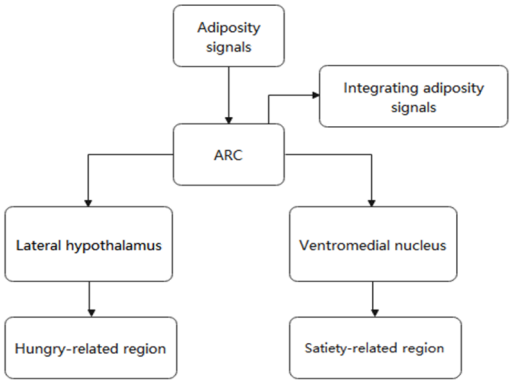

Figure 1: The metabolic pathways of food related signals in hypothalamus.

food intake and the coordinated expression of neuropeptide Y (NPY) and agouti related peptide (AgRP) is related with inhibiting of satiety by releasing AgRP neuron on melanocortin 4 receptor (MC4R) to antagonize with POMC pathway neuron (αMSH) (Zhan 2018). Notably, some signal hormones like ghrelin govern hunger by stimulating one of the two neuron routes, whereas some specific signaling hormones like leptin and insulin can control food intake by simultaneously affecting both neuron pathways.

Like the hypothalamus, NTS, as shown in Fig.2, is the integration site in the hindbrain for taste-relative information and vagal and circulating signals, NTS offer physicochemical property information and quantity about food to the POMC and AgRP neurons to rapidly promote satiety after meal digestion (Sohn 2015). Additionally, the NTS also express taste-relative information which is non-homeostasis factor to the ARC to control feeding behavior (Valassi, Scacchi, Cavagnini 2007).

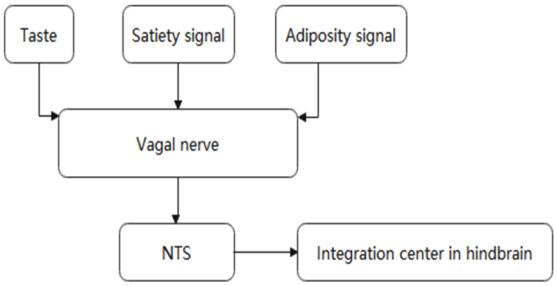

Figure 2: The metabolic pathways of food related signals in nucleus tractus so-litarius (hindbrain).

Although satiety and adiposity signals share the same neuron pathway, their biochemistry and duration of action are different. Satiety signals are short-term signals of negative feedback of the body's

rapid response, satiety signals control hunger sensation, satiety and feeding interval, it changes constantly with the start of eating (ghrelin excepted), while the adiposity signal is a long-term signal targeted at maintaining the body's energy balance, it does not change dramatically due to the beginning of eating behaviors ,but they constantly control the appetite through negative feedback of the amount of adipose tissue. The satiety signal that is transmitted to the NTS via the vagal and spinal nerves, is eventually transmitted to the neuron routes in the hypothalamus, while the adiposity signal, which express to the ARC via the median eminence or by crossing the blood-brain barrier (BBB) to enter the two specific neuron pathways (Abdalla 2017).

3 THE SATIETY SIGNAL- SHORT-TERM

Satiety signals are produced in the GI tract from one hour before the start of the meal to the completion of the meal as a signal to regulate food intake. Satiety signal production is linked to eating anticipation, such as the usual eating surroundings, daily habitual eating time and the aroma and beauty of food. The brain receives sensory stimulus or biological clock regulation, the external stimulus and internal regulation instruct the GI tract to create satiety signals and transmits them down the vagal and spinal nerves to the NTS (except ghrelin), then they express onto neuron pathways and causing hunger or satiety. Cholecystokinin (CCK), glucagon, glucagon-like peptide-1 (GLP-1), ghrelin (hunger signal), and peptide YY (PYY) are the most prominent satiety signals which have been studied. To improve obesity, significant pharmaceutical research has been conducted based on this information.

Interestingly, a national survey has found that fast eaters eat significantly more (for the same weight) than slow eaters (Zeng, Cai, Ma, et al 2018), owing to the fact that the slow eaters' satiety signal hasn't yet reached the POMC pathway to increase satiety and stop eating, whereas heavy eaters feel fuller after meals due to more satiety signals reaching MC4R receptors and increasing satiety. On the flip side of the capacity to regulate food intake quickly, most satiety signals have short half-lives, which will be discussed further in the particular satiety signals section.

3.1 Cholecystokinin (CCK)

CCK as the first satiety signal to be identified and investigated has been widely studied. CCK is produced in the duodenum and jejunum and acts on the CCK 1 receptor via the vagal afferent nerve to inhibit food intake by activating the POMC pathway. In a human trial of exogenous CCK injection, it was discovered that exogenous CCK decreased food intake in a dose-dependent manner. Furthermore, food intake in mice treated with a CCK 1 receptor antagonist was significantly greater (when compared to the placebo group), demonstrating the satiety-enhancing impact of endogenous CCK(Beglinger, Degen, Matzinger, D'Amato, Drewe Loxiglumide 2001).

Exogenous CCK injection, on the other hand, has been shown to have some limitations in rat experiments. The administration of exogenous CCK more than 15 minutes before feeding seemed to have no effect on the amount of food consumed by mice, whereas the treatment of CCK immediately before feeding significantly reduced the amount consumed by mice(Begg, Woods 2013). This also proved that CCK has a short half-life in human metabolism and that the injection time must be carefully regulated to get the desired effect of lowering consumption.

Additionally, when mice were continuously injected with CCK over a long period of time, the drop in food intake was shown to vanish after a very short amount of time. According to the findings of E.A. Duncan et al., rat consumption was significantly reduced in the first three days after receiving consecutive CCK injections compared to the saline group (control group), but there was no significant difference in consumption between the two groups from day 4 to the end of the experiment (day 11). On the other hand, from day one until the completion of the experiment (day 28), the intermittent group (exogenous CCK injections every three days) consumed significantly less sucrose than the control group (saline).

On the test of final day sucrose intake level, the consecutive CCK group (110.0 ± 6.2% of baseline) consumed significantly more sucrose than the intermittent CCK group (98.6 ± 2.5% of baseline), $t(16) = 1.72$, $p \leq 0.05$, and the saline group (97.4 ± 3.5% baseline), $t(17) = 1.83$, $p < 0.05$ (Duncan, Davita, Woods 2005). This state (consecutive CCK no effect) could be caused by behavioral tolerance or extinction of the learned respond (for endogenous CCK) of CCK receptors. Accordingly, the results of these rat trials are helpful in determining the

administration time and interval for exogenous CCK injection in clinical practice.

3.2 GLP-1

GLP-1, another key intestinal hormone, stimulates insulin synthesis and secretion triggered by glucose while inhibits glucagon secretion. The injection of exogenous GLP-1 was linked to a reduction in food intake (which was dose-dependent) and weight loss in mice, but it was shown that after a long-term infusion, the obese group's post-meal GLP-1 release gradually declined, providing a reference for clinical use (Kanoski, Hayes, Skibicka 2016). GLP-1's clinical application is additionally hampered by its short half-life, as GLP-1 can be rapidly inactivated in the body by an enzyme called Dipeptidyl Peptidase IV (DPPIV) (Maselli, Camilleri 2020).

GlP-1 levels typically peak approximately an hour before a meal, perhaps to promote insulin production by islet B cells to digest incoming nutrients (glucose). This is because insulin, as a long-term adiposity signal, needs to take a long time to reach ARC and induce satiety.

Long-acting GLP-1 agonists and DPPIV inhibitors based on GLP-1 mechanisms have been demonstrated to lower food intake in mice trials, although most of these medications (for humans) are still in development.

3.3 Ghrelin

Ghrelin, as the only hormone produced by GI tract that promotes appetite among satiety signals, expresses on ARC. Ghrelin stimulates the NPY and AgRP pathways to boost appetite, and the NPY pathway's activation also inhibits the POMC pathway to be further hunger(Abizaid, Liu 2006). Ghrelin levels spiked in the hour leading up to feeding and then plummeted back to baseline once feeding began (Begg, Woods 2013). This wide range of ghrelin levels also suggests that ghrelin, as a satiety signal, has a rapid and short-term potential to control eating behavior.

Ghrelin has also been linked to body weight self-control. According to the experimental outcomes, ghrelin levels are higher in anorexia patients and lower in obese patients (Begg, Woods 2013), implying that ghrelin is engaged in the negative feedback regulation of body weight change. The findings may also shed light on why people who lose weight struggle to manage their appetites. But chronic ghrelin administration for anorexia patients will limit fat utilization as a source of energy, it may be an unhealthy method for gaining weight. In addition, ghrelin has been linked to reproduction, glucose and lipid metabolism, gastric motility, acid secretion, sleep, and antiproliferative activity.

4 THE ADIPOSITY SIGNAL- LONG-TERM

Adiposity signal is a long-term hormone that informs the brain about the state of the body (the number of fat cells) and aids the body in changing its diet to maintain health. With the exception of insulin, other obesity signals are produced by adipose tissue as the signals to feedback information to the brain. The adiposity signals are named because these hormones are proportionate to body fat content. The two most well-studied adiposity signals, insulin and leptin, are proportional to the degree of obesity(Bagdade , Bierman, Porte 1967; Lönnqvist, Arner, Nordfors, Schalling 1995), and insulin and leptin promote catabolism while blocking anabolism and they activate or inhibit the appropriate neuron pathways to lower food intake by expressing on their respective receptors on the ARC via active transport to the blood-brain barrier (BBB).

4.1 Leptin

Leptin, the first adipocytokine that is identified, is the primary regulator of the "brain gut axis," with the bulk of leptin generated by white adipose tissue. To lower meal size and extend time intervals, leptin enters particular neuron pathways via activating leptin receptors on the ARC, stimulating the POMC pathway and inhibiting the NPY route. Leptin also has a long-term control on obesity through regulating energy metabolism by altering the energy utilization ratio of glucose and fat.

Both congenital leptin and leptin receptor deficiency contribute to obesity (which is very rare in humans), and it has been demonstrated that leptin and leptin receptor deficiency obesity patients treated with recombinant human leptin and leptin dramatically lowered their weight and food intake (Valassi, Scacchi, Cavagnini 2007).

However, the experiment discovered that persons with obesity who did not have a congenital deficit had much greater blood leptin levels, indicating that obesity is linked to leptin resistance. The molecular mechanism behind resistance is unclear now.

4.2 Insulin

Obesity can disrupt the body's energy metabolism and is the major cause of Type 2 Diabetes (T2D), it is mostly caused by insulin resistance induced by a lipid metabolism disorder. Insulin and leptin function in various ways. Insulin enters the ARC and activates the POMC Neuron, but it does not inhibit the AgRP and NPY pathways. Interestingly, insulin stimulated AgRP production while inhibiting NPY (Vettor, Fabris, Pagano, Federspil 2002). According to a randomized crossover trial for oral insulin in healthy male subject, as shown in Figure 3 and Figure 4, it can be seen that the total exposure [AUCIns338,0-∞] and maximum concentration [Cmax,Ins338] of insulin 338 were both significantly lower for 0 versus 360 minutes post-dose fasting (ratio [95 percent confidence interval (CI)]: 0.36 [0.26-0.49], $p < 0.001$, and 0.35 [0.25-0.49], $p < 0.001$, respectively) (Halberg et al 2019). This trial suggests insulin can reduce food intake by increasing satiation and so control body weight in terms of results.

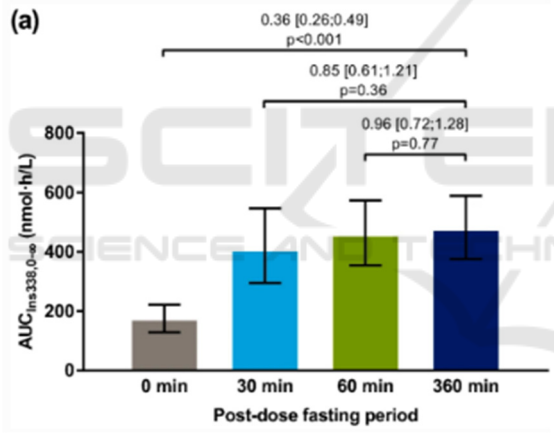

Figure 3:Post-dose fasting period (Halberg et al 2019).

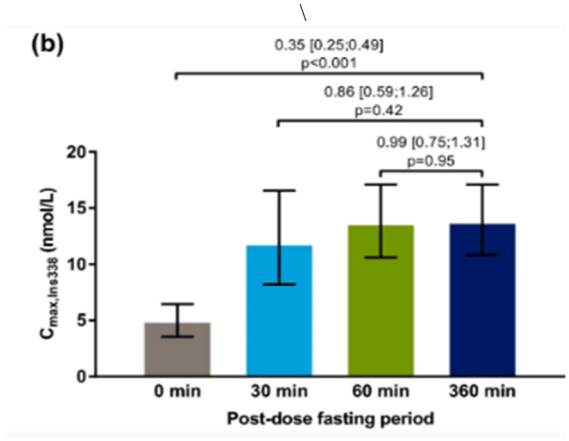

Figure 4: Post-dose fasting period (Halberg et al 2019).

The study of H.A. Halem et al. have shown that central insulin injections can significantly reduce intake in animal models (Halem, Taylor, Dong, Shen, Datta, Abizaid, Diano, Horvath, Culler 2005), but the major effect of insulin is to lower blood glucose through glycogen synthesis and accelerate glucose absorption in cells, which will let patients consume more food due to hypoglycemia, that is why it is impossible to use significant amounts of insulin to treat obesity in clinical treatment.

5 SIGNALS INTERACTION AND SENSITIVITY

As previously stated, adiposity and satiety signals are expressed in the same weight-control neuron pathways. Surprisingly, these hormones can alter the sensitivity of each other's receptors, for enhancing the appetite-controlling effect and this can be interpreted as a mechanism for the body to maintain weight effectively. For example, obese persons will have higher amounts of leptin which boosts insulin receptor sensitivity to improve production and lower blood sugar to preserve health. However, insulin and leptin, as long-term adiposity signals, can also influence the sensitivity of satiety signal represented by CCK (Begg, Woods 2013). For instance, patients who were losing weight had lower levels of insulin and leptin which affected a reduction in CCK 1 receptor sensitivity to prevent satiety, it is thought to be the body's regulation to maintain weight stability. These studies also suggest another reason why exogenous insulin and leptin injections might help people lose weight: increasing insulin and leptin can help people lose weight by modifying CCK and GLP-1 sensitivity.

6 CONCLUSIONS

In sum, satiety signal and adiposity signal are expressed via different integration centers (NTS and ARC) to the POMC and AgRP neurons that coordinate regulate food intake to keep the body weight, these biochemical pathways are essential for researchers to understand the underlying processes of obesity, such as changes in associated hormone levels and neuron pathway reinforcement, calorie restriction therapy also requires a deep understanding of the fundamental mechanism of obesity. A clinically significant weight loss benefit is not easy to occur without side effects from recognized satiety and

adiposity signals and pathways. Food intake homeostasis is a complicated system governed by numerous hormones, and the precise mechanism by which insulin and leptin influence satiety signal sensitivity need to be investigated further, the regulation of satiety signal sensitivity is a potential target for improving obesity clinically. This paper only discusses some important satiety and adiposity signal, but not include some novel studied signals such as GLP-2 and adiponectin. However, the future clinical treatment of obesity should also be focused on dietary control (mild case) and bariatric surgery (severe case), because of the complexity of human metabolic pathways and the side effects (resistance) caused by exogenous hormones injection.

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