Neuropeptide Y and peptide YY: important regulators of energy metabolism

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Purpose of review

An overview of recent developments documenting the neuropeptide Y (NPY) family's role in energy metabolism. Specifically focusing on site-specific functions of NPY and increasing evidence of peptide YY (PYY) as a weight loss therapeutic.

Recent findings

Studying the NPY family in hypothalamic nuclei, other than the arcuate and paraventricular nuclei, is a recent shift in metabolic research. NPY overexpression in the dorsomedial hypothalamus increases food intake whereas its ablation in this area reduces hyperphagia and obesity. Similarly, NPY exerts orexigenic effects in the ventromedial nucleus. However, specific arcuate Y2 receptor ablation leads to positive energy balance, suggesting the NPY family demonstrates location-specific functions. Peripherally, dual blockade of cannabinoid and NPY pathways has synergistic effects on weight loss, as does combined administration of PYY3–36 and oxyntomodulin in reducing food intake, perhaps due to the recently discovered role of PYY in mediating intestinal Gpr119 activity and controlling glucose tolerance.

Summary

Conditional Y receptor knockout models have provided deeper insights on NPY's functions according to location. Further study of PYY appears vital, due to recent evidence of its role in intestinal motility, with exercise positively influencing PYY levels.

Keywords

gut, hypothalamus, neuropeptide Y, obesity, peptide YY

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Introduction

The prevalence of obesity in modern society is increasing at an alarming rate, making it vital for deep understanding of obesity pathology. The neuropeptide Y (NPY) family of peptides and their Y receptors have been strongly implicated in the regulation of energy homeostasis. The NPY family consists of three 36-amino acid peptides: NPY, peptide YY (PYY) and pancreatic polypeptide, all of which influence energy balance via their unique interactions with G-protein-coupled Y receptors (Y1, Y2, Y4, Y5 and in mouse y6). NPY is widely expressed in the central and peripheral nervous systems, regulating feeding behaviour, body composition and energy homeostasis [1,2], inducing hyperphagia, as well as hormonal and metabolic changes that increase food efficiency and favour fat accretion [3,4]. PYY is released mainly from enterochromaffin (L) cells of the pancreas, small intestine and colon. There are two endogenous forms: the full length PYY1–36 and the truncated form PYY3–36, with both suppressing appetite and food intake [5,6], as well as delaying gastric emptying [7,8]. PYY has only recently been discovered in the hypothalamus of the human brain [9] and its function in the central nervous system (CNS) has not yet been elucidated. However, its location suggests a role in central regulation of energy metabolism. Similar to PYY, pancreatic polypeptide is also derived from the gut. Administration of pancreatic polypeptide reduces appetite and food intake [10]. Recently, it has been discovered that the mechanism by which pancreatic polypeptide reduces food intake is predominantly via stimulation of the anorexigenic α-melanocyte stimulating hormone signalling pathway, with direct actions on Y4 receptors in the arcuate nucleus (Arc) [11•].

This review will specifically discuss recent research on NPY and PYY interactions in the brain and with other regulators of energy balance.

Neuropeptide Y interactions within the brain

In the CNS, NPY is most highly expressed in the hypothalamic arcuate nucleus (Arc) [12]. Within the Arc, two neuronal populations with opposing effects on food intake exist: neurons co-expressing NPY and agouti-related peptide (AgRP), which stimulate food intake [13], and those co-expressing pro-opiomelanocortin

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(POMC) and cocaine and amphetamine-regulated transcript (CART), which suppress food intake [14].

Many people who lose excess weight are unable to keep the weight off, presumably in part due to activation of central signals, such as those of NPY, to stimulate appetite [15,16]. A recent study by Yu *et al.* [17••] may provide an explanation for this occurrence. In this study, animals were placed on a high-fat diet (HFD), leading to diet-induced obesity with increased body weight, fat mass and leptin. These animals were then placed on an energy-restricted diet, which successfully reversed the effects of the HFD on body weight and fat mass. However, in these animals, the expression of mRNA for the orexigenic *NPY* and *AgRP* was significantly increased in the Arc, whilst that of the anorexigenic *POMC* and *CART* was unchanged. This demonstrates that elevated hypothalamic expression of orexigenic peptides may contribute to the subsequent body weight regain often seen after periods of weight loss, by promoting food intake without a corresponding increase in the anorexigenic peptides.

Classically, the effects of the NPY system and its Y receptors on energy homeostasis have been studied in the Arc and the paraventricular nucleus (PVN). In recent studies, however, the emphasis has been shifted towards other nuclei of the hypothalamus. Yang *et al.* [18••] showed that overexpression of NPY in the dorsomedial hypothalamus (DMH) of lean animals via bilateral adeno-associated virus (AAV) injection caused an increase in food intake and body weight and exacerbated HFD induced obesity. The ablation of NPY in the same area, using bilateral injection of AAV-mediated RNA interference vectors, reduced the hyperphagia, obesity and glucose intolerance in obese mice. It also caused reductions in NPY content of the nucleus of the solitary tract and dorsal motor nucleus of the vagus, decreased meal size and increased inhibitory feeding responses. These results indicate that NPY in the DMH plays an important physiological role in modulating food intake, by decreasing meal size with modulation of within-meal satiation and energy balance. Additionally, this study successfully showed the potential of AAV-mediated gene modulation to produce long-lasting effects on energy balance. This experimental technique is becoming increasingly prevalent as the importance of elucidating site-specific Y receptor functions in the hypothalamus and periphery grows, demonstrating a directional change in the study of the NPY family and its receptors in energy metabolism.

In addition to the DMH, another area of the hypothalamus, the ventromedial nucleus (VMN), plays a crucial role in NPY-mediated regulation of energy balance, with its anorexigenic output suppressing feeding behaviours with the facilitation of leptin [19]. The VMN appears to signal satiety, with lesions in this area resulting in hyperphagic behaviour [20,21]. The VMN also has receptors for orexigenic peptides, in particular NPY [22]. It has been shown that NPY can directly inhibit neurons of the VMN via hyperpolarisation through activation of post-synaptic Y1 receptors [23••]. This was shown through the acquisition of whole-cell recordings of VMN neurons with NPY applied, resulting in a suppression of action potential firing. It was discovered that this occurred postsynaptically as pretreatment with tetrodotoxin, a blocker of activity-dependent synaptic transmission, did not alter NPY-mediated hyperpolarisation. Involvement of Y1 receptors was shown through a Y1 receptor agonist eliciting a similar response to that seen in the application of NPY, and a Y1 receptor antagonist completely blocking NPY-mediated hyperpolarisation. These results were not seen using antagonists for Y2 and Y5, the two other major Y receptors found in the VMN, showing the response is selective for Y1 receptors. This NPY suppression of VMN's anorexigenic output would likely promote an orexigenic effect and demonstrates interplay between anorexigenic and orexigenic neuropeptides in the hypothalamic control of energy balance.

Recent research is aimed at identifying not only sites of NPY family actions in energy balance regulation, but also the specific Y receptors involved. Specific ablation of Y2 receptors in the hypothalamus was found to lead to positive energy balance seen in increased food intake and body weight with consequent adiposity increases [24•]. Because the majority of hypothalamic Y2 receptors are expressed on NPY-containing neurons [25], ablation of only those Y2 receptors present in hypothalamic neurons expressing NPY was induced via a conditional knockout approach using doxycycline injection targeted to the Arc [24•]. This leads to a significant increase in *NPY* mRNA expression and a downregulation of *POMC* mRNA expression. This study provides evidence that Y2 receptors on NPY neurons are involved in regulating NPY and *POMC* mRNA levels in the Arc. Importantly, these results suggest a catabolic role for Y2 receptors on NPY-ergic neurons, in which their loss releases inhibition on NPY activity leading to anabolic effects. Additionally, the location-specific functions of NPY were again shown, making it clear that studying of site-specific NPY family peptides and its Y receptors via methods of selectively inducible receptor deletion is becoming increasingly vital.

Neuropeptide Y interactions with other regulators of energy balance

NPY pathways are connected to other pathways involved in energy metabolism control. Understanding of these interactions could lead to better treatments for obesity,

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given the amount of redundancy that exists in hypothalamic pathways that protect against negative energy balance. One such pathway that NPY interacts with in the regulation of energy balance is that of the cannabinoid system. Cannabinoids act via activation of cannabinoid receptors such as the cannabinoid-1 (CB1) receptor and are involved in the promotion of positive energy balance. CB1 antagonism alone can cause reductions in appetite [26], increased energy expenditure [27,28] and increased lipid metabolism in adipose tissue [26,29–31]. However, CB1 deletion has negative effects on bone mass, as demonstrated in CB1-deficient mice having a low bone mass phenotype. NPY also regulates bone mass, with global NPY knockout mice and specifically, mice lacking Y1 and Y2 receptors, showing increased bone mass due to increased bone formation [32–35]. The blocking of NPY-ergic pathways seems logical in discovering novel obesity therapies. It was shown that the antagonism of CB1 receptors via the drug Rimonabant, along with the global deletion of NPY signalling using $NPY^{-/-}$ mice has synergistic effects to reduce body weight and fat mass, without negative effects on bone [36•]. This was accompanied by a decrease in respiratory exchange ratio, suggesting the promotion of lipid oxidation. These results show the potential for pharmacological obesity treatments by the employment of dual CB1 and NPY antagonism.

Peptide YY in the regulation of energy metabolism

In contrast to NPY, which is obesogenic, PYY exerts anorexigenic effects. This is thought to occur via satiety signalling actions in the brain. However, PYY also has important effects in the periphery. It is known that PYY regulates intestinal motility [7,8]. The acylethanolamine receptor, Gpr119, has a similar expression pattern to PYY [37] and is also expressed by the L cells. A recent study by Cox *et al.* [38•] demonstrated that PYY has a critical role in mediating intestinal Gpr119 activity, through Y1 receptor mediation, hence affecting the speed at which food is digested. Selective Y receptor antagonists and specific transgenic mouse models and human colon mucosa were used in this study. It was demonstrated that oral Gpr119 agonism significantly reduced glycaemic excursions with significantly greater plasma insulin levels after glucose ingestion, in wild-type and $NPY^{-/-}$ mice but not in mice that lack PYY. These responses are stronger under conditions of high glucose concentrations, and showed that it is PYY that is required for the mediation of responses involving antihyperglycaemic effects of Gpr119. This confirms an important role of PYY in the metabolising of dietary glucose upon insulin release.

PYY having a role in the speed at which food is digested may help to explain a recent discovery in that both PYY1–36 and PYY3–36 resulted in prolonged gastric emptying of a solid meal in humans [39••], which had previously only been reported in animal studies [40,41]. However, the two forms of PYY have differing effects on gastric emptying and short-term metabolic control, with PYY3–36 having a stronger effect [39••]. These discoveries show that PYY treatment could be effective in weight loss therapies, by slowing gastric emptying and therefore prolonging satiety in humans. However, PYY3–36 is known to cause nausea in some individuals [42] and this side-effect needs to be addressed before treatments based on mimicking the action of PYY can be used.

A way of reducing the likelihood of nausea has been hypothesised, whereby PYY3–36 is used at lower concentrations in conjunction with other satiety-inducing hormones. This approach is also effective in decreasing appetite [43,44]. Elevated PYY3–36 levels and repeated oxyntomodulin administration can decrease food intake in both lean and obese subjects [5,45–47]. Oxyntomodulin is a glucagon-like peptide 1 (GLP-1) receptor agonist that is co-secreted postprandially with PYY3–36, and similar to PYY3–36, is elevated after bariatric surgery [48]. The therapeutic potential of the combination of lower doses of PYY3–36 and oxyntomodulin was recently studied [49••] to test whether a synergistic effect in reduction of food intake of obese humans would occur. This would eliminate the need for high individual hormone concentrations associated with adverse side-effects. It was found that the combined hormone treatment reduced energy intake by 42.7% compared to saline control and this value was significantly greater than the use of either hormone alone and did not induce any increases in nausea incidence. Therefore, treatments utilising PYY3–36 together with other satiety hormones seem key in weight loss and maintenance.

Aerobic exercise is known to enhance glucose uptake and reduce the risk or prevalence of metabolic disorders such as cardiovascular diseases and obesity [50]. Exercise is therefore adopted as a therapeutic for obesity, aiming at increasing energy output, with long-term exercise shown to increase plasma PYY levels [51]. A recent study by Ueda *et al.* [52••] found that a single 30-min session of high intensity exercise in lean participants, increased and specifically maintained PYY3–36 levels more effectively than in moderate exercise, with subsequent reduction in energy intake in both levels of exercise. This shows that exercise can function as a physiological regulator of hormone release in appetite control and that levels of PYY3–36 are positively correlated with exercise intensity. These data indicate that exercise programs, when used in conjunction with other therapeutics, are vital in the maintenance of a healthy weight. However, PYY3–36 is co-secreted with GLP-1 and a recent study by Ueda

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et al. [52••] showed that increases in GLP-1 levels are inversely correlated to energy intake. Therefore, the role of PYY3–36 in the reduction of energy intake in this instance requires further elucidation. A parallel study in obese participants would also be insightful, as we know the effects of PYY3–36 are preserved in obesity.

Conclusion

It has become clear that the NPY family and its Y receptors have varying functions according to their location in the CNS. Current technologies in conditional Y receptor knockout and site-specific transgenic models are being used to elucidate these functions, allowing identification of specific sites of action and functions of NPY and individual Y receptors. This was shown in the studies involving ablation and overexpression of NPY and Y2 receptors in areas of the hypothalamus, such as the DMN, VMH and Arc, demonstrating the broad spectrum of NPY family function and thus the importance of employing these specific technologies. Synergistic weight loss from combined NPY and endocannabinoid system disruptions, as well as PYY with satiety hormones, such as oxyntomodulin, have provided potential areas of future focus. It has been evidenced that successful weight loss therapeutics should also employ an exercise component. This may be partly due to observations that exercise has been shown to increase the levels of PYY and notably PYY3–36, an important promoter of satiety. Finally, the recent discovery of PYY in the hypothalamus of the human brain provides a promising avenue of research, as it implicates a role of PYY as a neurotransmitter in energy metabolism.

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- • of special interest
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