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Review

Neuropeptide Y Y_1 receptors in vascular pharmacology

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Abstract

The existence of neurogenic mediator candidates apart from noradrenaline and acetylcholine involved in the control of vascular tone has attracted enormous attention during the past few decades. One such mediator is neuropeptide Y (NPY), which is co-localized with noradrenaline in sympathetic perivascular nerves. Stimulation of sympathetic nerves in vitro and in vivo causes non-adrenergic vasoconstriction which can be blocked by experimental manipulations that inhibit NPY mechanisms. Thus, the vasopressor response to stimulation of sympathetic nerves can be attenuated by chemical or surgical sympathectomy, treatment with reserpine or other pharmacological agents, and tachyphylaxis to NPY or by NPY antagonists. The NPY field was long plagued by a lack of specific antagonists, but with the recently developed, selective, non-peptide and stable NPY antagonists it has now become possible to study subtypes of this receptor family. For instance, it has become clear that the NPY Y_1 receptor mediates most of the direct peripheral effects of NPY on vascular tone. These antagonists promise to stimulate NPY research and will likely unravel the true significance of NPY in cardiovascular control under physiological conditions as well as in pathophysiological states.

Keywords: Co-transmission; Neuropeptide Y; Neuropeptide Y Y_1 receptor; Pancreatic polypeptide; Peptide YY; Vascular tone

1. Introduction

The concept of co-transmission was originally presented by Burnstock (1976) (see also the work of Burnstock, 1988) who, through comparative studies on the evolution of the autonomic nervous system and in a series of experiments, has provided evidence that adenosine 5′-triphosphate (ATP) acts as a co-transmitter in sympathetic nerves. The neuronal co-existence hypothesis has now been generally accepted and widely expanded to include a number of postulated co-transmitters in central as well as peripheral nerve terminals. The significance of these co-stored agents in regulation of, i.e., vascular homeostasis still remains controversial, however. This is partly due to the lack of appropriate antagonists but also due to the fact that agents and drugs that were thought to affect only classical transmitters also influence these co-stored substances. Furthermore, in pathological states there are marked changes in synthesis, storage, release and functional effects of co-transmitters, which may indicate that experimental findings obtained under control conditions may not apply to the relevance of these agents in disease. The significance of neuropeptide Y (NPY) in cardiovascular homeostasis has just begun to unfold, thanks to the development of selective and highly potent NPY receptor antagonists and to the cloning of NPY receptor subtypes. This has greatly enhanced and stimulated the research in this area and in this paper we review some evidence suggesting that NPY is indeed of importance in the regulation of vascular tone.

2. Non-adrenergic vasoconstriction

Noradrenaline is generally considered to be the classical transmitter in the sympathetic nervous system, but accumulating evidence from both in vivo and in vitro experiments suggest the occurrence of α-adrenoceptor-independent vasoconstriction upon sympathetic nerve stimulation. As early as 1948, Folkow and Uvnäs (1948) reported that sympathetic nerve stimulation causes an adrenoceptor-independent vasoconstriction in the cat hindlimb. Reserpine pretreatment, which depletes the tissue content of noradrenaline (Carlsson, 1965), attenuates the vasoconstrictor response and this diminished vasopressor effect can be reversed to a large extent by simultaneous preganglionic

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denervation (Rosell and Sedvall, 1962), although the noradrenaline content is also almost totally depleted after denervation (Sedvall and Thorson, 1965). However, reserpine pretreatment depletes not only noradrenaline but also the co-stored vasoconstrictor NPY from sympathetic nerve terminals, an effect dependent on intact nerve activity (Lundberg et al., 1985b,c), thus suggesting that the remaining response may not be caused by incomplete blockade of adrenoceptors as initially proposed (Folkow and Uvnäs, 1948) or different fractions of noradrenaline stores with different sensitivities to reserpine (Sedvall and Thorson, 1965). Interestingly, the vasoconstrictor response to nerve stimulation after sympathetic decentralization combined with reserpine administration disappears after continuous nerve stimulation (Rosell and Sedvall, 1962). Furthermore, the vasoconstrictor response to sympathetic nerve stimulation in the rabbit basilar artery and cat submandibular gland consists of an initial noradrenaline component and a slowly developing second component attributed to another transmitter (Lee et al., 1976, 1980; Lundberg and Tatemoto, 1982). The release of this transmitter is inhibited by presynaptic α_2-adrenoceptor stimulation and the vasoconstriction is enhanced by exogenous noradrenaline. In addition, the vasoconstriction to sympathetic nerve stimulation in the human forearm is partly resistant to α-adrenoceptor blockade (Taddei et al., 1989). Several reports have demonstrated the existence of non-adrenergic vasoconstriction upon sympathetic nerve stimulation in a variety of species, as shown in Table 1. A general and characteristic feature of these results is the total inhibition, by α-adrenoceptor antagonism, of the vasoconstrictor effects exerted by applied noradrenaline, although a substantial guanethidine- or 6-hydroxydopamine-sensitive portion of the vasoconstrictor response remains upon nerve stimulation.

Table 1
Demonstrations of non-adrenergic vasoconstriction upon sympathetic nerve stimulation in different organs and blood vessels from various species under in vivo and in vitro conditions in which NPY has been suggested to be involved

Tissue	Ref.
In vitro	
Rabbit	
skeletal muscle	Öhlén et al., 1990
Guinea pig	
uterine arteries	Morris and Murphy, 1988
vena cava	Morris, 1991
Human	
mesenteric arteries/vein	Racchi et al., 1996
In vivo	
Cat	
submandibular gland	Lundberg and Tatemoto, 1982
spleen	Lundberg et al., 1984
oral mucosa	Edwall et al., 1987
nasal mucosa	Lundblad et al., 1987
Pig	
spleen	Lundberg et al., 1989
nasal mucosa	Lacroix et al., 1988b
kidney	Pernow and Lundberg, 1989
bronchi and lungs	Franco-Cereceda et al., 1995
Dog	
skeletal muscle	Pernow, 1988
coronary circulation	Tanaka et al., 1997
Rat	
mesenteric circulation	Donoso et al., 1997
Pithed bullfrog	Stofer et al., 1990

3. Neuropeptide Y

The 36-amino-acid residue peptide NPY (so-called because it starts and ends with tyrosine which is single-letter coded Y) was originally isolated from the porcine brain (Tatemoto et al., 1982) and belongs to the pancreatic polypeptide (PP) family. NPY shares considerable sequence homology with PP, which is produced by cells of the endocrine pancreas, and it was subsequently discovered that the avian PP immunoreactivity observed in neuronal tissue was actually NPY (Lundberg et al., 1982). The mature human peptide YY (PYY) and PP share 67% and 50% identity with human NPY, respectively. NPY has potent central, as well as peripheral biological effects including stimulation of food intake, hormone release, anxiolysis, memory effects and cardiovascular actions. Within the central nervous system NPY is co-stored with noradrenaline in areas known to be of importance for the maintenance of blood pressure, while in the periphery, NPY is particularly abundant in postganglionic perivascular and myocardial sympathetic neurons, implying regulatory functions for NPY in the control of the cardiovascular system.

3.1. Synthesis / storage

NPY is generated from a precursor form, 97 amino acids in length (Minth et al., 1984), and is one of the most widely distributed polypeptides yet discovered. NPY is found, in a variety of species, with marked homology suggesting that it subserves evolutionarily old and important functions. NPY is synthesized in the nerve cell body, whereupon it is stored in large dense-cored vesicles and transported to the peripheral nerve terminal by axonal transport (Fried et al., 1985). The molar ratio of noradrenaline:NPY has been estimated to be approximately 1:150 in sympathetic nerve terminals while in the cell body region the ratio is around 1:10 (Fried et al., 1985). However, the ratio between large and small dense cored vesicles varies between species, with a higher proportion of large vesicles in man compared to species such as rat and mouse (Thureson-Klein et al., 1987). In situ hybridization techniques have been used to localize high levels of NPY mRNA in the stellate ganglia, which contain a population of NPY immunoreactive cell bodies (Schalling et al., 1988). The

relative amount of NPY in sympathetic ganglia varies considerably, suggesting that NPY occurs in a subpopulation of noradrenergic neurons. NPY is generally co-stored with noradrenaline, but there have been reports of co-existence of NPY and acetylcholine and adrenaline, as well as various peptides such as dynorphin, somatostatin, vasoactive intestinal polypeptide and calcitonin gene-related peptide (see the works of McDonald (1988) and Lacroix (1989)).

NPY occurs in high concentrations in the cardiovascular system and NPY-immunoreactive sympathetic nerve fibres densely innervate the blood vessels, being more numerous around arteries than around the corresponding veins. In these sympathetic fibres, NPY co-exists with noradrenaline. NPY fibres are not only present within perivascular nerves but are also associated with myocardial cells and adrenaline-containing chromaffin cells of the adrenal medulla (Lundberg et al., 1982). The tissue content of NPY can be depleted by surgical sympathectomy as well as by treatment with 6-hydroxydopamine or reserpine, the latter effect in perivascular nerves being dependent on intact nerve activity since it can be blocked by preganglionic nerve transection or by ganglionic blocking agents like chlorisondamine (Lundberg et al., 1984, 1985c). The degree of neuronal activity also determines the extent of NPY depletion (Nagata et al., 1987; Nankova et al., 1996). Reserpine pretreatment simultaneously results in a compensatory increase in synthesis of NPY, as indicated by increased NPY mRNA followed by elevated NPY in the supply region, i.e., sympathetic ganglia (Schalling et al., 1988). The tissue content of NPY also increases in immobilization stress (see below). These diametrically-opposite effects on NPY suggest that the role of NPY may finally depend on the degree of neuronal activity.

3.2. Release

NPY is released in a guanethidine-sensitive manner from a variety of organs upon sympathetic nerve stimulation during electrical nerve stimulation and reflex sympathetic activation such as that seen in haemorrhagic hypovolaemia or endotoxin chock as well as in asphyxia and physical exercise. Moreover, human cardiovascular pathological conditions such as myocardial infarction (Hulting et al., 1990) and angina pectoris (Ullman et al., 1990) are associated with increased plasma levels of NPY. Interestingly, while cardiac ischaemia leads to a non-exocytotic release of noradrenaline, probably via a carrier-mediated mechanism (Schömig et al., 1984, 1985; Levi and Raiteri, 1993), NPY is not released by ischaemia in the isolated heart (Franco-Cereceda et al., 1989). Cardiac release of NPY in man is likely to be caused by increased sympathetic nerve activity (Franco-Cereceda et al., 1990) and can be enhanced by hypoxia (Kaijser et al., 1994). NPY release is favoured by high stimulation frequencies, i.e., strong sympathetic activation, and the NPY-overflow under in vivo conditions is strongly correlated with the vasoconstriction observed (see the works of Pernow (1988), Lacroix (1989) and Lundberg et al. (1989)). Pharmacological studies suggest that NPY and noradrenaline are co-released from sympathetic nerve terminals by exocytotic mechanisms that are dependent on Ca^{2+}-influx through N-type Ca^{2+} channels (Richardt et al., 1988; Haass et al., 1989). The release is enhanced after α-adrenoceptor blockade, β-adrenoceptor stimulation, or activation of angiotensin II receptors and is reduced by α-adrenergic stimulation, the latter indicating that NPY release is regulated prejunctionally by noradrenaline (see the works of Pernow (1988), Lacroix, 1989 and Linton-Dahlöf (1989)). Conversely, NPY inhibits both noradrenaline release from perivascular sympathetic nerves and cholinergic transmission (Dahlöf et al., 1985b; Potter, 1985; Franco-Cereceda et al., 1985). The co-stored substances NPY and noradrenaline thus interact reciprocally in modulating each other's release from sympathetic nerve terminals. This also implies that agents and conditions that influence noradrenaline release and receptor binding will have effects on NPY.

3.3. Receptors

After investigating the direct vasoconstrictor effects of NPY and related peptides, and their ability to potentiate noradrenaline-evoked vasoconstriction and to inhibit noradrenaline release, Wahlestedt et al. (1986, 1987) postulated the existence of separate post- and prejunctional NPY receptors named NPY Y_1 and NPY Y_2, respectively. The number of NPY receptor subtypes has since then continued to grow and today at least five distinct rhodopsin-like, G-protein-coupled receptors constitute the diverse family of NPY receptors (see Table 2), of which all but the NPY

Table 2
The family of presently identified NPY receptors with relative ligand activity (for the human receptor subtypes except for rat NPY_3)

Receptor subtype	with ligand activity
$\mathbf{Y_1}$	NPY ≥ PYY ≥ [Leu^{31}Pro^{34}]NPY ≥ [Leu^{31}Pro^{34}]PYY ≫ NPY (13–36) > PP > PYY (3–36) = *N*-acetyl[Leu^{31}]NPY (24–36)
$\mathbf{Y_2}$	NPY ≥ PYY ≥ PYY (3–36) ≥ *N*-acetyl[Leu^{28}Leu^{31}]NPY (24–36) = NPY (13–36) ≫ [Leu^{31}Pro^{34}]NPY = [Leu^{31}Pro^{34}]PYY ≫ PP
$\mathbf{Y_3}$	NPY ≥ [Pro^{34}]NPY ≥ NPY (13–36) > PP > PYY = [Leu^{31}Pro^{34}]PYY = PYY (3–36)
$\mathbf{Y_4}$	PP > PYY = [Leu^{31}Pro^{34}]PYY > [Leu^{31}Pro^{34}]NPY > NPY > PYY (3–36) > NPY (13–36)
$\mathbf{Y_5}$	NPY = [Leu^{31}Pro^{34}]NPY = PYY = [Leu^{31}Pro^{34}]PYY > PYY (3–36) = PP > NPY (13–36)

Adapted from the works of Balasubramaniam (1996) and Malmström (1997).

Y_3 receptor have been cloned. Of the different NPY receptors, it is mainly NPY Y_1 and NPY Y_2 receptors that have been suggested to be involved in sympathetic vascular control (Table 3).

The first NPY receptor to be cloned was the NPY Y_1 receptor identified in rat (Eva et al., 1990) with binding characteristics similar to that of the almost identical NPY Y_1 receptor that was later cloned from human tissue (Herzog et al., 1992; Larhammar et al., 1992; Larhammar, 1997). The NPY Y_1 receptor is mainly located postjunctionally in blood vessels, causes vasoconstriction and is coupled to cAMP/phospholipase C, with rises in intracellular Ca^{2+} ($[Ca]_i$) after activation, while the NPY Y_2 receptor is mostly presynaptically located, inhibits transmitter release and is associated with the inhibition of the adenylyl cyclase system and changes in $[Ca]_i$. It should be emphasized though, that activation of NPY Y_2 receptors can cause vasoconstriction in certain vascular beds (Rioux et al., 1986; Modin, 1994), and conversely, NPY Y_1 receptors may exist prejunctionally (Doods and Krause, 1991). The amino acid sequences close to the NPY termini are essential for receptor binding. Both NPY Y_1 and NPY Y_2 receptors are activated by the whole NPY molecule and the homologous PYY, but the NPY Y_1 receptor is not stimulated after alterations (elimination or substitution) of N-terminus residues, while C-terminus substitutions can be made without loss of ligand potency (Grundemar et al., 1992; Herzog et al., 1992; Larhammar et al., 1992; Fuhlendorff et al., 1990). Thus, all N-terminally truncated versions of NPY, such as NPY (2–36), NPY (3–36) and NPY (13–36), have no or low affinity for the NPY Y_1 receptor.

Activation of the NPY Y_2 receptor is independent of the N-terminus sequence but the receptor is potently activated by smaller C-terminal fragments such as NPY (13–36) (Colmers et al., 1991; Grundemar et al., 1993; Porter et al., 1994). The NPY Y_2 receptor may constitute a selective target for NPY Y_2-ligands. For instance, in the porcine brain NPY (3–36), representing about 35% of total NPY-like immunoreactivity, is a highly selective endogenous NPY Y_2 receptor ligand (Grandt et al., 1996). Although the NPY Y_2 receptor sequence is surprisingly different from that of the NPY Y_1 receptor (31% homology), cloned rat (Gerald et al., 1995) and human (Rose et al., 1995) NPY Y_2 receptors are almost identical. Thus, although the homology within the NPY receptor family is remarkably low, the respective NPY receptor subtype can show a highly conserved structure between mammalian species (see the work of Blomquist and Herzog (1997)). Since the cloned NPY Y_2 receptor is expressed in limited amounts in the periphery even though specific NPY Y_2 binding sites are present, the existence of an additional NPY Y_2 receptor subtype has been suggested.

In heart myocytes NPY (18–36) competitively inhibit ^{125}I-NPY binding, attenuate NPY-evoked inhibition of adenylyl cyclase activity and yet be devoid of any agonist activity per se (Balasubramaniam and Sheriff, 1990). Subsequently, a third NPY receptor subtype (Y_3) was described in the rat heart (see the work of Balasubramaniam

Table 3
Examples of localization and functional effects of NPY Y_1 and NPY_2 receptor subtypes which have been suggested to be involved in the peripheral regulation of vascular tone

Receptor subtype	Biological effect	Localization	Ref.
Y_1	vasoconstriction	rabbit saphenous vein	Cadieux et al., 1993
		guinea pig mesentery	Porter et al., 1994
		human subcutaneous arteries	Nilsson et al., 1996
		rat mesentery	Donoso et al., 1997
		pig kidney, hindlimb, guinea pig vena cava	Malmström, 1997
		cat skeletal muscle	Ekelund and Erlinge, 1997
		rat kidney	Bischoff et al., 1997
		hamster cheek pouch	Kim et al., 1997
		horse ureter	Prieto et al., 1997
		dog coronary circulation	Tanaka et al., 1997
	potentiation of NA vasoconstriction	human omental arteries	Bergdahl et al., 1996
	potentiation of phenylephrine, tyramine vasoconstriction	pithed rat	Zhao et al., 1997
	stimulation of Ca^{2+} efflux	rat cardiomyocytes	Horike et al., 1997
	increase $[Ca^{2+}]_i$	SK-N-MC cells	Rudolf et al., 1994
		pig aortic smooth muscle cells	Shigeri et al., 1995
Y_2	inhibit NA release	rat vas deferens	Porter et al., 1994
		human atrium, kidney rabbit kidney	Rump et al., 1997
	inhibit vagal efferents	rat vagus DMN	Chen and Rogers, 1997
	vasoconstriction	pig spleen	Modin, 1994
		dog saphenous vein	Pheng et al., 1997
	potentiation of NA contraction	horse ureter	Prieto et al., 1997
	inhibit vasoconstriction	guinea pig intestine	Neild and Lewis, 1995
	inhibit parasympathetic vasodilatation	dog nasal arteries	Lacroix et al., 1994

DMN = dorsal motor nucleus.

(1996)). It is also present in the rat nucleus tractus solitarius where it evokes cardiodepressor effects (Grundemar et al., 1991), as well as in the distal colon where it causes contraction (Dumont et al., 1994).

In addition, a fourth and fifth NPY receptor subtype (Y_4 and Y_5) have been cloned. The NPY Y_4 subtype is present in the periphery including the heart, skeletal muscle, lung, intestines, and centrally in the hypothalamus, thalamus and amygdala. The function of the NPY Y_4 receptor is currently unknown. The NPY Y_5 subtype is found centrally in the hypothalamus, where it is of importance in feeding behaviour, and with anticonvulsant effects (Bard et al., 1995; Lundell et al., 1995; Gerald et al., 1996; Hu et al., 1996; Woldbye et al., 1997). The functional characteristics of a postulated NPY Y_6 receptors remain to be further substantiated (Gregor et al., 1996).

The localization and functional effects of NPY receptors varies between species, organs and even within organs studied. In the pig kidney and hindlimb the NPY Y_1 is the sole vascular NPY receptor subtype. In the pig spleen, on the other hand, both NPY Y_1 and NPY Y_2 receptors are found and NPY Y_2 receptor agonists are 4 times more potent than NPY Y_1 receptors agonists in causing vasoconstriction. In the dog spleen, by way of contrast, NPY Y_1 receptors, but not NPY Y_2 receptors are involved in vasoconstriction, indicating that the canine splenic NPY Y_2 receptor may be situated in non-vascular components. Also, in the dog kidney NPY Y_1 receptors were found to be the predominant NPY receptor subtype (see the work of Malmström (1997)).

3.4. Neuropeptide Y Y_1 receptor antagonists

A thorough evaluation of a possible role of NPY in sympathetic vascular control has long been hampered by the lack of selective, non-peptide antagonists. The development of NPY antagonists has come about either through random screening or by the use of derivatives and fragments of the NPY molecule. By replacing Ile^{31} and Glu^{34} in porcine NPY with the corresponding residues from human PP (Leu and Pro, respectively) the first NPY Y_1 receptor antagonist was created and called [$Leu^{31}Pro^{34}$]-NPY (Fuhlendorff et al., 1990). Due to interaction with the NPY Y_4 and NPY Y_5 receptor subtypes, [$Leu^{31}Pro^{34}$]-NPY has a limited use as NPY Y_1 antagonist, though. Subsequently, a number of modifications of NPY and analogues, including the hexapeptide BRC 672 (corresponding to residues 22–27 of NPY) and the nonapeptide 1229U91 ((Ile-Glu-Pro-Dpr-Tyr-Arg-Leu-Arg-Tyr-NH_2)$_2$), have been used in attempts to achieve selectivity in NPY Y_1 receptor blockade. In addition, the peripheral effects of NPY Y_1 activation have been evaluated by the use of several non-peptide NPY Y_1 receptor antagonist such as benextramine (dithiobis(*N*-(*N*-(2-methoxybenzyl)-6-aminohexyl)-2-aminoethane)*N*,*N*-bis(6-(*o*-methoxybenzyl aminono)hexyl)cystamine) (see the work of Balasubramaniam (1996)). The lack of specificity and the fact that their binding is sometimes irreversible has limited their use, however.

Once it had been recognized that especially the Arg^{35} and Tyr^{36} of the C-terminal fragments are of major importance for the interaction with the NPY Y_1 and NPY Y_2 receptors, a number of analogues similar to the C-terminal part of NPY were developed, including BIBP 3226 ((*R*)-*N*2-(diphenylacetyl)-*N*-((4-hydroxyphenyl)methyl)-D-arginine-amide) (see the work of Doods et al. (1996) and Table 4). BIBP 3226 exerts no agonist activity on NPY Y_1 receptors and in typical NPY Y_1 receptor assays for binding studies the affinity of BIBP 3226 to the human and rat NPY Y_1 receptor is around 5 and 7 nM, with no affinity for the NPY Y_2 receptors (Abounader et al., 1995; Doods et al., 1996). The NPY Y_1 binding affinity corresponds well with the IC_{50} value of 27 nM for inhibition of NPY Y_1-evoked vasoconstriction in the rat kidney and pA_2

Table 4
Examples of identified NPY Y_1 receptor-mediated vasoconstriction as determined by antagonists used

Tissue	Antagonist	Refs.
human omental arteries	BIBP 3226	Bergdahl et al., 1996
subcutaneous arteries	BIBP 3226	Nilsson et al., 1996
mesenteric arteries, veins	BIBP 3226	Racchi et al., 1996
cerebral arteries	BIBP 3226	Abounader et al., 1995
rat kidney, pithed rat	BIBP 3226	Rudolf et al., 1994
tail artery	BIBP 3226	Gicquiaux et al., 1996
kidney	BIBP 3226	Bischoff et al., 1997
mesenteric vascular bed	BIBP 3226	Zukowska-Grojec et al., 1996; Donoso et al., 1997
pig hindlimb, kidney	BIBP 3226	Malmström, 1997
dog coronary circulation	BIBP 3226	Tanaka et al., 1997
guinea pig vena cava	BIBP 3226	Malmström, 1997
hamster cheek pouch	GW 383 GW 1229	Kim et al., 1997
guinea pig blood pressure	SR 120819A	Serradeil-Le Gal et al., 1995
guinea pig vena cava	SR 120107A	Malmström, 1997
pig kidney	SR 120107A	Malmström, 1997

values around 8 in various vascular preparations. The NPY Y_1 selectivity of BIBP 3226 has been demonstrated in various NPY Y_1 receptor assays including rat cortex and the human neuroblastoma cell line SK-N-MC in which ^{125}I-NPY receptor binding and NPY-evoked stimulation of cAMP production (SK-N-MC) was inhibited (Rudolf et al., 1994, 1997). Thus, BIBP 3226 selectively binds to the NPY Y_1 receptor and has 1000- to 10 000-fold lower affinity for NPY Y_2 receptors in vascular preparations from several species including guinea pig, rabbit, rat and man. The binding of BIBP 3226 is approximately equal in all species tested so far and thus, BIBP 3226 does not discriminate between vascular NPY Y_1 receptors among species.

Tritiated BIBP 3226 can be used as a highly selective radioligand for the NPY Y_1 receptor (Entzeroth et al., 1995). Thus, displacement of [^{3}H]BIBP 3226 binding to NPY Y_1 receptors has been demonstrated in membrane preparations from the dog and pig spleen by using cold BIBP 3226, NPY Y_1 agonists, as well as SR 120701A ((1-(2-(2-(2-naphtyl-sulfamoyl)-3-phenylpropionamido)-3-(4-(*N*-(4-(dimethylamino-methyl)-*trans*-cyclohexylmethyl) amidino)phenyl)propionyl)pyrrolidine) (Lundberg and Modin, 1995; see the work of Malmström (1997)). Stereoselectivity for BIBP 3226 has been demonstrated as the *S*-enantiomer of the *R*-configured BIBP 3226 (denoted BIBP 3435) has 1000-fold less affinity for the NPY Y_1 receptor (Rudolf et al., 1994) and may therefore be used as a control substance when evaluating NPY Y_1 receptor blockade by BIBP 3226 (Doods et al., 1996).

Other recently identified low molecular weight antagonists with similar affinity for the NPY Y_1 receptor as BIBP 3226 in several species include SR 120107A and 120819A (1-(2-(2-(2-naphtylsulfamoyl)-3-phenylpro-pionamido)-3-(4-(*N*-(4-(dimethyl-aminomethyl)-*cis*-cyclohexyl-methyl) amidino)phenyl)propionyl)-pyrrolidine) (Serradeil-Le Gal et al., 1994, Serradeil-Le Gal, 1997), the latter of which is also orally active. SR 120107A was first reported to displace NPY Y_1 binding in rat cortex and in the human neuroblastoma cell line SK-N-MC cells (Serradeil-Le Gal et al., 1994) and it was soon demonstrated that also Y_1-mediated vasoconstriction was antagonized by SR 120107A. SR 120701A is equipotent to BIBP 3226 in antagonizing NPY Y_1 responses in vitro, i.e., guinea pig vena cava and rat vas deferens (Serradeil-Le Gal et al., 1994; Malmström, 1997), as well as in the pig in vivo (Malmström, 1997). The orally active SR 120819A, however, has slightly lower affinity than BIBP 3226.

GW 282 (Tyr-Arg-Leu-Arg-Tyr-Dpr-Pro-Ile-Glu-Pro-Dpr-Tyr-Arg-Leu-Arg-Tyr)$NH_2)_2$) and GW 1229 ((Tyr-Arg-Leu-Arg-Tyr-Dpr-Pro-Glu-Ile-Ile-Glu-Pro-Dpr-Tyr-Arg-Leu-Arg-Tyr)$NH_2)_2$) are two more newly described NPY Y_1 antagonists which block the NPY-evoked vasoconstriction in the rat and hamster (Daniels et al., 1995; Kim et al., 1997)

Using in vitro vascular preparations, the NPY Y_1 blocking properties by BIBP 3226 have been demonstrated in the rat perfused kidney, guinea pig vena cava, rabbit vas deferens, human cerebral arteries and rabbit saphenous veins and ear arteries (Abounader et al., 1995; Doods et al., 1995; Jacques et al., 1995; Malmström, 1997). The structural similarities of the various mammalian NPY Y_1 receptor are apparent from the fact that the pK_b value for BIBP 3226 is similar in NPY Y_1 preparations from different species. Furthermore, the pA values for the antagonism evoked by SR 120107A and BIBP 3226 in the guinea pig caval vein are similar, and no agonist effect was observed, further demonstrating NPY Y_1-selective antagonism. In accord, SR 120107A and BIBP 3226 does not influence the vasoconstrictor effect of endothelin, vasopressin, noradrenaline, angiotensin II or phenylephrine in the rat or pig in vivo (Doods et al., 1995; Malmström, 1997).

In vivo porcine experiments have also demonstrated the high selectivity of BIBP 3226 in antagonizing the response to NPY Y_1-mediated vasoconstriction in the kidney and hindlimb while leaving the NPY Y_2-mediated vasoconstriction in the spleen unaffected (Malmström, 1997). Also in the pithed rat model, BIBP 3226 is a selective NPY Y_1 receptor antagonist (Doods et al., 1995). The NPY-blocking effect of BIBP 3226 are relatively short-lasting, in contrast to the effects of SR120819A, which 4 h after oral administration still inhibits the pressor effect of NPY Y_1 receptor agonists in the guinea pig (Serradeil-Le Gal et al., 1995). Neither BIBP 3226 nor SR 120107A influence the outflow of noradrenaline or NPY from the pig spleen or kidney, suggesting that prejunctional NPY Y_1 receptors are of relatively minor importance in these organs.

3.5. Vascular effects of neuropeptide Y

A possible physiological role of NPY was originally suggested in a study on the cat submandibular gland, where a peptidergic-like, i.e., slowly developing and long-lasting, α-adrenoceptor-independent vasoconstriction was observed after sympathetic stimulation (Lundberg and Tatemoto, 1982). A similar effect could be reproduced by injections of NPY. Later this phenomenon was described in several preparations (see Table 1). The existence of a large non-adrenergic component is especially apparent following sympathetic nerve stimulation with high frequencies and irregular bursts, which also favours NPY release (Lacroix et al., 1988a; Pernow et al., 1987a,b; Modin, 1994).

NPY causes profound pressor effects when administered in vivo. The increase in blood pressure by NPY is due to increased vascular resistance, as well as increased cardiac stroke volume secondarily to an increased venous return (MacLean and Hiley, 1990). The sensitivity of different organs to i.v.-administered NPY largely depends on the species investigated. In the rabbit (Minson et al., 1989) and rat (Gardiner et al., 1988), the renal vascular

bed is most sensitive while the splenic circulation is most sensitive in the pig (Rudehill et al., 1987). In man, NPY has been demonstrated to cause constriction of the coronary (Clarke et al., 1987), skeletal muscle (Pernow et al., 1987a,b) and renal and splanchnic (Ahlborg et al., 1991) vascular beds. Supersensitivity to the pressor effects of NPY following chemical or surgical sympathectomy has been demonstrated both in the rat (Nield, 1987; Mabe et al., 1987; Benarroch et al., 1990) and pig (Lacroix, 1989). Since in the pig nasal mucosa also $\alpha\beta$metATP- and α_2-agonist-evoked vasoconstriction was enhanced, the observed supersensitivity could to some extent reflect changes in intracellular pathways rather than specific up-regulation of receptors.

Reserpine is a useful tool for evaluating the effects of NPY under in vivo conditions (Lundberg et al., 1985b,c). Thus, reserpine pretreatment depletes the peripheral tissue stores of noradrenaline while leaving those of NPY largely unaffected provided the neuronal activity has been impaired pharmacologically (by clonidine, guanethidine or chlorisondamine) or surgically (by denervation). High-frequency stimulation of sympathetic nerves in a variety of organs under in vivo conditions while there is still NPY (and ATP, see above) in the peripheral nerve terminals reveals only a long-lasting vasoconstriction strongly correlated with NPY outflow and subject to fatigue upon repeated stimulation, probably owing to restricted terminal resupply of NPY by axonal transport (see the works of Pernow (1988) and Lacroix (1989)). However, taking into account that noradrenaline inhibits NPY release, the nerve stimulation-evoked NPY release after noradrenaline depletion by reserpine is likely to be overestimated.

ATP mechanisms have been evaluated in some of these in vivo models. In the pig nasal mucosa (Lacroix et al., 1988b), $\alpha\beta$metATP mimics the vascular responses to sympathetic nerve stimulation after α-adrenoceptor blockade combined with reserpine pretreatment, while ATP given intra-arterially causes a short-lasting vasoconstriction followed by vasodilatation. It should be emphasized, however, that endogenously released ATP is likely to reach receptors other than those activated by exogenous ATP. Furthermore, since $\alpha\beta$metATP inhibits NPY release in reserpine-pretreated pigs but not in controls, it is difficult to draw conclusions about the contribution of ATP in reserpine-resistant sympathetic vasoconstriction. It seems clear that after depletion of noradrenaline and NPY by reserpine pretreatment, no ATP component can be demonstrated in many vascular preparations. Therefore, the use of highly selective NPY Y_1 receptor antagonists such as BIBP 3226 may not only reveal NPY functions but also unmask possible ATP-mediated vascular effects. Actually, incomplete blockade of human mesenteric vasoconstriction by BIBP 3226 may indicate a role for ATP in sympathetic vasoconstriction (Racchi et al., 1996).

It has been difficult to consistently show vasoconstrictor effects of NPY in vitro while, in vivo, NPY is almost always a potent vasoconstrictor regardless of the vascular bed studied (Rudehill et al., 1986). This may be related to the fact that experiments using in vitro techniques study relatively large blood vessels whereas in the intact animal, NPY exerts its main effects on small resistance vessels (Hughes et al., 1988; Franco-Cereceda, 1989). The vascular reactivity to NPY is also rapidly lost in isolated organ models (Allen et al., 1983; Franco-Cereceda et al., 1985). There have been, however, many reports on potent vasoconstrictor effects of NPY in several different isolated blood vessel preparations, including cat cerebral arteries (Edvinsson et al., 1983; Laher et al., 1994), rabbit blood vessels (Edvinsson et al., 1984), human coronary arteries (Franco-Cereceda and Lundberg, 1987), human mesenteric veins, renal and skeletal muscle arteries (Pernow et al., 1987a,b), guinea pig uterine artery and vena cava (Morris and Murphy, 1988; Morris, 1991) and the rat femoral artery (Lundberg et al., 1985a). The vasoconstrictor effect of NPY is slow in onset, long-lasting and endothelium-independent; repeated administration of NPY induces tachyphylaxis and the response can be blocked by antiserum to NPY.

Strong evidence for direct participation of NPY in sympathetic vasoconstriction in vitro has been presented by Morris and Murphy (1988) and Morris (1991) in experiments on guinea pig uterine arteries and vena cava, where vasodilator axons had been surgically removed prior to the experiments. Thus, the neurogenic contraction and the contraction evoked by exogenous NPY, but not noradrenaline, were reduced by trypsin (which cleaves peptides containing the amino acids lysine or arginine), and following NPY desensitization, the slow phase of the neurogenic vasoconstriction, but not the prazosin-sensitive portion, was reduced.

The vasoconstrictor effect of NPY is not influenced by α- or β-adrenoceptor blocking agents (Lundberg and Tatemoto, 1982) but can be attenuated by Ca^{2+}-channel blockers like nifedipine, verapamil, diltiazem and nimodipine (Edvinsson et al., 1983; Edvinsson, 1985; Pernow, 1988). More recently it was suggested that the sustained contractions in response to NPY are mediated through a prolonged smooth muscle depolarization with continuous refilling of calcium stores (Fallgren et al., 1990).

The development of highly selective NPY Y_1 antagonists has provided us with tools to address the existence of NPY-mediated sympathetic vasoconstriction. The long-lasting, adrenoceptor-independent, vasoconstriction of the guinea pig vena cava in response to electrical field stimulation in vitro is substantially shortened in the presence of BIBP 3226, while the initial fast response, which is sensitive to alpha-adrenoceptor blockade, remains unchanged (Malmström, 1997). Also after depletion of the noradrenaline stores by reserpine pretreatment (see above), the non-adrenergic sympathetic vasoconstriction in the pig kidney and hindlimb is markedly reduced by NPY Y_1 blockade using either BIBP 3226 or SR 120701A (Malmström,

1997), supporting the suggestion that NPY and NPY Y_1 receptors are involved in the vascular responses enumerated in Table 2.

However, in animals with intact noradrenaline levels it has been more difficult to demonstrate involvement of NPY receptors mediating sympathetic vasoconstriction. This may be due to the prejunctional inhibitory effect of noradrenaline on NPY release. BIBP 3226 attenuates the guanethidine-sensitive increase in perfusion-pressure in the rat mesenteric bed evoked by electrical field stimulation, without influencing the concomitant release of NPY (Donoso et al., 1997). BIBP 3226 has also been used to demonstrate that NPY reduces the rat renal blood flow by acting through NPY Y_1 receptors but has, surprisingly, no effects on diuresis, natriuresis or calciuresis (Bischoff et al., 1997). In the cat skeletal muscle, NPY activation of BIBP 3226-sensitive NPY Y_1 receptors caused constriction preferentially of small arteries (Ekelund and Erlinge, 1997). Usually BIBP 3226 has been administered by bolus injections of up to 3 mg/kg i.v. but it should rather be infused over an extended period of time (Malmström, 1997).

It has been difficult to demonstrate a selective and dose-dependent vasodilatation in response to the NPY Y_1 antagonists when administered in vivo suggesting that there is no basal endogenous NPY tone. Furthermore, neither BIBP 3226 nor the NPY antagonist 1229U91 (blocking both NPY Y_1 and NPY Y_2 receptors) influenced the blood pressure in spontaneously hypertensive rats (SHR; Doods et al., 1995; Tadepalli et al., 1996). The possible existence of an intrasynaptically located non-NPY Y_1 receptor subtype that is insensitive to BIBP 3226 seems unlikely and needs further experimental substantiation (see the work of Doods et al. (1995)). Zukowska-Grojec et al. (1996) demonstrated that BIBP 3226 partially restored blood pressure in cold-stressed rats, suggesting that the level of sympathetic tone may indeed determine the effect of NPY antagonists. Caution is advised in interpreting these findings though, since hypotensive effects of NPY antagonists (i.e., both the active and inactive enantiomers of BIBP) may actually represent non-specific effects such as histamine release due to mast cell activation.

3.6. Central cardiovascular effects of neuropeptide Y Y_1 receptor activation

The nucleus tractus solitarius is the relay nucleus for integrating cardiovascular reflexes and is a key area in central cardiovascular control. Here, the cardiovascular effects of NPY involve both the activation of NPY receptors and the modulation of other neurotransmitter receptors such as glutamate, angiotensin II, vasopressin and α-adrenoceptors (see the work of Yang et al. (1994)). NPY administered centrally to rats evokes vasodepressor and bradycardic responses; C-terminal fragments evoke vasopressor effects and can counteract the effect of NPY (Aguirre et al., 1995), an effect especially apparent in SHR. Furthermore, NPY Y_1 receptor binding is lower in SHR than in other rat strains. Dominance of NPY Y_2 transduction in the nucleus tractus solitarius may therefore be of importance in the development and treatment of hypertension.

3.7. Interaction with noradrenaline

Although direct contractile effects of NPY are usually not as apparent in vitro as in vivo, NPY often enhances the vasoconstrictor effect of noradrenaline in vitro (Edvinsson et al., 1984; Ekblad et al., 1984; Glower, 1985; Wahlestedt et al., 1985), as well as in vivo (Dahlöf et al., 1985a; Revington and McCloskey, 1988; Linder et al., 1996). NPY also potentiates the vasoconstriction response to phenylephrine, sympathetic nerve stimulation (Dahlöf et al., 1985b), histamine (Ekblad et al., 1984; Han and Abel, 1987), tyramine (Waeber et al., 1988), angiotensin and vasopressin and $\alpha\beta$metATP (Saville et al., 1990). In some, but not all vessels, NPY does not influence the effects of prostaglandin $F_{2\alpha}$, serotonin or high potassium concentrations (Edvinsson et al., 1984), indicating that the potentiation is dependent on the vascular preparation studied. Therefore, this effect may not be caused by a general change in smooth muscle reactivity with increased Ca^{2+}-influx (Glower, 1986; Andriantsitohaina and Stoclet, 1988) but rather suggests that NPY induces specific changes in receptor characteristics and/or second messenger systems. NPY-evoked contractions are not influenced by removal of the endothelium (Pernow and Lundberg, 1988; Fallgren et al., 1990) and a possible involvement of the endothelium in the NPY-induced enhancement of noradrenaline-evoked contractions (Daly and Hieble, 1987) is thus unlikely (Budai et al., 1989). NPY inhibits forskolin-induced adenylyl cyclase stimulation (Fredholm et al., 1985) and this pertussis toxin-sensitive inhibitory pathway has been suggested to be involved in the potentiating effect of NPY on noradrenaline-evoked vasoconstriction (Kassis et al., 1987). Although the vasoconstrictor effect of NPY is highly dependent on calcium influx, the potentiating effect is not influenced by nifedipine but seems rather to require sodium influx followed by mobilization of intracellular Ca^{2+} and increased phospholipase C activity; this would be an alternative explanation for the synergism between NPY and noradrenaline (Wahlestedt et al., 1985, 1990). Nifedipine does not influence NPY-evoked inhibition of noradrenaline release, a fact which excludes the possibility of any presynaptic action of this drug.

Interestingly, BIBP 3226 attenuated both the direct vasoconstrictor effect of NPY in the rat kidney and the potentiation of the noradrenaline-evoked vasoconstriction in the rat mesentery, clearly suggesting that NPY Y_1 receptors mediate NPY-evoked potentiation of vascular effects exerted by other vasoconstrictors.

3.8. Physiological and pathophysiological implications of neuropeptide Y in sympathetic transmission

Plasma levels of NPY are correlated with those of noradrenaline and an increase in plasma noradrenaline by reflex sympathetic discharge is accompanied by an increase in NPY levels, with an increasing NPY ratio the higher the frequency (see the works of Pernow (1988) and Lacroix, 1989). The actual contribution from various possible sources, such as the brain, peripheral nervous system, enteric nervous system and the adrenals, to plasma NPY may differ under various conditions, however. Resting NPY plasma levels are low in most species, including man (around 20 pM; Pernow, 1988), with a biphasic disappearance curve and half-lives of 4 and 20 min, for the two respective slopes (Pernow et al., 1987a,b). Sympathetic activation by exercise releases NPY (Morris et al., 1986), but the actual contribution of NPY in sympathetic transmission under physiological conditions remains to be established.

With regard to pathophysiological situations, there are many reports of possible NPY involvement in a variety of cardiovascular disorders. Thus, experimental ligation of the coronary arteries reduces cardiac levels of NPY (Han et al., 1989) and an increased NPY outflow from the human heart is observed in response to cardiac ischaemia (Franco-Cereceda et al., 1990). Since the peripheral plasma NPY- and noradrenaline-levels were also increased, it is likely that an enhanced sympathetic discharge, rather than an energy deficiency, caused the alterations in NPY levels and the release from the heart. This is supported by the finding that total stop-flow ischaemia of isolated hearts does not release NPY (Franco-Cereceda et al., 1989).

Elevated plasma levels of NPY are found in patients with left heart failure, angina pectoris and myocardial infarction, indicating that NPY may contribute to the clinical signs of haemodynamic disturbance observed in these conditions (Maisel et al., 1989; Ullman et al., 1990; Hulting et al., 1990). Intracoronarily-administered NPY in humans with angina pectoris causes cardiac ischaemia (Clarke et al., 1987). The potent direct coronary vasoconstrictor effect of NPY can be prevented by Ca^{2+}-channel blocking agents (Franco-Cereceda et al., 1985; Franco-Cereceda, 1989) whereas α-adrenoceptor blockade is ineffective (Allen et al., 1983; Aizawa et al., 1985), implying that NPY may be involved in coronary vasospasm, which is known to respond to inhibition of Ca^{2+} influx but responds poorly to α-adrenoceptor blockade (see the work of Corr et al. (1990)).

NPY Y_1 but not NPY Y_2 receptor function is inhibited by nitric oxide-donors (Dötsch et al., 1997), which suggests that NPY-evoked vasoconstriction may not merely be counteracted by direct vasodilator effects of nitric oxide, but also more directly by suppression of the NPY Y_1 receptor; this may have implications for nitrate treatment of coronary vasospasm. Interestingly, age and hyperlipidaemia enhance the coronary vasoconstrictor response to NPY (Corr et al., 1993). In addition, NPY stimulates proliferation of smooth muscle cells and cardiomyocytes (Shigeri and Fujimoto, 1993; Millar et al., 1994) with possible pathological implications in cardiac disease states. Subarachnoid haemorrhage is associated with increased NPY levels in the cerebrospinal fluid (Abel et al., 1988) and decreased neuronal levels of NPY, suggesting that NPY may also contribute to cerebral vasospasm (Jackowski et al., 1989).

In SHR, the inhibitory effect of NPY on noradrenaline release is weaker and the vasoconstrictor effect of NPY is stronger than in normotensive rats, evidence which is in support of a role for NPY in the development and maintenance of hypertension (Westfall et al., 1988). Elevated plasma levels of NPY have been detected in patients with hypertension (Edvinsson et al., 1991) and hypertension in phaeochromocytoma is also associated with highly elevated plasma levels of NPY (up to nM; see the work of Adrian et al. (1983)). The finding that BIBP 3226 partially normalized the elevated blood pressure in cold stressed rats without influencing NPY release or the noradrenaline-evoked tachycardia, further stresses that important actions of NPY and NPY antagonists may depend on the level of sympathetic activation (Zukowska-Grojec et al., 1996).

NPY is preferentially released by high-frequency stimulation and the vasoconstrictor activity of NPY is most apparent during stimulation that leads to a high degree of sympathetic nerve activity. Adrenergic desensitization by increased neuronal discharge is reversed by NPY. This may represent an additional mechanism for modulation of sympathetic transmitter effects, and could be of use in reversing therapeutically-induced desensitization to adrenergic drugs (Wahlestedt et al., 1990). The vasoconstrictor effect of NPY may also be beneficial in the treatment of hypotension induced by for instance endotoxaemia (Evéquoz et al., 1988), a condition in which plasma NPY levels are elevated (Watson et al., 1988).

4. Summary and concluding remarks

It spite of tremendous advances in technology and methodology in the last few decades, advances that have opened up new possibilities of studying previously poorly known biologically active agents, the extent to which NPY contributes to neurotransmission under physiological and pathophysiological conditions still remains unclear. An abundance of indirect evidence strongly implies important functions for NPY in cardiovascular control. The recent development of antagonists selective for the different NPY receptor subtypes has given us the tool we need to properly address the questions, ''how is NPY involved in basal vascular control and what are its role in cardiovascular disease?'' We are likely to see some of these questions answered within a few years.

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