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Neuropeptide Y Crosstalk: in Health and Disease

Rasha Babiker[1]*, Nada Tawfig[2], Grisilda Vidya Bernhardt[3], Suresh Kumar Srinivasamurthy[4], Pooja Shivappa[3], Abdalla Ahmed Eldaw Elamin[5], B K Manjunatha[3], Walaa Salah Mohammed[6], Tarig H Merghani[1] , Rahman, Muhammed Mustahsen[2] ,Matalka, Ismail I[7] , El-Tanani, Mohamed[8]

[1]Department of Physiology, RAK College of Medical Sciences, RAK Medical & Health Sciences University, Ras Al Khaimah, UAE.

[2]Department of, RAK College of Dental Sciences, RAK Medical & Health Sciences University, Ras Al Khaimah, UAE.

[3]Department of Biochemistry, RAK College of Medical Sciences, RAK Medical & Health Sciences University, Ras Al Khaimah, UAE.

[4]Department of Pharmacology, RAK College of Medical Sciences, RAK Medical & Health Sciences University, Ras Al Khaimah, UAE.

[5]Department of Anatomy, RAK College of Medical Sciences, RAK Medical & Health Sciences University, Ras Al Khaimah, UAE.

[6] Center of translational and medicinal research, RAK Medical & Health Sciences University, Ras Al Khaimah, UAE.

[7]RAK Medical & Health Sciences University, Ras Al Khaimah, United Arab Emirates.Email:

[8]RAK College of Pharmacy, RAK Medical & Health Sciences University, Ras Al Khaimah, United Arab Emirates.

[1]rashababiker@rakmhsu.ac.ae, tarig@rakmhsu.ac.ae, [2]nada.tawfig@rakmhsu.ac.ae, mustahsen@rakmhsu.ac.ae, [3]grisilda@rakmhsu.ac.ae, pooja@rakmhsu.ac.ae, manjunatha@rakmhsu.ac.ae, [4]suresh@rakmhsu.ac.ae, [5]abdalla@rakmhsu.ac.ae, [6]walaa@rakmhsu.ac.ae, [7]president@rakmhsu.ac.ae, [8]eltanani@rakmhsu.ac.ae

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Abstract

Neuropeptide Y (NPY) is a multifunctional peptide that plays a significant role in various physiological processes, including energy balance, appetite regulation, cardiovascular function, immune modulation, and stress response. This manuscript provides an extensive review of NPY's mechanisms of action and its therapeutic potential across multiple biological systems. NPY exerts its effects primarily through five G-protein-coupled receptors: Y1, Y2, Y4, Y5, and Y6, each contributing uniquely to distinct physiological outcomes.

The Y1 receptor is extensively involved in appetite stimulation, vasoconstriction, and anxiety modulation, while the Y2 receptor primarily regulates neurotransmitter release and energy homeostasis. Notably, the Y4 receptor plays a critical role in regulating pancreatic secretions, gut motility, and appetite, making it a potential target for managing metabolic disorders and digestive health. On the other hand, the Y5 receptor is key in stimulating

appetite and increasing energy intake and body weight, highlighting its significance in obesity and weight management therapies.

NPY's cardiovascular effects, such as blood pressure regulation and heart rate modulation, underscore its potential in treating conditions like hypertension and heart failure. Additionally, NPY demonstrates neuroprotective properties by supporting neuronal survival, enhancing synaptic plasticity, and mitigating neuroinflammation, which positions it as a promising candidate for therapeutic strategies in neurodegenerative diseases like Alzheimer's and Parkinson's. Its ability to reduce anxiety and enhance stress resilience further extends its therapeutic potential to mental health disorders.

In the context of periodontal disease, NPY influences inflammatory responses, bone metabolism, and tissue remodeling, underscoring its role in both systemic and localized disease management. This comprehensive review emphasizes the diverse roles of NPY and its receptors, advocating for further research to fully explore their clinical applications and optimize therapeutic strategies for a range of health conditions.

INTRODUCTION

NPY Structure and Physiological Functions

Neuropeptide Y (NPY) is a 36-amino acid peptide synthesized in GABAergic neurons, where it acts as a neurotransmitter[1]. It plays a crucial role in numerous physiological and homeostatic processes within both the central and peripheral nervous systems [1-3]. NPY is synthesized from a 97-amino acid precursor known as pre-pro-NPY, which is processed to its mature form through the catalytic actions of prohormone-converting enzymes and carboxypeptidase-like enzymes. This processing results in the biologically active form, NPY1-36 [4]. The human NPY family also includes peptide YY (PYY) and pancreatic polypeptide (PP), two enteric peptides that share a characteristic hairpin-like structure known as the PP-fold [5]. NPY interacts with multiple receptors, including Y1, Y2, and Y5, each with distinct physiological roles. Y1 receptors are involved in regulating food intake, anxiety, and cardiovascular functions; Y2 receptors modulate neurotransmitter release and energy homeostasis; and Y5 receptors are associated with feeding behavior and body weight regulation [6]. NPY predominantly binds to the Y1 receptor, which is highly expressed in the brain, heart, blood vessels, and adipose tissue, playing a significant role in regulating food intake, anxiety, blood pressure via vasoconstriction, and cardiac function. It also binds to the Y2 receptor, mainly found in the central nervous system, where it inhibits neurotransmitter release, thereby modulating food intake and promoting energy homeostasis. Additionally, NPY interacts with the Y5 receptor, primarily located in brain regions that regulate feeding behavior, stimulating appetite, and contributing to energy intake and body weight regulation. While the Y6 receptor is a non-functional pseudogene in humans, it serves similar roles in feeding and energy regulation in other species [7-9]. [Table 1]. As a neurotransmitter, NPY serves as an important neuromodulator in the brain, influencing various physiological functions such as feeding behavior, energy homeostasis, and circadian rhythms [10,11]. It also plays a role in the modulation of anxiety, depression, and stress. In the cardiovascular system, NPY acts as a significant sympathetic co-transmitter, extensively distributed throughout the central and peripheral nervous systems, where it is involved in multiple physiological processes including vasoconstriction and angiogenesis [12]. Moreover, NPY plays a regulatory role in the respiratory and gastrointestinal systems by modulating smooth muscle tone and inflammation [13]. In the endocrine system, NPY regulates hormone secretion, including insulin and glucagon, and serves as a neuroprotective peptide influencing immune function and inflammation [13]. In addition to its physiological roles, NPY, and its receptors are being explored for their

therapeutic potential in various organ systems and diseases. Further research is needed to optimize the detection and evaluation of NPY, focusing on overcoming challenges related to cost, stability, formulation design, and development [14].

Table 1: summarizes the different types of NPY receptors, their localization, functions, and clinical links

NPY Receptor Type	Localization	Function	Clinical Link	References
Y1R	Neurons in the CNS (especially hypothalamus), vascular smooth muscle cells, adipocytes, immune cells	Regulates blood pressure (vasoconstriction), appetite stimulation, immune response modulation	Hypertension, obesity, anxiety disorders	[1,3,4,17,31]
Y2R	Presynaptic neurons in the CNS (hypothalamus, brainstem), gastrointestinal tract	Inhibits neurotransmitter release, modulates appetite and gastrointestinal motility	Obesity, gastrointestinal disorders	[4,15]
Y4R	Brainstem, gastrointestinal tract, pancreatic cells	Regulates digestive processes and energy homeostasis	Digestive disorders, appetite control	[19,20]
Y5R	Neurons in the hypothalamus	Mediates feeding behavior and appetite regulation	Obesity, eating disorders	[24,38]
Y6R (Pseudogene in Humans)	Non-functional in humans; functional in some other species in brain regions related to feeding and energy regulation	Non-functional in humans; involved in feeding and energy regulation in other species	None in humans; potential roles in metabolic regulation in other species	[6,7]

NPY and Regulation of Appetite and Obesity

The regulation of food intake involves a complex interaction between integrating centers in the brain and peripheral signals from the gastrointestinal tract and adipose tissue. NPY is widely distributed within the central nervous system and plays a crucial role in regulating hunger and energy balance. It stimulates appetite (orexigenic effect) through the activation of various receptors that are essential for compensating energy deficits and maintaining normal body weight [15]. The primary source of NPY release in the brain is the arcuate nucleus of the hypothalamus. Several peripheral signals influence NPY release, thereby communicating the body's

energy status to the brain. NPY levels increase in response to ghrelin, low energy stores, fasting, and exercise, and decrease in response to hormones that induce satiety, such as leptin, insulin, glucagon-like peptide 1 (GLP1), and peptide YY (PYY), which is structurally similar to NPY [16,17]. Experimental studies have shown that stimulation of NPY release from neurons in the solitary tract nucleus enhances hunger, leading to increased food intake and body weight [18].

In addition to directly stimulating appetite centers, NPY indirectly influences hunger by counteracting the appetite-suppressing effects of leptin and insulin [19,20]. NPY also reduces stress and anxiety by antagonizing the effects of stress hormones, such as corticotropin-releasing hormone (CRH) and glucocorticoids, which inhibit appetite [21].

NPY's role in metabolism regulation is closely linked to its effects on appetite and energy stores. Beyond its orexigenic effect, NPY from the arcuate nucleus reduces energy expenditure by inhibiting the release of thyroid hormones and decreasing the activity of certain neurons in the hypothalamus, such as proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) neurons, which are involved in regulating appetite and energy balance through the production of anorexigenic (appetite-suppressing) peptides [22,23]. In the gastrointestinal tract, NPY delays gastric emptying and slows intestinal transit time, which reduces the release of nutrients to the intestinal mucosa and delays the release of satiety signals. Modifying dietary content could potentially be an option for obesity treatment, as it may influence the release of satiety factors [24,25]. Furthermore, NPY enhances the rewarding and pleasurable sensations associated with eating by increasing dopamine release in the limbic system via Y1 receptors [26].

Abnormal NPY levels can contribute to various eating disorders, including obesity. Appetite and obesity are closely related, influenced by genetic abnormalities, psychological factors, hormonal imbalances, diseases, environmental factors, and food availability. Elevated NPY production in the hypothalamus and other brain regions is implicated in the development of obesity by increasing food intake and food-seeking behavior [27]. NPY Y1 and Y2 receptors in adipose tissue stimulate adipocyte proliferation and fat storage, leading to obesity [28]. Additionally, activation of NPY receptors in adipose tissue promotes the recruitment of macrophages, resulting in inflammation and the secretion of pro-inflammatory cytokines, which further drive adipose tissue proliferation and fat deposition [29]. **[Figure1]**

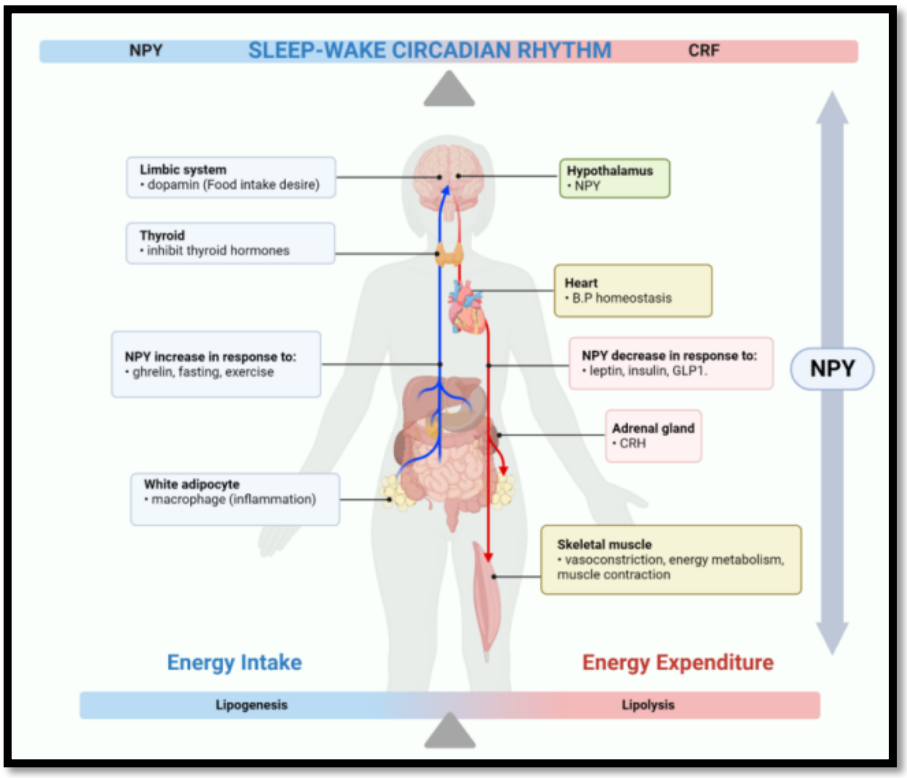

Figure 1: Illustrates the role of NPY and CRF in regulating sleep-wake circadian rhythm and their influence on energy balance. NPY promotes energy intake and lipogenesis by increasing food intake desire through dopamine release in the limbic system and stimulating fat storage in white adipocytes. Conversely, CRF contributes to energy expenditure and lipolysis by regulating heart rate, blood pressure, and metabolism in skeletal muscle and reducing appetite via the hypothalamus. Both NPY and CRF coordinate these processes within the body's circadian rhythm, influencing various physiological responses related to energy homeostasis. Illustration Created with BioRender.com

NPY: Neuropeptide Y, CRF: Corticotropin-Releasing Factor, CRH: Corticotropin-Releasing Hormone, PYY: Peptide YY, GLP-1: Glucagon-Like Peptide-1, B.P: Blood Pressure

OBJECTIVES

NPY Blood Pressure Regulation and cardiovascular system (CVS) diseases

NPY is a vasoactive peptide and a neurotransmitter released by the sympathetic nerve endings in the heart [30]. Recent studies have shown that NPY modulates cardiovascular functions by 1) inducing vasoconstriction, 2) decreasing parasympathetic activity, 3) increasing myocyte calcium loading, and 4) inhibiting cardiovascular sympathetic nervous system activity (SNA) through its action in the dorsomedial hypothalamus and the paraventricular nucleus of the hypothalamus [30, 31]. Due to these modulatory effects, it is not surprising that elevated NPY levels have been linked to conditions such as congestive heart failure and atrial fibrillation [30, 32]. It has been suggested that NPY may contribute to atrial fibrillation by increasing 1) peripheral vascular resistance, 2) cardiac afterload, and 3) myocardial oxygen consumption, which can lead to myocardial ischemia and exacerbate pathological changes in cardiac structures [32]. In the context of atherosclerosis, NPY has been found to contribute to its pathophysiology by affecting energy metabolism, local plaque inflammatory response,

platelet activation and aggregation, as well as emotions related to stress and anxiety [33]. **[Figure 2].** Regarding other cardiovascular diseases such as hypertension, coronary heart disease, pulmonary hypertension, and left ventricular hypertrophy (LVH), NPY is recognized as one of the contributing factors [34, 35]. Interestingly, the effects of NPY on myocardial infarction appear to be paradoxical. Some in vivo studies have demonstrated a curative effect of NPY in acute myocardial infarction, while other studies have shown that NPY is a major contributor to myocardial ischemia and infarction [34, 36]. The mechanisms underlying these contrasting effects are not yet fully understood [36]. Some literature suggests that the disease itself may cause the disruption of NPY levels rather than NPY being the cause of the disease [30]. Regarding NPY receptors, the NPY Y1 receptor primarily mediates the vasoconstrictor effects, inhibits SNA, and induces NPY-associated cardiac hypertrophy [31, 35, 37]. The NPY Y5 receptor, while potentially contributing to vasoconstriction and cardiac hypertrophy, also represents a promising therapeutic target for cardiovascular disease (CVD) by promoting reverse cholesterol transport [35, 38, 39]. On the other hand, activation of the Y2 receptor is linked to angiogenesis, cardiomyocyte differentiation, and endothelial cell proliferation [40]. Since the discovery of NPY in 1982, its extensive role in various physiological and pathological states, including those of the cardiovascular system, has been continuously explored. Recent studies suggest that the boundary between the therapeutic and pathological effects of NPY may be dose-dependent. Therefore, further detailed research and clinical trials are necessary to clarify the precise role and optimal dosage of NPY in all NPY-associated cardiovascular effects [41]

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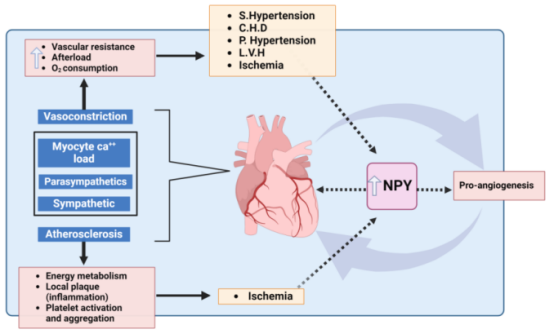

Figure 2: Illustrates the role of NPY in cardiovascular functions and its involvement in promoting pro-angiogenesis. NPY affects several cardiovascular processes, including vasoconstriction, myocyte calcium load, parasympathetic and sympathetic nervous system activities, and atherosclerosis, contributing to conditions such as hypertension, ischemia, and CHF. NPY also influences vascular resistance, arterial function, and oxygen consumption, impacting energy metabolism, local inflammation, and platelet activation, which can lead to ischemia. NPY plays a significant role in cardiovascular health by regulating vascular and myocardial functions and promoting new blood vessel formation. Illustration Created with BioRender.com

S.Hypertension: Systemic Hypertension, C.H.D: Coronary Heart Disease, H.F: Heart Failure
LVH: Left Ventricular Hypertrophy, IHD: Ischemic Heart Disease.

NPY in Stress response and Stress related disorder

Hans Selye originally described stress in the 1930s as the body's response to acute, nonspecific harmful agents [42]. However, modern definitions of stressors focus on their ability to disrupt homeostasis [43]. When homeostasis is disturbed, sensory systems detect the change and transmit this information to the brain, where adaptive systems respond based on the extent of the disturbance and the perception of stress. Neuropeptide Y (NPY) is known to be an endogenous anxiolytic peptide that plays a crucial role in the stress adaptation process, along with other major biological pathways such as the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system [44]. Studies have shown that individuals with higher levels of Y1 and Y5 receptors in the amygdala tend to experience lower levels of anxiety [45]. Furthermore, the Y1 and Y2 receptors have been

associated with anxiolytic effects in the forebrain and pons, respectively [46]. NPY expression in the brain is influenced by stress, and the production and expression of stress-induced NPY depend on the type and duration of the stressor, as well as the brain region involved [47,48]. The involvement of NPY in the brain's stress response and its anxiolytic properties promote resilience and the ability to cope with stress [49,50]. Evidence supports the resilience-promoting properties of NPY; for instance, studies have reported that women who have suffered childhood sexual abuse (CSA) or other traumas have lower plasma levels of NPY compared to women without such experiences. These women are also twice as likely to develop post-traumatic stress disorder (PTSD) as adults compared to men [52]. A double-blind, placebo-controlled trial has demonstrated that a single dose of intranasal NPY can reduce symptoms of Major Depressive Disorder (MDD), with antidepressant effects observed between 5 and 48 hours after administration [53]. In a longitudinal study by Karrlson et al. [54], women with Fibromyalgia Syndrome underwent a cognitive behavior therapy program. The study revealed improvements in pain, depression, and stress markers, along with a decrease in plasma NPY levels. It was concluded that high plasma NPY levels are not the cause of stress responses; rather, the stress level triggers an NPY response, which enhances the ability to manage stress. As stress diminishes, NPY levels decrease. Individuals with an insufficient NPY response to stress often experience maladaptive stress responses, suggesting that NPY may have evolved as a mechanism to aid in coping with stress. A recent review highlighted that NPY, Spexin (SPX), Substance P (SP), and Cholecystokinin (CCK) are effective in managing anxiety and depression. The review emphasized the importance of understanding these pathways, as receptor agonists or antagonists could serve as invaluable tools for treating various disorders, including mental health conditions and other physiological functions influenced by neuropeptides [55].

Neuropeptide and sleep regulation

Neuropeptides are well-documented for their roles in an organism's adaptability to environmental challenges, including sleep [56]. NPY has been shown to modulate sleep patterns in rat models [57,58]. The nocturnal intraperitoneal administration of an NPY Y2 receptor agonist significantly increased non-rapid eye movement (NREM) sleep and suppressed food intake. However, intracerebroventricular and lateral hypothalamic injections of NPY were observed to suppress both NREM and rapid eye movement (REM) sleep in rats during the first hour following administration[58]. The balance between NPY and corticotropin-releasing factor (CRF) is highlighted in an earlier study that evaluated their coadministration [59]. CRF was found to increase sleep latency and reduce the duration of sleep, effects that were reversed by the coadministration of NPY in a rat model [59]. This study underscores the importance of the balance between NPY and CRF in the hypothalamic neuropeptide pathway in the context of depression and anxiety.

Neurons expressing NPY receptors in the mediobasal hypothalamus play a crucial role in regulating the sleep-wake circadian rhythm and eating behaviors [60]. Rats with lesions in these NPY receptor-expressing neurons displayed hyperphagia, obesity, and disrupted sleep-eating circadian rhythms. The diverse roles of NPY receptors are well-documented in the literature. The anxiolytic effects of intracerebroventricular (i.c.v.) administration of NPY are mediated by both Y1 and Y5 receptors, while the sedative actions of NPY are primarily mediated by Y5 receptors [61]. Additionally, i.c.v. administration of NPY was found to potentiate ethanol-induced sedation, and chronic NPY administration prevented ethanol-induced tolerance and reduced withdrawal hyperexcitability [62]. Human studies on NPY administration align with its sedative effects [63,64]. Administration of NPY has been shown to enhance sleep duration and reduce sleep latency while suppressing cortisol levels [63]. However, in aged, depressed patients, NPY reduced sleep latency and REM latency without

decreasing cortisol levels [64]. Nonetheless, increased prolactin levels in both cases and controls suggest potential GABA_A receptor-mimicking and CRF-blocking actions. The neuropeptide orexin has been well-characterized for its involvement in the sleep-wake cycle and feeding behavior in several earlier studies [65-67]. The orexin pathway is effectively utilized in the treatment of insomnia, with three orexin receptor antagonists—suvorexant, lemborexant, and daridorexant—approved for use [68,69]. Notably, orexin A-induced food intake is also partially mediated by the NPY pathway in the arcuate nucleus [66], and the appetite-stimulating effects of NPY are mediated through the orexin pathway [70]. Thus, NPY could be a promising candidate for the treatment of insomnia, with the added benefit of its orexigenic effects.

METHODS

NPY in Epilepsy and Neurodegenerative Diseases:

Neurodegenerative diseases encompass a diverse group of progressive neurological disorders characterized by the selective loss of specific neuronal populations, leading to a gradual decline in cognitive, motor, and behavioral functions. These disorders exhibit a wide range of epidemiological, clinical, neuropathological, and management characteristics[71]. Neurodegenerative disorders affect various age groups, with genetic factors being significant in early-onset cases, while aging is the predominant risk factor for conditions such as Alzheimer's Disease (AD) and Parkinson's Disease (PD) in older adults[72]. Common pathological features of these diseases include protein misfolding, cellular stress, and inflammation, which lead to neuronal damage and the accumulation of abnormal proteins in specific brain regions[73]. NPY plays a crucial role in regulating several functions, including brain activity and stress response[74-76]. Altered levels of NPY have been observed in certain neurodegenerative diseases, suggesting its involvement in immune regulation and central nervous system (CNS) inflammation[77]. High concentrations of NPY, primarily from GABAergic neurons, inhibit excitatory amino acid transmission and are involved in various functions, such as epilepsy, learning, memory, feeding, and endocrine activities [78,79]. The Y1 and Y2 receptors are highly expressed in brain regions important for memory, including the hippocampus, amygdala, thalamus, hypothalamus, and cerebral cortex. In contrast, Y4 receptors are limited to a few areas, while Y5 receptors are present in several limbic regions, including the hippocampus, cingulate cortex, and thalamic and hypothalamic nuclei. Notably, Y6 receptors are found only in certain mammals [80]. AD is marked by a decline in learning and memory, characterized by the accumulation of amyloid plaques, tau tangles, and other protein aggregates, as well as the loss of neurons and synaptic dysfunction [81]. A study comparing the concentrations of NPY-like immunoreactivity (NPYLI) in post-mortem brains of AD patients and healthy controls found that NPYLI is significantly reduced in the cerebral cortex of AD patients [82]. Another study reported decreased NPY mRNA expression in the hippocampus and cortex of a mouse model of AD [83]. NPY may protect neurons from death by reducing calcium influx into presynaptic nerve terminals, which can be harmful due to the formation of calcium-permeable pores caused by amyloid beta (Aβ) peptides. By lowering intracellular calcium levels, NPY inhibits voltage-gated calcium channels and can dynamically regulate adult neurogenesis [84,85]. Given its ability to promote neurogenesis, support nerve growth, reduce excitotoxicity, regulate calcium balance, and suppress neuroinflammation, NPY represents a promising therapeutic target. Conversely, PD is characterized by the loss of dopamine-producing neurons in the substantia nigra and the presence of Lewy bodies, composed primarily of the protein alpha-synuclein, in the remaining neurons[86]. Research has shown a significant increase in NPY in the brains of both animal models and humans with PD, particularly in the striatum, a region crucial for movement control, and other areas associated with dopamine signaling [87]. These findings suggest that NPY could be a potential target for future therapeutic applications.

Huntington's Disease (HD) is an inherited neurodegenerative disorder that specifically damages the cerebral cortex and striatum. It is caused by an abnormal expansion of the polyglutamine chain in the huntingtin protein, resulting from a repetition of the CAG trinucleotide sequence in the IT15 gene [88]. Studies have demonstrated that NPY expression is increased in the basal ganglia, cortex, and subventricular zone of individuals with HD [89]. Beyond its anti-inflammatory effects, NPY also inhibits glutamate release, thereby preventing glutamate excitotoxicity in HD[90].

In epilepsy, seizures are caused by an imbalance between excitation and inhibition in the brain. Excitation is primarily mediated by the neurotransmitter glutamate, while inhibition is mainly mediated by GABA. Neuropeptides expressed by interneurons play crucial roles in how these neurons regulate excitability. A study in rats found that NPY injections prevented picrotoxin-induced epileptic behavior by blocking $GABA_A$ receptors [91]. Further research in mice also showed a reduced susceptibility to seizures due to NPY's potent anti-excitatory and anti-epileptogenic effects[92,93]. Genetic studies have demonstrated that rats engineered to overexpress NPY exhibit protective effects against epileptogenesis [94]. Therefore, increasing the normal expression of NPY results in decreased susceptibility to seizures, suggesting that NPY may have a protective role in epilepsy development.

NPY in Memory and Learning

NPY molecules are high-density peptides crucial for memory and learning. These molecules exhibit gradual and diffuse release patterns and have trophic and neuromodulatory effects [95]. NPY is primarily produced in GABAergic interneurons within the brain and is released following prolonged neuronal activity. Additionally, NPY can diffuse into the brain from the bloodstream across the blood-brain barrier or be located in some projection neurons and astrocytes [96]. In this context, Y4 receptors are predominantly found in the gastrointestinal tract and are scarcely present in the central nervous system, while Y5, Y2, and Y1 receptors are more abundant in the brain [97,98]. The neuroprotective effects of NPY primarily target the Y2 receptor, as these effects are nullified when a selective Y2 receptor antagonist is administered [99]. Neuropeptides function as major neural signaling molecules, modulating synaptic output both directly and indirectly, and serving neuroendocrine roles. These peptides, similar to small neurotransmitters, are vital for several activities, including their evolving connection to memory and learning [100]. The hippocampus has the highest concentration of Y2 receptors, which are crucial for tasks involving object localization, spatial learning, and memory [101]. The neuroprotective effect of NPY on spatial memory, observed in mice treated with amyloid-β 1–40, was eliminated by pretreatment with BIIE0246, a selective Y2 receptor antagonist. This provides initial evidence that these receptors are involved in the protective benefits of NPY in an animal model of Alzheimer's Disease (AD) [102]. Neuropeptides have been identified as regulators of cognitive pathways across different brain regions according to their distribution, and they also participate in circuits associated with depression and anxiety [103]. Research indicates that the effects of the NPYergic system on long- and short-term memory can either enhance or impair cognitive functions, depending on the brain region and dosage involved [104,105]. Studies on NPY receptor expression have shown that repeated blockage of Y2 receptors alters spatial memory tasks [106]. Acute blockage of NPY Y2 receptors significantly improved spatial memory retrieval in rats trained in the Morris water maze, with this improvement linked to changes in metabolic activity in brain regions involved in spatial memory processing [107]. Numerous neuropeptides, including but not limited to nociceptin, opioid peptides, and corticotropin-releasing factors, have also been associated with cognitive processes such as learning and memory, based on various biochemical, physiological, and behavioral criteria [108].

While NPY significantly impacts cognitive functions and memory in the central nervous system, its role extends beyond neural processes to various peripheral systems. This multifunctionality is evident in its involvement in immune regulation and inflammation, as demonstrated in periodontal disease, where NPY contributes to inflammatory modulation and tissue remodeling.

Role of NPY in Periodontal Disease

Periodontitis is an inflammatory condition primarily caused by bacteria in dental plaque. However, the presence of bacteria alone is insufficient to cause severe periodontal tissue deterioration. The degree of inflammatory responses to plaque bacteria's lipopolysaccharide (LPS) component determines the severity and extensiveness of gingival inflammation. This inflammation results from complex interactions between soluble substances and cells, which must be rigorously tracked to protect the body and promote healing [95]. Besides being a cause of tooth loss, periodontitis is linked to various systemic problems in developing and developed countries [109].

Evidence suggests a neurogenic component in the inflammatory process of periodontitis. Neurogenic inflammation acts as a defense mechanism, but excessive or chronic activation may cause harm rather than healing [110]. This inflammation results from chemical reactions involving irritant receptors on sensory neurons, producing inflammatory neuropeptides. Neuropeptides, physiologically active peptides produced by neurons, function as biological messengers through extracellular receptors on target cells [111]. Neuropeptides are the largest class of transmitter chemicals with a vast range of known actions. Their extensive evolutionary history and high degree of conservation suggest a significant role in evolution. They are present in primary sensory neurons, somatosensory neurons, autonomic pre- and post-ganglionic nerves, and neurons throughout the (CNS) [112].

Periodontal tissues are widely innervated by myelinated nerve fibers closely associated with blood vessels. These fibers lose their myelin covering as they pass through the ligament, ending as free non-myelinated endings or in various specialized receptors. Human fibers that innervate periodontal tissues are immunoreactive to several neuropeptides, including SP, calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), and neuropeptide Y (NPY). In the rat periodontal ligament, VIP, CGRP, and NPY have been linked to blood vessels, indicating their role in modulating blood flow in this location [113]. In the sympathetic nervous system, NPY co-localizes with the classical neurotransmitter norepinephrine (NA). While distinguishing the relative contributions of NPY and NA can be challenging, NPY has several clear-cut activities, such as regulating the immune response, vasoconstriction, angiogenesis, and trophic qualities that may aid in tissue remodeling [114-116]. External shocks such as pH shifts, temperature fluctuations, stress, and varying exposure to endotoxins can particularly harm the oral cavity. If these conditions persist, they may trigger neurogenic inflammation in vulnerable tissues [117,118].

The discovery of neuropeptides in gingival crevicular fluid (GCF) and the finding that peptidergic neurons extensively innervate the gingivae have led to a growing consensus that imbalances in certain neuropeptides may play a role in modulating periodontal diseases [119,120]. In periodontal disease, NPY is released from sympathetic nerve fibers and significantly influences periodontal health and disease progression [120]. NPY plays a multifaceted role in periodontal disease through its effects on bone metabolism, inflammation modulation, immune cell regulation, vascular function, neurogenic inflammation, and tissue remodeling. NPY impacts bone metabolism by regulating osteoblast and osteoclast activity, inhibiting osteoclastogenesis to reduce bone resorption, which is crucial in preventing tooth loss associated with periodontitis. It also promotes osteoblast

survival and activity, enhancing bone formation and repair to maintain alveolar bone integrity [121]. NPY acts as an anti-inflammatory agent by inhibiting the release of pro-inflammatory cytokines such as Interleukin-1 beta (IL-1β), Interleukin-6 (IL-6), and Tumor Necrosis Factor-alpha (TNF-α), helping to control excessive inflammation that can lead to tissue destruction. Additionally, it stimulates the release of anti-inflammatory cytokines, promoting a balanced immune response [122-124]. NPY influences immune cells by modulating macrophage activity, promoting the M2 phenotype associated with anti-inflammatory and tissue repair activities, and affecting the migration and function of neutrophils, dendritic cells, and T cells, contributing to a controlled and effective immune response [125, 126]. Through its vasoconstrictive properties mediated by Y1 and Y2 receptors, NPY regulates blood flow within periodontal tissues, ensuring adequate tissue perfusion and oxygenation for health and repair processes [113]. Moreover, NPY is involved in neurogenic inflammation, acting as a mediator released from nerve endings in response to stimuli and contributing to the local immune response and tissue remodeling in periodontal tissues. Alongside other neuropeptides like substance P and CGRP, NPY plays a significant role in the crosstalk between the nervous and immune systems, influencing the inflammatory milieu within the periodontium [111]. Finally, NPY promotes tissue remodeling and repair processes by enhancing fibroblast proliferation and migration, essential for maintaining the structural integrity of periodontal tissues, and stimulating the production of extracellular matrix components such as collagen, vital for tissue repair and regeneration [114-116]. **[Figure3]**NPY is a multifunctional neuropeptide with significant roles in modulating inflammation, immune responses, vascular function, bone metabolism, neurogenic inflammation, and tissue remodeling in periodontal disease. Its diverse actions highlight the complex interplay between the nervous system and the immune system in periodontal health and disease [122-126].

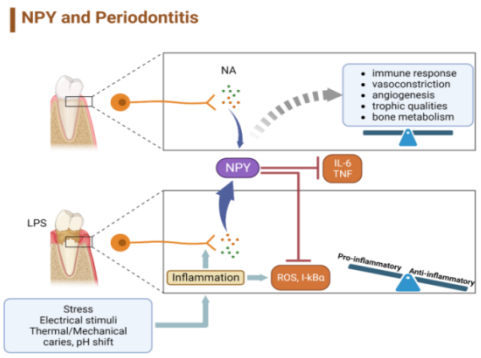

Figure 3: Shows the role of Neuropeptide Y (NPY) in periodontitis, focusing on its effects on inflammation and interaction with norepinephrine (NA). NPY is released in response to various stimuli, influencing immune response, vasoconstriction, angiogenesis, and bone metabolism. The lower panel illustrates how lipopolysaccharides (LPS) from bacterial plaque trigger inflammation, with NPY modulating cytokines like IL-6 and TNF-α. Reactive oxygen species (ROS) and factor kappa B (IκBα) are key mediators in balancing pro-inflammatory and anti-inflammatory responses within periodontal tissues. Illustration Created with BioRender.com

NPY: Neuropeptide Y, NA: Nerve Activity, LPS: Lipopolysaccharides, ROS: Reactive Oxygen Species, IκBα: Inhibitor of kappa B alpha, IL-6: Interleukin-6, TNF: Tumor Necrosis Factor

RESULTS

Distinct Roles of NPY, PYY, and PP in Hypertension, Stress, Obesity, and Beyond

NPY, PYY, and PP belong to the same peptide family and share a high degree of sequence similarity, particularly in the conserved N-terminal and C-terminal regions that are crucial for their biological function [5]. The N-terminal region typically contributes to their ability to bind to Y receptors, with the first few amino acids being identical or similar across all three peptides, which is essential for receptor interaction. The C-terminal

region is also highly conserved, playing a vital role in receptor binding and activation by maintaining the peptide's structure and ensuring proper binding [7,8]. These peptides exert their biological effects primarily by binding to Y receptors (Y1, Y2, Y4, Y5, and Y6), which are G-protein coupled receptors (GPCRs) that mediate various physiological responses [6]. NPY primarily binds to Y1, Y2, Y5, and Y6 receptors, each subtype involved in different physiological processes. Y1 receptors are associated with appetite stimulation and vasoconstriction, while Y2 receptors play a role in the feedback inhibition of NPY release and the reduction of food intake. PYY has a high affinity for Y2 and Y5 receptors, and its truncated form, PYY3-36, selectively binds to Y2 receptors, inhibiting appetite by slowing gastric emptying and reducing gastrointestinal motility. PP primarily interacts with the Y4 receptor, which regulates pancreatic secretion and potentially influences appetite and energy homeostasis [6-8]. Specific regions within these peptides, such as the C-terminal tyrosine-amide and the core sequence from positions 4 to 8, are crucial for their biological activity and receptor specificity. The C-terminal tyrosine-amide is conserved across all three peptides, playing a significant role in maintaining the peptides' structure necessary for high-affinity receptor interaction. The core sequence contributes to the binding affinity and selectivity for different Y receptors, with the Y5 receptor binding requiring the presence of specific residues in this sequence [6,13]. **[Figure4]** Despite their sequence similarity, NPY, PYY, and PP have distinct functional roles due to differences in their receptor binding profiles and the tissues where they are expressed and act. This functional diversity is essential for regulating various physiological processes, including appetite control, circadian rhythms, and stress responses [4]. NPY is heavily involved in stress responses, cardiovascular regulation, obesity, sleep, neuroprotection, and cognitive functions. PYY mainly regulates appetite and energy balance, indirectly affecting cardiovascular health and cognitive functions, while PP primarily influences digestive and pancreatic functions. Understanding these peptides' distinct and overlapping roles can help develop targeted therapies for various physiological and pathological conditions [15-21]. **[Table 2].**

Table 2: Summarizes the roles of NPY, PYY, and PP in various physiological and pathological conditions.

Condition	NPY	PYY	PP
Hypertension and Cardiovascular Disease	Increases blood pressure through vasoconstriction; influences cardiac contractility [12].	Indirectly influences cardiovascular health through appetite regulation and obesity management [131].	Minimal direct role; may influence hypertension through appetite and body weight regulation [20].
Stress	Reduces anxiety and stress response through Y1 and Y2 receptors [44].	Minimal direct involvement; stress can alter PYY levels affecting appetite [20].	Minimal direct involvement; PP levels can change in response to stress [132].

Obesity	Stimulates appetite and reduces energy expenditure, contributing to obesity [127].	Reduces appetite by binding to Y2 receptors, promoting satiety and weight management [133].	Reduces appetite via Y4 receptors, contributing to body weight regulation [133].	
Sleep Regulation	Modulates sleep-wake cycles and influences REM sleep [65,68].	Limited direct role; may influence sleep through appetite regulation [134].	No significant role in sleep regulation [134].	
Neurodegenerative Diseases		Promotes neuronal survival and provides resistance to neurodegenerative damage [74,82,90].	Minimal direct role; gut-brain interactions influenced by PYY could impact brain health [135].	Not well-established; minimal evidence of involvement in neurodegenerative diseases [135].
Memory and Learning		Enhances memory and learning by modulating synaptic plasticity in the hippocampus [104,108].	Minimal direct impact; affects cognitive functions indirectly through metabolic regulation [135].	No significant evidence linking PP to memory and learning.
Periodontal Disease	Modulates inflammation and immune responses, potentially affecting		Limited direct involvement; systemic metabolic	Minimal direct involvement; no significant impact on

	periodontal disease [110].	states influenced by PYY may affect oral health [136].	periodontal disease.

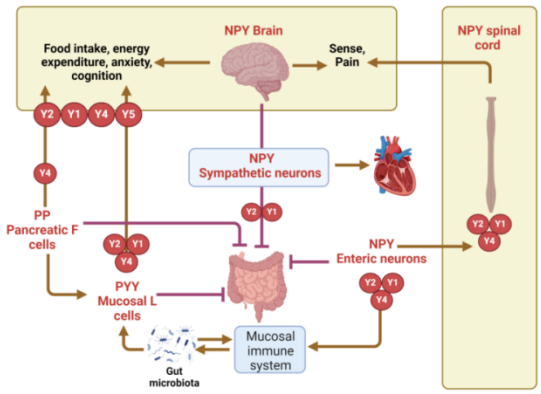

Figure 4: Illustrates the complex distribution and functions of Neuropeptide Y (NPY) and its interactions with various Y receptors (Y1, Y2, Y4, Y5) across different tissues. NPY, primarily located in the brain, spinal cord, sympathetic neurons, and enteric neurons, modulates multiple physiological processes including food intake, energy expenditure, anxiety, cognition, and pain perception. In the gut, NPY released from enteric neurons and mucosal L cells, along with Peptide YY (PYY) from mucosal L cells, influences the gut microbiota and mucosal immune system. Pancreatic polypeptide (PP) secreted by pancreatic F cells acts through Y receptors to regulate pancreatic function. The figure highlights the extensive cross-talk between the central nervous system, peripheral organs, and the immune system, showcasing the diverse roles of NPY and related peptides in maintaining physiological homeostasis.

DISCUSSION

Clinical Implications

- Obesity and Metabolic Disorders: Due to its role in appetite regulation and energy balance, NPY is a target for therapeutic interventions in obesity and metabolic syndrome [16,17].
- Cardiovascular Diseases: NPY's involvement in blood pressure regulation and cardiovascular stress responses makes it a potential target for treating hypertension and heart failure [36].
- Mental Health: Given its role in stress and anxiety modulation, NPY-based therapies are being explored for treating anxiety disorders and depression [27].
- Neurodegenerative Diseases: NPY's neuroprotective effects suggest potential therapeutic applications in diseases such as Alzheimer's and Parkinson's [73].
- Periodontal Disease: NPY plays a crucial role in periodontal disease by modulating inflammation, immune responses, and tissue remodeling. Targeting NPY receptors or adjusting its levels could offer innovative therapeutic strategies to control inflammation, enhance tissue repair, and prevent bone loss, potentially improving clinical outcomes in periodontitis [122-124].

Potential Therapeutic Applications of Targeting NPY and Its Receptors

- Targeting Neuropeptide Y (NPY) and its receptors (Y1R, Y2R, Y4R, and Y5R) holds significant promise for the management of various diseases due to NPY's widespread physiological influence. In cardiovascular diseases, NPY's role in modulating blood pressure and heart rate suggests that NPY

receptor antagonists could be developed to mitigate conditions like hypertension, congestive heart failure, and atrial fibrillation. By blocking specific NPY receptors, it may be possible to reduce vasoconstriction, lower peripheral resistance, and improve cardiac output, thereby offering a novel approach to cardiovascular therapy [12].

- In metabolic disorders, such as obesity and type 2 diabetes, NPY antagonists targeting Y1R and Y2R receptors could help regulate appetite and energy homeostasis. NPY is known to stimulate hunger and food intake, so inhibiting its action could contribute to weight loss and better glycemic control. This approach could be particularly beneficial for patients who have not responded well to traditional treatments [20, 127]
- NPY's anti-inflammatory properties make it a compelling target for treating inflammatory and autoimmune diseases. By modulating the release of pro-inflammatory cytokines and promoting anti-inflammatory pathways, NPY receptor agonists could potentially be used to treat conditions like rheumatoid arthritis, inflammatory bowel disease, and even periodontal disease. This anti-inflammatory action could also be harnessed in neurodegenerative diseases, where inflammation plays a critical role in disease progression. Enhancing NPY activity in the brain could protect neurons, reduce excitotoxicity, and slow down diseases like Alzheimer's and Parkinson's [128].
- Moreover, NPY's involvement in stress response and mental health suggests its potential in managing stress-related disorders such as anxiety, depression, and post-traumatic stress disorder (PTSD). NPY receptor modulators could be developed to enhance stress resilience and coping mechanisms, providing a new avenue for psychological therapies [129].
- Finally, in the context of periodontal disease, targeting NPY could help in controlling inflammation, improving immune response, and enhancing tissue regeneration. This could lead to new treatments that not only manage symptoms but also promote healing and prevent tooth loss [130].
- Overall, the therapeutic applications of targeting NPY and its receptors are vast, with potential benefits spanning cardiovascular, metabolic, inflammatory, neurodegenerative, mental health, and dental fields. Further research and clinical trials are essential to develop safe and effective NPY-based therapies.

Conclusion

Neuropeptide Y (NPY) plays a crucial role in regulating metabolic homeostasis, immune response, and cardiovascular functions. Its diverse actions highlight its potential as a therapeutic target for various chronic diseases. However, further studies are needed to fully understand the distinct physiological effects of NPY receptors, particularly Y4R and Y5R, and to optimize therapeutic strategies involving NPY.

Research Gaps and Future Directions

- Detailed Mechanisms: While the general functions of NPY are well-documented, the detailed mechanisms of its actions, particularly through Y4 and Y5 receptors, need further exploration.
- Therapeutic Development: More research is required to develop NPY-based therapeutic agents and understand the optimal dosing and delivery methods for treating various conditions.
- Physiological Variability: Understanding how NPY function varies across different physiological states and conditions will be crucial for developing targeted therapies.

Author Contributions

R.B., Conceptualization, Writing—original draft, review and drawing of the figures; N.T.H., Conceptualization, writing, design of the manuscript and the theoretical framework; G.V.B, Writing—original draft and editing; S.K.S, Writing—original draft and editing; P.S, Writing—original draft and editing; A.A.E.E, Writing—original draft and editing; B.K.M, Writing—original draft and editing; W.S.A, Writing—original draft and editing; T.H.M, Conceptualization, Writing—original draft and editing; R.M.M, Supervision, validation and editing; I.M, Conceptualization and supervision; E.M, Conceptualization, Validation and editing, All authors have read and agreed to the published version of the manuscript.

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