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Mini-review

NEUROPEPTIDE Y FAMILY OF PEPTIDES: STRUCTURE, ANATOMICAL EXPRESSION, REGULATION, RECEPTORS AND PHYSIOLOGICAL FUNCTIONS

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ABSTRACT

The Neuropeptide Y family of peptides consists of neuropeptide Y (NPY), peptide YY (PYY) and pancreatic polypeptide (PP), which share a similar structure known as a PP- fold. There are four known human G-protein coupled receptors for the PP - fold peptides, namely Y1, Y2, Y4 and Y5, each of them being able to bind at least two of the three endogenous ligands. All three peptides are found in the circulation acting as hormones. Although NPY is only released from neurons (sympathetic, parasympathetic and nonadrenergic, noncholinergic), PYY and PP are primarily found in endocrine cells in the gut, where they exert such effects as inhibition of gall bladder secretion, gut motility, and pancreatic secretion. Initial studies with transgenic animals confirmed the well-established action of NPY on metabolism, food-intake, vascular systems, memory, mood, neuronal excitability, and reproduction. In general, NPY is an inhibitory neurotransmitter and exhibits anxiolytic, anti-stress, anti-depressant, anti-convulsant and antinociceptive actions. More recently, NPY has been found to be a key factor in regulation of ethanol consumption and neuronal development.

Key words: neuropeptide Y family, peptide YY, pancreatic polypeptide, Y-receptors.

INTRODUCTION

The NPY family of peptides consists of neuropeptide Y (NPY) and the two gut hormones, peptide YY (PYY) and pancreatic polypeptide (PP).

The first member of this family, PP was discovered as a contaminant in extracts of chicken insulin (1, 2). Its name was initially used to designate the entire family of related peptides, the PP family. Larhammar et al. (3) showed that NPY has remained much more conserved throughout evolution than PP, and furthermore, it seems to be evolutionarily older than PP. Thus, the family would be more appropriately called the NPY family.

In 1982 Tatemoto (4) isolated a structurally related peptide from pig intestine. The peptide had tyrosines in both ends and was therefore named peptide YY after the single letter abbreviation for tyrosine (Y) (5). Because many gut peptides also occur in the brain, the existence of neural PYY was hypothesized. In the same year Tatemoto et al. (6) found a similar peptide in pig brain homogenates. This brain peptide also displayed Y residues at its termini, but it was named neuropeptide Y to indicate its neural origin.

A fourth family member, peptide Y (PY) exists in fish, which lack PP, and was isolated by Andrews et al. (7). It is unlikely that a mammalian ortholog of PY exists.

STRUCTURE

NPY, PYY and PP, together with the fish PY, share a common hairpin-like three – dimensional structure called the PP-fold (8). All four peptides are 36 amino acids long (except chicken PYY, which is 37) with an amidated carboxyterminus. NPY is one of the most evolutionary conserved peptides known. Only two of the 36 amino acids of NPY are variable between mammals. PYY has evolved at a higher rate than NPY and has eight variable amino acids between different orders of mammals, whereas the third member of the PP-fold family of peptides, PP, has evolved very rapidly and is one of the least-conserved peptides known (5).

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ANATOMICAL EXPRESSION

NPY is widely distributed and released from specific central neurons and peripheral neurons that include nonadrenergic, noncholinergic (NANC), sympathetic and sensory nerves (9).

In fact, neural tissue is the primary NPY-producing area, although its expression seems to be extended to cells derived from the neural crest, including the adrenal medulla (10, 11). The highest NPY levels in the mammalian brain are found within hypothalamic nuclei, particularly the paraventricular nucleus, arcuate nucleus, suprachiasmatic nucleus, median eminence, and dorsomedial nucleus (12). Except for the suprachiasmatic nucleus, which receives major inputs from intergeniculate leaflet, the major source of NPY in these nuclei appears to be from neurons in the arcuate nucleus (13). High levels of NPY expression can also be found within cerebral cortex including the hippocampal formation, the inner layer of the olfactory bulb, striatum, septum, amygdala, and the basal forebrain. The level of thalamic NPY expression is among the lowest in the mammalian CNS, but high levels of expression have been found in the reticular nucleus and the intergeniculate leaflet of the ventral thalamus (14). In certain species (such as rats), extra-neuronal NPY is found in high concentrations in platelets and this source contributes significantly to plasma NPY levels, which otherwise are derived predominantly from sympathetic neuron activity.

In contrast to the neuronal localization of NPY, PYY is mainly expressed in the endocrine cells of the mucosal layer of the mammalian inferior gut (ileum and colon), although it is also localized within the superior gastrointestinal tract (15). The central expression in mammals is exclusively found over neurons in the medulla oblongata.

PP is mainly expressed in the pancreas. The pancreatic PP cells have been demonstrated to be different from those storing insulin, glucagon or somatostatin, however in some species PP cells are scattered on the exocrine parenchyma and the ductal epithelium rather than within the islets. PP cells also occur in the gastrointestinal tract during the early developing states of tetrapods (15).

REGULATION

NPY is regulated by several other neuropeptides and hormones. Two hormonal signals that act on NPY neurons are ghrelin and leptin (16). Ghrelin is 28 amino acid peptide that is released from the gut and binds to a specific G-protein-coupled receptor (GPCR) to signal release of growth hormone from the pituitary (17, 18). Both intravenous and intracerebroventricular injections of ghrelin result in a dose-dependent increase in growth hormone levels in plasma (18). Interestingly, this peptide is present in neurons of hypothalamic arcuate nucleus where ghrelin acts to increase the hypothalamic levels of NPY and feeding and body weight in rats (19, 20). In contrast, the adipose hormone leptin acts as a satiety factor possibly by inhibiting NPY release in the hypothalamus (21). Another peptide system, the melanocortins, has been found to interact with NPY (22-23). When co-injected intracerebroventricularly, the endogenous agonist α-melanocyte-stimulating hormone dose-dependently inhibits NPY-induced feeding (24). Between NPY and hypothalamic-pituitary-adrenal axis a complex relationship exists. It seems to include positive feedback between NPY and adrenal corticosteroids and negative feedback between NPY and corticotrophin-releasing factor (25).

PYY is released post-prandial (26) from the L-cells of the gut, where it is co-stored with glucagon-like peptide-1 and is found in the circulation as the N-terminally truncated PYY_{3-36} (27). Release of PYY is stimulated by nutritive factors, in particular, the presence of fat in the ileum and colon (28). Short-chain fatty acids administration into isolated perfused rabbit and rat colon increased PYY concentration in the circulation (29, 30).

PP is released in proportion to meal calorie content, though it is interesting to note that lipid digestion is required to generate the lipid-induced rise in circulating PP (31).

RECEPTORS

NPY – related peptides bind to a large and very heterogeneous family of G-protein-coupled receptors (GPCRs) belonging to the rhodopsin like superfamily (class 1) of receptors. Five NPY family receptors have been cloned from mammals (Y1, Y2, Y4, Y5 and y6). Several additional receptors have been postulated from pharmacological profiles using various tissue preparations (32). The International Union of Pharmacology recommended that the overtly NPY-preferring (not cloned) Y3 receptor should remain undesignated and gave the y6 receptor the lower case designation because it is a

pseudogene in mammals (9). An unusual feature of the Y receptor family is their lack of sequence identity, particularly between Y1, Y2, and Y5 receptors, that are only 30% identical (9). Cloned Y-receptors have all been shown to couple to inhibitory G-proteins (G_i) and thus mediate inhibition of cAMP synthesis (33, 34). The Y1 receptor has also been shown to activate mitogen-activated protein kinase in gut epithelial cells (35). Furthermore, whereas protein kinase C seems to be necessary for Y5 receptor signalling, a protein kinase C-independent pathway may also be involved in Y1, Y2, and Y4 signalling (36). Y1, Y2, Y4, and Y5 receptors can also couple to phospholipase C to provoke release of Ca^{2+} from intracellular stores (37).

The Y1 receptor was the first NPY family peptide binding receptor to be cloned. Most of the vascular and antinociceptive effects of NPY are transduced via the Y1 receptor (38, 39). The centrally induced vascular effects of NPY (reduced blood pressure and heart rate) are signalled mainly through Y1, as are many of the psychological functions of NPY, such as decreased anxiety and depression (40). The feeding response of NPY is Y1-dependent (41, 42). In addition, the ability of NPY to regulate ethanol consumption is also mediated by Y1.

The Y2 receptor is mainly located presynaptically where it acts as an autoreceptor, inhibiting further release of neurotransmitter (43, 44). This may explain why agonists specific for the Y1 receptor are anxiolytic whereas Y2 agonists appear to be anxiogenic (40). The same opposing relationship between Y1 and Y2 is evident for the central effects of NPY on blood pressure as Y2 specific agonists increase blood pressure whereas activation of central Y1 receptors decreases it (45). The Y2 receptor is also directly involved in some of the vascular effects of NPY (46). In addition, Y2 mediates NPY-induced angiogenesis and its effects on circadian rhythms (47). Like Y1, the Y2 receptor is highly conserved between species with more than 90 % identity between orders of mammals (48).

The third NPY family receptor to be identified by cloning was a receptor with high affinity for PP – Y4 receptor. The most interesting feature of the Y4 receptor is perhaps the low degree of sequence identity between species. When comparing the rat and human sequences, only 75% of the amino acids are identical, making Y4 one of the most rapidly evolving GPCRs known (49). As PP is the preferred ligand at the Y4 receptor, it is likely that this receptor mediates many of effects on GI tract, produced by PP like rabbit ileum contractions (50).

The third Y receptor stimulated by endogenous NPY is the brain-specific Y5 receptor, known for a while as the 'feeding receptor' (9). Activation of the Y5 receptor also results in a decrease in energy expenditure (51). Other effects of NPY that are mediated by the Y5 receptor are reproduction through inhibition of luteinizing hormone release (52) and regulation of brain excitability and seizures (53).

The y6 receptor was first cloned in rabbit and mouse (54). Later, when the human ortholog was cloned, it was found to be a non-functional pseudogene because of a frameshift mutation causing an in-frame stop codon.

The existence of an NPY-preferring receptor, often referred to as the Y3 receptor, has been inferred from pharmacological studies of a variety of tissues (55). The typical rank order of peptide potency of the receptor is NPY>NPY 13-36>PYY. Despite numerous attempts, no cloned receptor has been identified with a Y3 –like pharmacology. Recently, it was shown that bovine chromaffin cells, which display typical Y3-like pharmacology, express high levels of the Y1 receptor (56). One explanation for the lack of cloning success with the Y3 receptor is that Y1 receptors display a different pharmacological profile in these areas or that the Y3 binding profile is in fact the result of a mix of several of the cloned receptors.

PHYSIOLOGICAL FUNCTIONS

One of the most studied NPY functions concerns the effect on energy balance when administrated centrally (15). NPY is one of the most powerful orexigenic agents and is thought to be substrate of the mammalian central -effector anabolic pathways. Studies in rat have demonstrated that intracerebroventricular injections dramatically increase food intake in satiated animals but prolonged treatment results in weight gain and obesity (13). Homozygous mutant mice lacking NPY from central, peripheral (and enteric) neurones fed and grew normally, exhibited a normal response to starvation (57) although they were hypersensitive to the satiety factor, leptin (which normally inhibits NPY release).

In humans NPY levels are changed in all conditions involving a disturbed energy balance, such as anorexia, bulimia neurosa, and diabetes. In general NPY is an inhibitory neurotransmitter and exhibits anxiolytic, anti-

stress, anti-depressant, anti-convulsant and anti-nociceptive actions, in addition to its hypertensive, and potent appetite stimulating effects and its capacity to shift circadian rhythms. One of the most important developments in NPY research is the recent finding that NPY regulates ethanol consumption. The role of NPY as a potential regulator of alcohol consumption has been investigated in transgenic mice where an inverse correlation between NPY levels and drinking has been shown. At this point, it is unclear how these findings related to the well-established anxiolytic actions of NPY. Furthermore, a point mutation (leucine to proline) in the pre-pro NPY gene has been associated with higher alcohol consumption in humans (58).

NPY was initially shown to exhibit a surprisingly weak direct vasoconstrictor response but a powerful potentiation of noradrenaline-induced vasoconstriction in a variety of rabbit isolated blood vessels. In most sympathetic neurones, NPY coexists with noradrenaline and ATP (but not in the same vesicles) and the three main mechanisms of NPY action are: (a) direct Y1 – mediated vascular contractile effects; (b) amplification of adrenoceptor (alpha1)- mediated vasoconstriction, and (c) prejunctional Y2-mediated suppression of noradrenaline, ATP and NPY release (59).

Another vascular effect is stimulation of smooth muscle proliferation (47). Several studies have identified a trophic role for NPY in the nervous and vascular systems and in cardiac hypertrophy (60). Evidence for hypertrophic effects of NPY comes from studies of adult rat cardiac myocytes in culture (60). Twenty-four hour incubation of 7-day cultures with 10 nM NPY increases total cell protein by 45%, and both decreased protein degradation and increased synthesis contribute to the hypertrophy. In addition, several cardiovascular dysfunctions as well as some tumour diseases are associated with increased plasma levels of NPY (61).

In the intestine, NPY (and PYY) are potent anti-secretory agents in rodent and human tissues (62) and in patients infused with PYY (63). Data from numerous studies suggest that PYY is important in energy and glucose homeostasis. Batterham et al. (64) demonstrated that peripheral administration of PYY3-36 at physiological doses significantly reduced food intake in rodents and man. Aged female mice lacking PYY have increased bodyweight and fat mass.

PYY is released in the GI tract in response to meals. Many of the GI effects described for PP, including inhibition of gall bladder secretion, gut motility, and pancreatic secretion, can also be provoked by PYY (65). Other peripheral effects produced by PYY are the inhibition of fluid and electrolyte secretion in the intestinal tract (66) and vasoconstriction (67).

PP is almost exclusively expressed in endocrine pancreas and is released in response to meals (68). The effects of PP, including inhibition of pancreatic secretion, gall bladder activity, and intestinal motility, are mainly located in the GI tract (65). Recently, PP has been found to inhibit ileum contractions (50) and to stimulate colon contractions (69). In addition, PP affects metabolic functions, including glycogenolysis, and decreases fatty acid levels (60). However, binding sites for PP have been found in several rat brain regions including the interpeduncular nucleus, hypothalamus, and brainstem (70), suggesting that PP may also have direct effects of brain function. This may explain why intracerebroventricular injection of PP has been found to stimulate feeding in several different species of experimental animals (71). In animal models, peripheral PP administration increased energy expenditure in addition to its effects on food intake (72). Chronic administration of PP to obese mice slows body weight gain and peripheral over-expression of PP reduced food intake and body weight (73). PP appears to have the potential to act as a long-term appetite suppressor, and thus may be a suitable target for anti-obesity drug design.

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