PYY (Peptide YY)

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1. Core Definition

PYY, or **Peptide YY**, also known as **peptide tyrosine tyrosine**, is a crucial short peptide hormone primarily involved in the regulation of appetite and satiety. This endogenous signaling molecule is released postprandially, meaning after a meal, from specialized enteroendocrine L-cells located predominantly in the distal small intestine (ileum) and the colon. Its principal physiological role is to signal fullness to the brain, thereby contributing to the cessation of food intake and the maintenance of energy homeostasis.

Composed of 36 amino acids, PYY belongs to the larger neuropeptide Y (NPY) family of peptides, which includes NPY itself and pancreatic polypeptide (PP). While the full-length PYY(1-36) is initially released, it is rapidly cleaved in the circulation by the enzyme dipeptidyl peptidase-4 (DPP-4) to form **PYY(3-36)**. This truncated form is considered the main biologically active form of PYY, responsible for mediating most of its anorexigenic effects.

The release of PYY is a direct response to the presence of nutrients in the gastrointestinal tract, acting as a direct feedback mechanism from the gut to the central nervous system. By communicating satiety, PYY plays a fundamental role in coordinating digestive processes, optimizing nutrient absorption, and preventing overconsumption, thereby acting as a powerful anorexigenic (appetite-suppressing) signal within the complex gut-brain axis.

2. Etymology and Historical Development

The name **Peptide YY** is derived from its chemical structure, specifically the presence of tyrosine residues (represented by the letter 'Y' in the one-letter amino acid code) at both its N-terminal and C-terminal ends. This distinctive structural feature is shared with other members of the NPY family, highlighting a common evolutionary origin and functional relatedness among these important signaling molecules. The nomenclature reflects an early understanding of its composition as researchers began to characterize the myriad peptides involved in physiological regulation.

The discovery and initial characterization of PYY emerged during an era of intensified research into gut hormones and their roles in regulating physiological processes beyond mere digestion. As scientific understanding of the intricate communication between the gastrointestinal tract and the brain expanded, PYY was identified as a significant player in this complex network. Early studies focused on isolating and identifying various peptides found within the gut lumen and intestinal tissues, gradually revealing their diverse functions.

Over time, PYY's critical role as a satiety hormone became increasingly clear. Its identification and functional elucidation were pivotal in advancing the understanding of metabolic regulation, obesity, and diabetes. This progress facilitated a paradigm shift, recognizing the gut as a major endocrine organ capable of influencing systemic energy balance and appetite control, paving the way for further research into therapeutic interventions targeting these pathways.

3. Key Characteristics and Mechanisms

Structure and Synthesis

PYY is synthesized as a prepropeptide, which undergoes proteolytic processing to yield the mature 36-amino acid peptide. As noted, the primary circulating form is PYY(3-36), generated by the action of dipeptidyl peptidase-4 (DPP-4) on the full-length PYY(1-36). This enzymatic cleavage is crucial for its biological activity, as PYY(3-36) exhibits a significantly higher affinity for specific receptors than its full-length counterpart, underscoring the importance of precise post-translational modification in hormone function.

The peptide is predominantly produced and released by **enteroendocrine L-cells**, which are scattered throughout the gastrointestinal mucosa, with the highest concentration found in the ileum and colon. These specialized cells act as nutrient sensors, responding directly to the presence of macronutrients--fats, proteins, and carbohydrates--in the intestinal lumen. This strategic localization ensures that PYY is released when digested food components reach the distal parts of the gut, providing a signal that reflects the overall nutrient load and caloric content of a meal.

Physiological Release and Regulation

The release of PYY is a tightly regulated process, directly correlating with nutrient ingestion. Following a meal, as digested food components transit through the small intestine and reach the ileum and colon, they stimulate the L-cells to secrete PYY into the bloodstream. The magnitude and duration of PYY secretion are proportional to the caloric content and composition of the meal, with fats and proteins generally eliciting a stronger and more sustained release than carbohydrates.

Significantly, the consumption of **fibers**, such as those found in leafy vegetables, fruits, and whole grains, has been known to increase PYY levels. This effect is thought to be mediated through several mechanisms. Dietary fiber, particularly soluble and fermentable types, can slow gastric emptying and intestinal transit, allowing for prolonged contact of nutrients with L-cells in the distal gut. Furthermore, the fermentation of fiber by colonic bacteria produces short-chain fatty acids (SCFAs), which can directly stimulate PYY release from L-cells, providing a crucial link between gut microbiota, diet, and host appetite regulation.

Mechanism of Action

PYY exerts its anorexigenic effects primarily by binding to and activating **Y receptors**, a subfamily of G-protein coupled receptors. The most critical of these is the Y2 receptor, which is widely expressed in both the peripheral and central nervous systems. Upon release from the gut, PYY circulates in the bloodstream and can cross the blood-brain barrier to act directly on specific brain regions involved in appetite control, or it can signal indirectly via afferent vagal nerve pathways.

In the central nervous system, particularly within the arcuate nucleus of the hypothalamus, PYY(3-36) binds to Y2 receptors on neurons. This binding inhibits the activity of orexigenic (appetite-stimulating) neurons that co-express neuropeptide Y (NPY) and Agouti-related peptide (AgRP). Concurrently, PYY can stimulate the activity of anorexigenic (appetite-suppressing) neurons that produce pro-opiomelanocortin (POMC). This dual action effectively shifts the balance towards reduced food intake and increased satiety, promoting a feeling of fullness after eating.

Beyond its central effects, PYY also has important peripheral actions. It plays a role in regulating gastrointestinal motility and secretion, often slowing gastric emptying and intestinal transit. This delay in food passage contributes to prolonged satiety by extending the time nutrients remain in the gut and allowing for more thorough digestion and absorption. Furthermore, as exemplified by the satiety felt after eating an apple, **PYY can increase water and electrolyte absorption in the colon**. This action contributes to overall fluid and electrolyte balance and may enhance stool consistency, reflecting its broader involvement in maintaining gut health and function.

4. Significance and Impact in Metabolism

PYY's significance in metabolic regulation stems from its pivotal role in the "ileal brake" mechanism. When undigested nutrients, particularly fats, reach the distal small intestine (ileum), PYY and other gut hormones are released. This hormonal signal then travels upstream to slow gastric emptying and intestinal motility, effectively putting a "brake" on the digestive process. This allows for more complete digestion and absorption of nutrients in the proximal small intestine, prevents nutrient overload in the colon, and significantly extends the feeling of satiety, thereby optimizing energy harvest and preventing excessive food intake.

The impact of PYY on metabolic health is profound. Dysregulation of PYY secretion or sensitivity has been implicated in various metabolic disorders. Individuals with obesity, for instance, often exhibit blunted postprandial PYY responses, meaning they release less PYY or are less sensitive to its effects after a meal. This impaired signaling can contribute to a perpetual state of hunger and reduced satiety, fostering overeating and weight gain. Understanding these dysfunctions is critical for developing targeted interventions for obesity and related metabolic syndromes.

Moreover, PYY does not act in isolation but is part of a complex and highly integrated network of

gut hormones, including glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK), and ghrelin. These hormones interact synergistically and antagonistically to finely tune appetite, regulate glucose homeostasis, and control gastrointestinal function. The collective action of these peptides ensures a robust and adaptive system for energy balance, highlighting PYY's indispensable contribution to the overall metabolic landscape.

5. Clinical Relevance and Therapeutic Potential

Given its potent anorexigenic properties, PYY has garnered significant interest as a potential therapeutic target for the management of obesity and related metabolic disorders. Pharmacological strategies aim either to administer exogenous PYY or PYY analogs, or to enhance endogenous PYY secretion. Clinical trials have explored the effects of intravenous or subcutaneous administration of PYY(3-36) in humans, consistently demonstrating a reduction in food intake and body weight, often accompanied by favorable metabolic changes such as improved glucose tolerance.

However, the development of PYY-based therapies faces several challenges. The native peptide has a short half-life due to rapid degradation by circulating enzymes like DPP-4, necessitating frequent injections, which can be inconvenient for patients. Research efforts are therefore focused on designing more stable and longer-acting PYY analogs, or on developing alternative delivery methods, such as oral formulations that protect the peptide from degradation or stimulate its release naturally. Combination therapies, pairing PYY agonists with other anorexigenic agents, are also being explored to achieve more comprehensive and sustained weight loss.

The clinical relevance of PYY extends to understanding the mechanisms behind the success of bariatric surgery, such as Roux-en-Y gastric bypass. Patients undergoing these procedures often experience significant and sustained weight loss, along with remission of type 2 diabetes. A key contributing factor is the dramatic post-operative increase in postprandial PYY secretion, along with other gut hormones like GLP-1. This enhanced hormonal response is believed to contribute substantially to the profound changes in appetite, satiety, and glucose metabolism observed in these patients, offering valuable insights into physiological pathways that can be harnessed for therapeutic benefit.

6. Debates and Criticisms

Despite its promising role, the clinical application and understanding of PYY are not without debates and criticisms. One significant area of discussion concerns the variability in PYY's efficacy and impact across different individuals and studies. Factors such as genetic predispositions, baseline body weight, dietary habits, and the presence of co-morbidities can influence an individual's PYY response, making it challenging to predict universal therapeutic outcomes. This

inherent variability highlights the need for personalized approaches in obesity management.

Another point of contention arises from the complexity of appetite regulation itself. PYY is just one component within a vast and intricate network of hormonal, neuronal, and psychological signals that control hunger and satiety. Critics argue that targeting a single hormone like PYY, while effective in reducing food intake acutely, may not be sufficient for sustained weight loss in complex metabolic disorders like obesity, where compensatory mechanisms or adaptations to prolonged hormonal manipulation can occur, potentially leading to a plateau in treatment effectiveness over time.

Methodological challenges in PYY research also contribute to ongoing debates. These include difficulties in accurately measuring the active forms of PYY in circulation, accounting for circadian rhythms and meal-induced fluctuations, and differentiating between the physiological effects of endogenous PYY and the pharmacological effects of exogenously administered high doses. Furthermore, some studies have shown conflicting results regarding the long-term efficacy or the precise contribution of PYY to overall energy balance, underscoring the need for more rigorous and standardized research designs to fully elucidate its therapeutic potential and limitations.

Further Reading

Peptide YY - Wikipedia
Peptide YY: a review of its physiology and therapeutic potential - NCBI
Peptide YY - ScienceDirect Topics