

Summary

Dan Larhammar and Erik Salaneck

Evolutionary perspective on the NPY-PYY-PP peptides and their receptors

The neuropeptide Y (NPY) system in mammals includes three peptides and 4-5 receptors that are involved in a broad range of functions, primarily in the cardiovascular, nervous and endocrine systems. As it is generally assumed that complexity increases during evolution, it has come as a surprise that the NPY system was quite complex already at the dawn of vertebrate evolution with two peptides (NPY and PYY) and at least seven receptor subtypes. Thus, mammals have lost 2-3 receptors. Amphibians and sharks, in contrast, have retained the original repertoire. Information is still scarce about the functions of individual receptor subtypes in non-mammals and the tissue distribution differs considerably across vertebrate classes. Surprisingly, receptor subtypes Y₁ and Y₅ which stimulate appetite in mammals have been lost in many ray-finned fishes. On the other hand, prominent cardiovascular effects have been described in both sharks and mammals. Thus, some functions have changed whereas others seem to have remained conserved over long evolutionary periods.

Key words: neuropeptide Y, peptide YY, pancreatic polypeptides, G-protein-coupled receptor, gene duplication, phylogeny, pseudogene, ortholog, chromosome, synteny, paralogon, evolution, vertebrate, gnathostome

Summary

Magnus M. Berglund, Philip A. Hipskind and Donald R. Gehlert

Function, distribution and molecular pharmacology of NPY-family receptors

Neuropeptide Y (NPY) is a 36 amino acid peptide discovered in the early 1980s that belongs to a family of peptides that includes pancreatic polypeptide (PP) and Peptide YY (PYY). NPY is widely distributed in the central nervous systems while PYY and PP appeared to function primarily as endocrine peptides. The abundance and distribution of these peptides in various tissues suggest their importance in a variety of physiological processes. These peptides produce their biological effects through four G-protein coupled receptors (Y₁, Y₂, Y₄, Y₅). Recent advances in the study of the functional roles of these receptors through knockout mice, anatomical localizations, molecular pharmacology and traditional small molecule development ever revealed the potential for their participation in a variety of diseases. In this review, we summarize many of these advances and the continuing potential for the scientific investigation of this peptide family.

Key words: NPY, PP, PYY, distribution, dimerization, GPCR, Y₁, Y₂, Y₄, Y₅, signal transduction, mutagenesis, obesity, feeding, blood pressure, ethanol, anxiety, antagonists

Summary

Eric Grouzmann and Noureddine Brakch

NPY processing in neuronal and non-neuronal tissues by proconvertases

Neuropeptide Y (NPY) like many other peptides is generated after several proteolysis processing steps of a propeptide. The proNPY is cleaved at its dibasic site by prohormone convertases,

which generate NPY1-39 and C-flanking peptide of NPY (CPON). Two further sequential modifications at the C-terminus by the carboxypeptidase and the peptidylglycine α -amidating monooxygenase, respectively, lead to the biologically active amidated NPY1-36. The amide moiety is essential for NPY activity and prevents degradation by carboxypeptidases. There is increasing body of evidence suggesting a regulation of NPY processing and inactivation, which yields peptide fragments with receptor-specific actions. The dipeptidyl peptidase IV (DPP IV) by cleaving the Tyr-Pro dipeptide from the NPY's N-terminus, and aminopeptidase P (AmP) by removing the N-terminal Tyr generates NPY3-36 and NPY2-36, respectively. These fragments lose their affinity for the Y1 receptor, and become Y2/Y5 receptor agonists. This paper will summarize the knowledge of tissue-specific processing of proNPY and the regulation of biologically active NPY(s) generation by proteolysis.

Key words: ProNPY, NPY, NPY1-39, NPY1-37, NPY1-36, proconvertases, PC1/3, PC2, furin, prohormone thiol protease

Summary

Rolf Mentlein

Dipeptidyl-peptidase IV and aminopeptidase P: molecular switches of NPY/PYY receptor affinities

Cell-surface or soluble peptidases are involved in the activation, partial or complete inactivation of bioactive peptides. This review describes the peptidases involved in the post-secretory regulation of the biological activities of peripheral and central neuropeptide Y (NPY) and of circulating peptide YY (PYY). Both peptides are N-terminally truncated by aminopeptidase P (APP) and dipeptidyl peptidase IV (DPP IV, CD26) thereby generating metabolites of altered receptor selectivity: The truncated forms lose their affinity and potency to Y1 and partially Y5 receptors, but not to Y2 receptors. Since the peptidase-fragments NPY(3-36) and PYY(3-36) can be found in serum and many tissues, DPP IV-cleavage appears to be a major post-secretory conversion in vivo. NPY- and PYY-conversion plays peripherally a role in NPY-induced vasoconstriction, angiogenesis and peripheral inflammation, in the central nervous system in PYY-/NPY-mediated food intake and anxiolytic effects. These regulatory processes should be considered as potential side or desired new effects of DPP IV-inhibitors that are currently in clinical phase III studies for the treatment of diabetes. Apart from the NPY-/PYY-convertases DPP IV and APP, few endo-peptidases (neprilysin, meprin and others) are known that inactivate both peptides completely.

Key words: peptide inactivation, peptidase, endopeptidase, aminopeptidase, cell-surface peptidase, neuropeptides, peptide hormone, receptor subtype, neuropeptides Y, peptide YY, CD26, dipeptidyl-peptidase IV, aminopeptidase P, endothelial cells, smooth muscle cells, blood pressure regulation

Summary

Sammy Bedoui and Stephan von Hörsten

NPY, NPY receptors and DPPIV in innate immunity and autoimmune disorders

NPY is abundantly distributed and regulated in the CNS, the endocrine, and the immune system of mammals. A multidirectional communication between these supersystems is now well established and achieved – along with other mediators - via NPY being released in the central and the peripheral nervous system. Within these multiple pathways of communication, NPY acts directly (e.g. via the sympathetic nervous system), indirectly (e.g. via modulation of the stress response in the CNS), and/or in concert with other transmitters (e.g. as a co-neuroimmune-transmitter in combination with catecholamines) on immune cells as its target for neuroimmunomodulation. The presence of NPY containing fibers in lymphoid organs and the release of NPY within the local microenvironment allows for a direct interaction between NPY and immune cells. In addition, it becomes more and more clear that different leukocyte subpopulation express receptors for NPY, which may – all in all – justify the consideration of NPY as a neurotransmitter with cytokine-like properties. This perspective becomes even more compelling considering the evidence for NPY dependent immune modulation in various autoimmune diseases. However, what is missing in this regard is clear evidence for constitutive and/or inducible production of NPY by leukocyte subpopulations themselves. As a further upcoming challenge for future research on the role of NPY in immune regulation is the need for a deeper understanding of the degradation of NPY by dipeptidyl-peptidase IV and associated changes in receptor specificity. Most likely, conversion of NPY plays a role in many NPY-modulated processes including but not limited to inflammation as well as its induction and repair. In the present chapter we will systematically go through this evidence for an important role of NPY in immune regulation and provide recent information on the status of the above-mentioned open questions.

Key words: NPY, sympathetic innervation, NPY receptor, neuroimmune interaction, respiratory burst, phagocytosis, cytokine, multiple sclerosis, rheumatoid arthritis

Summary

Mónica De la Fuente and Sonia Medina

NPY and phagocytic cell functions

NPY modulates general functions of phagocytic cells by increasing PKC activity and decreasing cAMP levels to improve the functions of these cells. However, these results show a broad range of variations depending on several factors such as the presence of other neurotransmitters, different cells present in the assay, the age of the animals, the activation state of the cells, the duration and time of the stimulus, and the time of day and year in which the study is carried out. Currently, a relevant subject such as the effect of NPY on phagocytic cell function is scarcely known and with conflicting data. For this reason, more research is proposed for extending and clarifying it. However, it is necessary to take into account the great number of factors that are not usually considered in the experimental protocols and can exert an influence on the findings. Only a rigorous control of these factors in future research will allow one to understand the role that this neurotransmitter plays in the functions of immune cells.

Key words: NPY, phagocytic cells, macrophages, phagocytic process, presence of norepinephrine, presence of lymphocytes, aging, activation state, biological rhythms

Summary

Basile N. Landis, Isabelle Plouin-Gaudon and Jean-Silvain Lacroix
Neuropeptide Y in allergic and respiratory disorders

Neuropeptide Y (NPY) is associated with several neurological and immunological pathways involved in airway homeostasis. The smooth muscle tone in both airway wall and blood vessels, mucus glands, the muco-ciliary transport system and the local immune mechanisms are influenced by NPY. Functional studies with different NPY analogues suggest an important role of this neuropeptide in prejunctional modulation of neurotransmitter release from both sensory and parasympathetic nerves. Thus, NPY has important modulator effects on neurogenic inflammation and the release of both cytokine and oxidative agents. Several aspects regarding the role of NPY in the pathophysiological mechanisms of airway diseases suggest that the development of selective agonists and antagonist could have potential therapeutic applications.

Key words: neuropeptide Y, airway, nasal mucosa, vascular smooth muscle, mucus, sympathetic nerves, parasympathetic nerves, sensory nerves, neurogenic inflammation, neuromodulation, inflammation, immune system

Summary

Bradley K. Taylor
NPY analgesia: moving from acute to chronic pain

Previous reviews have described the behavioral effects of NPY in models of acute pain, as well as changes in NPY and NPY receptor gene expression in pain pathways following tissue or nerve injury. Particularly striking is the massive up-regulation of NPY in the cell bodies and central terminals of sensory neurons. This chapter focuses on the functional relevance of the NPY system to the development and modulation of chronic pain. Emphasis is given to recent studies demonstrating that agonists and antagonists at NPY receptors modulate the behavioral, biochemical, and molecular markers of inflammatory and neuropathic pain. The results indicate that the development of novel NPY agonists should yield a powerful new pharmacotherapy for the treatment of chronic pain.

Key words: neuropeptide Y, inflammation, pain, allodynia, hyperalgesia, nociception, substance P, NPY receptor, neuropathic

Summary

Meit Björndahl, Renhai Cao, Luxun Xue and Yihai Cao
NPY-induced angiogenesis in retinopathy and wound healing

The finding that NPY acts as an angiogenic factor has linked NPY to physiological and pathological angiogenesis-dependent processes, such as wound healing and retinopathy. It also raises a possibility for development of therapeutic approaches that can be used in the treatment of angiogenesis-related diseases by either agonizing or antagonizing the function of NPY. Understanding of the underlying mechanisms by which NPY induces angiogenesis would help us to design these therapeutic agents.

Key words: NPY, Y2 receptor, angiogenesis, neovascularization, diabetes, retinopathy, wound healing

Summary

William P. Gray and Helen E. Scharfman
Neuropeptide Y and hippocampal neurogenesis

From a systems neurobiological perspective, the regulation of NPY expression appears to be important for adapting the individual's behavioural responses to chronic stress. Dysregulation of the NPY system is thus likely to contribute to the pathophysiology of anxiety and depression. Given the emerging importance of adult dentate neurogenesis in the regulation of anxiety and depression, the demonstration that NPY is an important modulator of dentate neurogenesis raises the possibility that the neurogenic effect of NPY may be an important mechanism for its anxiolytic and antidepressant effects. NPY modulation of neurogenesis may also be important for supporting certain forms of hippocampal dependent learning and memory. The source of subgranular zone (SGZ) NPY is most likely to be from hilar and SGZ interneurons, raising the intriguing possibility that dentate neurogenesis is modulated by hilar interneuron activity.

Summary

Massimiliano Ruscica, Elena Dozio, Marcella Motta and Paolo Magni
NPY family of peptides in endocrine, breast and prostate tumors

The neuropeptide Y (NPY) family of peptides (pancreatic polypeptide, peptide YY and NPY) has been involved in many physiological actions, like food intake, reproduction, and neuroendocrine, cardiovascular and cognitive functions, but also in the modulation of tumor progression, with effects on cell proliferation, matrix invasion and metastatization, and angiogenesis. The oncological relevance of NPY-related peptides has been recently extended to endocrine-related cancer: neuroendocrine tumors, breast and prostate cancer. The relevance of these peptides may derive from either the expression of specific receptors by the tumor, which is then a target of extratumorally-produced NPY-related peptides, or the tumoral production of these peptides, which may act locally and/or reach the bloodstream generating systemic effects, or the combination of peptide secretion and receptor expression, leading to autocrine/paracrine promotion or suppression of cancer progression. The study of the role of the NPY-family of

peptides in endocrine-related tumors may help to clarify tumor biology, as well as to indicate novel diagnostic markers and therapeutical approaches.

Key words: neuropeptide Y, pancreatic polypeptide, peptide YY, NPY receptors, neuroendocrine tumors, pituitary tumors, pheochromocytoma, neuroblastoma, ectopic ACTH-secreting tumor, breast cancer, prostate cancer, tumor progression, cell proliferation, metastatization, angiogenesis



<http://www.springer.com/978-3-7643-7159-3>

The NPY Family of Peptides in Immune Disorders,
Inflammation, Angiogenesis, and Cancer

Zukowska, Z.; Feuerstein, G.Z. (Eds.)

2005, XV, 260 p., Hardcover

ISBN: 978-3-7643-7159-3

A product of Birkhäuser Basel