Journal of Animal Science and Veterinary Medicine
Volume 10(6), pages 522-527, December 2025
Article Number: C5A98C3A8
ISSN: 2536-7099
https://doi.org/10.31248/JASVM2025.621
https://integrityresjournals.org/journal/JASVM
Review Article

Leptin: The key lean peptide – A review

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Received 29th October 2025; Accepted 19th December 2025

ABSTRACT: Feeding ensures the provision of substrates for energy metabolism, a vital process for the survival of every living organism and therefore is subject to intense regulation by brain homeostatic and hedonic systems. At present, our understanding of the circuits and molecules regulating the process has tremendously increased in large part due to the availability of animal models with genetic lesions, involving 'satiety and appetite centres'. To this point, in this review, roles played in homeostatic modulation of feeding by systemic mediators, involving anorexigenic peptides led by leptin and its major cohorts, such as insulin, alpha-melanocyte-stimulating hormone (α-MSH), cocaine and amphetamine-regulated transcript (CART)and bombesin which act on brain systems utilizing orexigenic peptides led by neuropeptide Y (NPY), agouti-related peptide (AgRP)and their cohorts, such as galanin (GAL), melanin-concentrating hormone (MCH) and orexins (OXs) amongst other mediatorsbased on the dual-control theory of feeding were highlighted and discussed. Furthermore, we examined the mechanisms for taste and nutrient preferences and reward systems that provide food with its intrinsically reinforcing properties and explored the links between the homeostatic and hedonic systems that ensure intake of adequate nutrition. Therefore, the understanding of these molecular networks regulating feed intake could, in the future, lead to designing better therapeutic targets for animal set-point weights and weight loss in obesity.

Keywords: Appetite, dual theory, peptides, satiety, weight.

INTRODUCTION

When animals eat, a number of interrelated signals are generated that provide the central nervous system with information about the nutritional state of the animal. The cascade of sequential signals so produced influences changes in the levels of several peptides involved with animal feeding behaviour within specific regions of the brain, leading ultimately to increasing or decreasing appetite (Zhang *et al.,* 1994). The intricate interplay of activities of the peptides is significantly involved in eliciting various nutritional activities, resulting in the set-point concept for better value capture on the part of the animal farmer.

Here, it should be noted that feeding provides substrate for energy metabolism that is vital to the survival of every living animal and, therefore, is subjected to intensive regulation by the brain's homeostatic and hedonic systems. Homeostatic mechanisms for regulating feeding to ensure adequate nutrition, it is important for the brain to have intrinsic circuitry that regulates the levels of various nutrients in the blood and in the stores (Johansen *et al*., 2025). It is possible to argue that the homeostatic drive for feeding is not intrinsically related to the rewarding aspects of the behaviour. However, avoiding or terminating the discomfort associated with hunger provides a strong drive for feeding.

Additionally, the feeling of contentment that accompanies a full stomach may itself be rewarding, and in the absence of a homeostatic drive to eat, food consumption loses much of its allure (loss of appetite). Therefore, to understand the rewarding nature of food, it is necessary first to understand the brain mechanisms that support homeostatic drive for feeding to maintain the set-point. The brain mechanisms for regulating homeostatic drive to eat are based on a model of two-opposing cell

groups. The lateral hypothalamus (LH) drives feeding, and the ventromedial hypothalamus (VMH) inhibits it to cause satiety to stop eating. The peptides that populate the LH that instigate feeding are known as orexigenic peptides; whereas peptides that populate the VMH that inhibit feeding are known as anorexigenic peptides (Fu, 2025). These concepts were better understood by advances in the mid-1990s that were based upon the discovery that a systemic peptide, leptin, produced in the adipose tissue during periods of plenty, is a necessary stimulus for satiety (Zhang *et al.,* 1994).

Here, we outline the circuitry of recent developments that have clarified and thus enhanced our present understanding of the dual-theory mechanisms of feeding to achieve the set-point goal in animal production. The leading orexigenic peptides are neuropeptide Y (NPY) and its cohorts. On the other hand, the leading anorexigenic or satiety peptide is leptin and its cohorts. Thus, the mechanisms, including their cohorts on how they are involved in the regulation of energy intake and expenditure (energy homeostasis) based on the dual theory, will be briefly elucidated. For NPY, its cohorts to be covered in this review are: Agouti-related peptide (AgRP), galanin (GAL), melanin-concentrating hormone (MCH) and orexins. The anorexigenic peptides to be covered in this review are: leptin, insulin, alpha-melanocyte-stimulating hormone (α-MSH), cocaine and amphetamine-regulated transcript (CART) and bombesin. However, before detailing the interplay between orexigenic and anorexigenic peptides in the regulation of feeding, the dual control theory of feeding will briefly be revisited.

The dual-control theory of feeding

The dual-control theory is based on a homeostatic understanding of hunger and satiety based on the hypothalamus. Two distinct sections of the hypothalamus are principal modulators in the dual control concept of feeding (Cheon *et al.,*2025). In brief, a decline in glucose activates the LH and activity within the LH gives rise to hunger. In turn, hunger motivates the search for and consumption of food. Eventually, the food consumed is broken down to release glucose. Glucose motivates the VMH. Activation of the VMH causes or triggers the feeling of satiety in the animal, resulting in the inhibition of further eating. The schematic of these is shown in Figure 1. From Figure 1, lesions in the VMH or LH significantly affect the eating behaviour of the animal, as demonstrated in Table 1.

Animals with lesions to their lateral hypothalamus (LH) would exhibit severe loss of body weight as a result of their refusal to eat (aphagia) and drink (adipsia). To these points, therefore, LH lesions will reduce the set-point for the body weight of the animal; nevertheless, at a new lower level. Conversely, lesions to the ventromedial hypothalamus would increase the set-point for the body weight of the animal, with higher fat body content due to the inactivation of the VMH (Yeung and Tadi, 2023). From the fore-stated therefore, it is the balance of activities between the LH and the VMH that gives rise to the desired set-point of body weight of the animal for better value capture. The cascades are modulated by NPY and its cohorts, as well as leptin and its cohorts. NPY and leptin are the major modulators of LH and VMH activities, respectively. These will be covered in this review.

OREXIGENIC PEPTIDES AND MODES OF ACTION IN STIMULATING FEED INTAKE

Neuropeptide Y (NPY)

NPY is a 36-amino acid peptide. The arcuate nucleus (ARC) in the LH is the major site of its expression. The most potent function of NPY is stimulation of food intake. Administration of NPY induces striking hyperphagia and obesity. For instance, central administration of NPY reduces brown fat thermogenesis, suppresses sympathetic nerve activity and inhibits the thyroid axisin order to reduce energy expenditure. Additionally, NPY induces hyperinsulinaemia, hypercortico-steronaemia and reduced plasma testosterone levels (Engström Ruud *et al.,*2020). NPY mRNA levels and NPY release in the ARC respond to changes in energy status, being increased after fasting and food restriction and decreased after refeeding (Sun *et al.,* 2025). Due to the high potency of NPY on food intake, the NPY neurons are potential hypothalamic targets for leptin and inhibition of the synthesis and release of NPY seems to explain at least in part the ability of leptin to induce hypophagia and weight loss. Five NPY receptors have been identified, namely: Y_1, Y_2, Y_3, Y_4 and Y_5. Y_5 receptors have been implicated as the most potent receptors that mediate the feeding effects of NPY (Marsh *et al.,* 1998). The Y_5 receptor is thus expressed at relatively high levels in the LH close to the site where NPY acts most potently to stimulate feeding (Huang *et al.,* 2021).

Agouti-gene Related Peptide (AgRP)

AgRP is a 132-amino acid peptide. Within the central nervous system, AgRP is also exclusively expressed in the ARC and AgRP mRNA co-localises with NPY in 95% of NPY-positive cells in the nucleus (Faour *et al.,*2025). It has been demonstrated that NPY and AgRP are the most potent orexigenic peptides as they are co-produced. As a potent orexigenic peptide, AgRP uniquely acts as an endogenous antagonist of the melacortin-3receptor (MC3R) and melanocortin-4 receptor (MC4R) that are the key receptors of the melanocortin systems in inducing a reduction in food intake (Deem *et al.* 2021). Details of this will be given under the melanocortin mode of action as an anorexigenic peptide. However, it is likely that AgPRplays

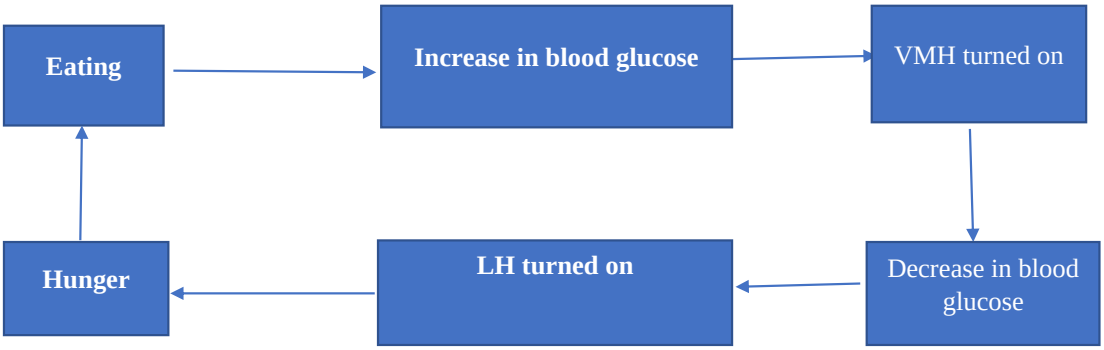

Figure 1. Evidence of the dual circuit control centres of feeding.

Table 1. Lesions on the VMH orLHand its effect on feeding behaviour.

Area of hypothalamus	Effect of lesioning	Effect of stimulating
VMH	Increases feed intake	Deceases feed intake
LH	Decreases feed intake	Increases feed intake

more modulatory role in feeding during conditions of high energy needs, such as during pregnancy and lactation, during which it has been shown to also be more expressed (Catalbas *et al.,* 2024).

Galanin (GAL)

GAL is a 29-amino acid peptide. GAL is found in the brain and in the gut. GAL coexists with NPY in several regions of the brain. GAL is an orexigenic peptide that demonstrates a preference for fat intake (Barson *et al.,* 2010). GAL is also involved in modulating learning, memory, feeding, inflammation, pain threshold control, sexual behaviour, insulin and pituitary hormone release (Lang and Kofler, 2011). As earlier alluded to, acute central administration of galanin has been reported to increase fat consumption (Barson *et al.,* 2010).

Melanin-concentrating hormone (MCH)

MCH is a 19-amino acid peptide and is recognised as an orexigenic neuropeptide. As an orexigenic peptide, it is highly expressed in the LH and has demonstrated orexigenic effects after ICV infusion (Li *et al.,* 2025). Interest regarding the effector mechanisms by which MCH exerts its orexigenic influence largely focuses on the MCHR1 receptors in the hypothalamus (Sears *et al.,* 2010). MCH is also thought to be involved in motivational aspects of eating.

Orexins

The orexins are 28-amino acid peptides and are also known as the hypocretins (1 and 2), equivalents of orexins (A and B). The orexins, being orexigenic peptides, are produced in the LH area, though they have extensive projections to many regions. The orexins bind to orexin receptor 1 (OXR1) and 2 (OXR2), arising from two separate genes. The distribution of the two receptors is different. Within the hypothalamus, OX1R is the most highly expressed in the hypothalamus (Vraka *et al.,* 2023). Orexin-containing neurons project to the NPY-containing neurons in the central nervous system (CNS), and NPY neurons express the OX1R (Guo *et al.,* 2018), indicating that NPY also receive neurons' excitatory signals from orexin-containing neurons in the LH in its mode of action in stimulating feed intake.

ANOREXIGENIC PEPTIDES AND MODES OF ACTION IN INHIBITING FEED INTAKE

Leptin

Leptin is a 167-amino acid peptide and has been identified as the most potent anorexigenic peptide (Zhang *et al.,* 1994). Leptin acts in concert with its cohorts suppress appetite and regulate energy expenditure. Leptin is mainly secreted by the adipocytes (Sabaratnam, 2025). However, it has been found in the stomach and pituitary gland. Nevertheless, the adipose tissue (AT) remains its main source, accounting for 95% of leptin production (Rolls, 2011). Circulating leptin levels are usually positively correlated with body mass index (BMI) and AT mass. Adipocytes are known to possess large numbers of growth hormone (GH) receptors (GHR), and it is a known fact that GH directly regulates leptin expression (Lissett *et al.,* 2001).

Again, the production of leptin is hugely influenced by many regulators, mostly stimulated by insulin and blood glucose but inhibited by sympathetic activity, lipolytic catecholamines and free fatty acids (FFA). As previously alluded to, leptin production positively correlates with AT mass and is independent of adiposity. For these reasons, leptin levels are higher in women than in men (Cheng *et al.* 2022). In humans, there is a highly organised pattern of leptin secretion over a 24-h period. In general, the circadian pattern is characterised by basal levels between 08:00 and 12:00 hours, and rising progressively to peak between 24:00 and 04:00 hours, and receding steadily to a nadir by 12:00 hours (Sinha *et al.,* 1996). The nocturnal rise in leptin secretion is entrained to mealtime, probably due to cumulative hyperinsulinemia of the entire day (Reytor-González *et al*. 2025). Here, it is also imperative to state that leptin is secreted in a regular pulsatile fashion with an inter-peak interval of about 44-minutes, and the circadian rhythm is attributable solely to increased pulse height (Shi *et al.,* 2022). Starvation reduces transport, whereas re-feeding increases the transport of leptin across the BBB (Reytor-Gonzalez *et al.,* 2025).

Leptin is transported across the BBB by a saturable transport system (Shi *et al.,* 2022) and exerts its anorectic effect in the hypothalamus, where NPY/AgRP and CART neurons express leptin receptors (Nakagawa and Hosoi, 2023). Leptin inhibits NPY/AgRP neurons and activates CART neurons (Sabaratnam, 2025), suggesting that CART is one of the major anorexigenic peptides leptin uses in modulating feed intake and set-point weight.

Insulin

Insulin is a 51-amino acid peptide. Insulin is an adiposity signal. Plasma insulin concentrations correlate with peripheral insulin sensitivity, which in turn is linked to total body fat depots and fat distribution, visceral fat being a key determinant (Schwartz *et al.,* 2000). Insulin secretion by the pancreas increases rapidly after a meal, exerting an anorectic effect via the CNS (Antasouras *et al.,* 2024). It enters the CNS via saturable receptor-mediated transport across the BBB. Central administration of insulin reduces feeding and body weight in rodents and primates (Vasselli *et al.,* 2017). In the hypothalamus, the actions of insulin on food intake and body weight are mediated by NPY and the melanocortin system (Dodd *et al.,* 2021). To these points, therefore, reduced expression or deletion of insulin receptors in the brain leads to hyperphagia and obesity.

Alpha-melanocyte-stimulating hormone (α-MSH)

The α-MSH is a 13-amino acid peptide. α-MSH plays a prominent role in regulating feeding (Kalra *et al.,* 1999). The central melanocortin system modulates energy homeostasis via its antagonist influence on the orexigenic activities of AgRP (Morano *et al*., 2022), indicating that the effector mode of action of α-MSHis to suppress the orexigenic action of AgRP on food intake.

Cocaine-and amphetamine-regulated transcript (CART)

CART is a 116-amino acid peptide. CART is the third-most-abundant transcript in the hypothalamus (Lau and Herzog, 2014). Food deprivation decreases CART expression, while peripheral leptin treatment in *ob/ob* mice increases CART expression, suggesting that CART at least in part exhibits its anorectic effect via leptin influence (Hill, 2010). Central administration of CART inhibits feeding (Kristensen *et al.,* 1998) and CART-knock-out mice display a predisposition to become obese on a high-fat diet (Asnicar *et al.,* 2001), an age-related increase in body weight and impaired glucose metabolism (Wierup *et al.,* 2005), supporting the role of CART in the hypothalamic mechanism regulating food intake.

Bombesin

Bombesin is a 14-amino acid peptide and is widely distributed in the mammalian gut. Plasma levels of bombesin markedly increased after food intake (Wynne *et al.,* 2005). Peripheral or central injection of bombesin reduces food intake. It also activates the sympathetic nervous system. In animals that have been starved or have ventromedial hypothalamic lesions, bombesin produces a profound drop in temperature because the sympathetic nervous system cannot be activated (Bray, 2000).

CONCLUSIONS

The modulation of energy balance around the desired set-point of the animal is critically based on the dual theory of feeding and is mediated by two distinct sets of peptides, namely: the orexigenic and anorexigenic peptides. The peptides' activities are controlled by various regions of the CNS. The CNS regions that control energy homeostasis is accessible to circulating peptides, as discussed above. Within the CNS are specific neuronal populations that recognise peptide signals and act in the network to integrate the multiple inputs regulating appetite or feed intake. Specifically, the hypothalamus is a centre of integration of various nutrient signals. It can also sense and integrate variations in adiposity and gastric peptides, as well as nutrients. It integrates these signals to coordinate behavioural and metabolic effectors of energy homeostasis.

Also, as discussed earlier, it is quite evident that the efficacy of drugs acting on a single molecular target may be limited by compensatory feedback mechanisms.

However, with our current understanding of underlying energy balance, it is highly plausible that, in the near future, combined therapies that act on both peripheral and central targets can be sought. Therefore, understanding these molecular networks modulating feed intake could result in designing better therapeutic targets for animal set-point weights or weight loss in obesity.

CONFLICT OF INTEREST

The authors declare no competing interests.

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