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Role of neuropeptide Y in the regulation of kidney function

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Introduction

Neuropeptide Y (NPY), a 36-residue peptide is a sympathetic co-transmitter stored and released together with noradrenaline by adrenergic nerve terminals of the sympathetic nervous system. Structurally, NPY shares high homology with two other members of the pancreatic polypeptide family, Peptide YY (PYY) and pancreatic polypeptide (PP). These two closely related peptides are produced and released by the intestinal endocrine cells and pancreatic islet cells respectively, and acts as hormones [1, 2]. Although NPY was originally isolated from the brain and is highly expressed in the central nervous system (CNS), it has been clearly demonstrated that NPY exhibits a wide spectrum of biological activities in peripheral organs such as the cardiovascular system, the gastrointestinal tract and the kidney [3–9]. The following chapter will focus primarily on the kidney and summarize shortly our knowledge on the role of NPY in the regulation of renal function. Two excellent reviews on the subject have been published in the past by Presson et al. [8] and Bischoff and Michel [9].

NPY and the kidney

NPY localization in the kidney

Shortly after its original identification in the early eighties by Tatemoto et al. [10], NPY was reported to exist in the dense plexus of nerve fibers around the renal juxtaglomerular apparatus, by immunohistochemical staining [11]. Since then, numerous studies have confirmed the presence of the peptide in the kidney of man, rat, monkey, mouse, hamster and guinea pig [11–14]. The peptide has been localized to adrenergic nerve endings in all segments of the renal arterial system [15, 16], including the juxtamedullary regions, and afferent and efferent arterioles at the vascular pole of the glomeruli [14]. Moreover, using

specific antibodies against the C-flanking region of NPY, positive staining was found in the renal tubules but not in glomeruli of the human kidney [17]. This suggests that the peptide may also be generated in the nephron itself and not only in sympathetic terminals innervating the kidney.

NPY receptors and signaling

The biological actions of NPY are mediated through G-protein coupled receptors that are also activated by the two other peptides family members, PYY and PP [9, 18]. Six receptor subtypes (denoted Y_{1-5} and y^6) have been identified in mammalian tissues [18, 19]. There is convincing evidence for the presence of the Y_1 receptor subtype in the kidney, based on mRNA expression studies by Northern blotting, reverse transcriptase polymerase chain reaction (RT-PCR), and *in situ* hybridization [20, 21]. In addition to the expression in renal blood vessels, media and intima, mRNA of Y_1 was also localized to the renal collecting ducts, loop of Henle, and juxtaglomerular apparatus [21]. Radioligand binding studies as well as pharmacological characterization with selective NPY agonists/antagonists provided further evidence for the existence of the Y_1 and probably Y_2 in the kidney of various species [9]. However, it appears that considerable heterogeneity exists in this regard. Thus, some studies have demonstrated abundant NPY binding in the rabbit kidney and significantly less or negligible binding in the human and rat kidney [9]. In the renal papilla, high-affinity binding sites to the related peptide PYY were identified, and are thought to be of the Y_2 subtype in the rabbit kidney, and of the Y_1 subtype in the rat kidney [22]. Finally, the natriuresis and diuresis caused by NPY in rats have been suggested to be mediated in part by Y_5 receptor, based on pharmacological characterization [23, 24]. Yet, several studies failed to detect mRNA expression of Y_5 outside of the CNS [24, 25]. This might suggest the existence of a novel, currently unidentified, Y_5-like receptor in the kidney, or alternatively, that these effects of NPY could be mediated indirectly by the actions of the peptide in extra-renal tissue [24].

As pointed out earlier, all NPY receptors belong to the family of seven transmembrane domains of the G-protein coupled receptors. Renal NPY receptors preferentially act through the pertussis toxin-sensitive G_i/G_0 family, and are predominantly linked to inhibition of adenylate cyclase [9]. In addition, there is evidence that NPY receptors may be positively linked to intracellular calcium $[Ca^{2+}]_i$ through stimulation of Ca^{2+} channels, stimulation of phospholipase C, and mobilization of Ca^{2+} from intra-cellular stores [18]. Finally, in the isolated kidney preparation, NPY has been reported to stimulate prostaglandin E_2 and I_2 production in a Ca^{2+} calmodulin-dependent manner, suggesting a possible coupling between the NPY receptor and phospholipase A_2 [26].

Effects of NPY on renal function

Renal blood flow and renal vascular resistance

Renal vasoconstriction associated with an increase in mean arterial pressure (MAP) is perhaps the best documented and most consistent finding following exogenous administration of NPY [8, 9]. Numerous studies utilizing both *in vivo* and *in vitro* techniques have demonstrated the capacity of the peptide to reduce renal blood flow (RBF) and increase renal vascular resistance (RVR) in various species including rat, rabbit, pig and man [23, 26–34]. Compared with other blood vessels, such as the mesenteric and hindlimb vascular beds, the kidney appears to be uniquely sensitive to the vasoconstrictor effect of the peptide [31]. Intrarenal infusion of NPY reduced RBF to a greater extent than systemic infusion of the peptide [29]. In the split hydronephrotic rat kidney, systemic infusion of low non-pressor doses of NPY produced a non-uniform pattern of vascular reactivity, causing a significant constriction of the proximal and distal parts of the arcuate artery with all doses [35]. No constriction was seen at the interlobular artery or the larger part of the afferent arteriole. The very distal part of the afferent arteriole adjacent to the glomerulus and the proximal efferent arteriole responded in a similar way to the arcuate arteries [35]. This pattern suggests a differential sensitivity of various segments of the renal vasculature to the vasoconstrictor effect of the peptide. The NPY-induced increase in RVR appears to be mediated by the Y_1 receptor subtype, since it could be mimicked by the Y1-agonist [Leu(31), Pro(34)] NPY, and blocked by the selective Y1-receptor antagonist BIBP 3226 in various species [36, 37]. Moreover, studies in the isolated perfused kidney of rat demonstrated that NPY-induced vasoconstriction could be inhibited by pertussis toxin treatment [38], by the Ca^{2+} channel blockers, diltiazem and nifedipine and also by removal of Ca^{2+} from the perfusates [26]. Additional studies by Bischoff et al. [9] also suggested that release of Ca^{2+} from intracellular stores may be responsible for the sustained phase of vasoconstriction during continuous infusion of the peptide. Taken together, these findings suggest that both inhibition of adenylate cyclase and alterations in $[Ca^{2+}]_i$ may be involved in mediating the renal vasoconstrictor effect of NPY. The $[Ca^{2+}]_i$ dependence of NPY mediated vasoconstriction may also explain the finding that in various vascular beds including the kidney, NPY can potentiate the effects of other vasoconstrictor agents [4]. In particular, studies in the isolated perfused rat kidney demonstrated that the renal vasoconstriction elicited by norepinephrine, arginine vasopressin, and by angiotensin II was enhanced by NPY [26]. Similarly, NPY potentiated the renal vasoconstricting effect of the α_1-agonist methoxamine, and this effect could be blocked by the Y_1 antagonist BIBP 3226 [39]. This phenomenon may be of importance in pathophysiological situations with high sympathetic outflow and increased demand for vasoconstriction.

Glomerular filtration rate

Despite the potent vasoconstrictor effect of NPY on renal vasculature, it appears that this effect is not associated with a similar reduction in glomerular filtration rate (GFR). Indeed, most of the studies in which this parameter was evaluated show only minor or no alterations in GFR in response to NPY administration [23, 29, 30, 40]. In the study of Evequoz et al. [41] it was shown that NPY infusion in the rat did not alter GFR when given alone. However, when GFR was increased by prior administration of the β-receptor agonist isoproterenol, NPY caused a significant reduction in GFR [41]. The finding that GFR was minimally affected by the same doses of NPY that caused a substantial reduction in RBF might suggest that the peptide has a greater vasoconstricting effect on the efferent than on the afferent arteriole. Indeed, this notion is compatible with the finding of Dietrich et al. [35] in the split hydronephrotic kidney that NPY constricted only the very distal part of the afferent arteriole but not its larger more proximal part. Recently, it has been shown that the sympathetic innervation of the glomerulus consists of two distinct populations of axons, type I and II [42]. Type I axons almost exclusively innervate the afferent arteriole, whereas type II axons are equally distributed on the afferent and efferent arterioles. Interestingly, NPY was located only in type II but not type I axons [42]. The functional significance of this finding and whether it may account for the preservation of GFR in the face of reduced RBF remain to be elucidated.

Effects of NPY on renal electrolytes excretion

Considering the potent renal vasoconstrictor action of NPY, a decrease in electrolyte and water excretion could be expected following the administration of the peptide. However, the available data at present suggest that NPY may exert either a natriuretic [23, 28–30, 43] or an antinatriuretic [40, 44] action, depending on the experimental conditions and the species utilized. While in early studies, conducted in dogs and primates, NPY tended to decrease sodium and water excretion, studies in the rat kidney demonstrated clearly an increase in the excretion of sodium, water, calcium and perhaps potassium [9, 29, 45]. The natriuretic/diuretic effect was observed in rats during systemic infusion of the peptide, central intracerebroventricular administration, as well as in the isolated perfused kidney [28, 29, 46]. Studies in humans with the related PYY peptide also revealed a significant increase in urinary sodium excretion following intravenous administration of the peptide [34]. While an antinatriuretic response can be easily explained on the basis of the potent vasoconstrictor properties of the peptide and its effect on renal hemodynamics, the natriuresis/diuresis appears to be mediated by a tubular action that deserves additional explanation. Several mechanisms were offered to explain this finding [9]. A potential mechanism that could account for the

NPY-induced natriuresis is the phenomenon of pressure natriuresis, secondary to the NPY-related increase in MAP [47]. However, controlling renal perfusion pressure by a supra-renal aortic clamp and renal decapsulation did not block the NPY-induced diuresis [29]. This suggests that pressure natriuresis is not the predominant factor in mediating the natriuresis/diuresis caused by systemic NPY administration [9, 29]. An interesting observation in the original study of Bischoff et al. [29] was that systemic infusion of NPY produced a greater natriuretic response compared with intrarenal infusion of the peptide at equal doses. In an additional study, the same group demonstrated that the natriuretic effect of NPY could be mimicked by the Y_5 agonist PYY_{3-36}, and not affected by the classical Y_1 antagonist BIBP 3226 [23]. Since the Y_5 receptor is not expressed in the kidney, the authors hypothesized that Y_5-like receptors in extra-renal tissues may be involved in the mediation of NPY-induced natriuresis and diuresis [24]. In an attempt to identify the mediator pathways linking the extrarenal NPY receptors to the increase in renal sodium, water and calcium excretions, additional experiments were performed. Thus, acute renal denervation did not alter the tubular actions of NPY, suggesting that the putative mediator acts as a hormone rather than a neurotransmitter [48]. Moreover, the NPY-induced diuresis and natriuresis were enhanced by the angiotensin II-converting enzyme inhibitor ramiprilat, not modified by the angiotensin II receptor antagonist losartan, and strongly inhibited by the bradykinin B_2 receptor antagonist icatibant [48]. Based on these findings the authors concluded that bradykinin could be the mediator of the tubular effects of NPY. However, more recent experiments by the same group failed to support this conclusion [49]. Thus, infusion of NPY that caused a four-fold increase in sodium excretion did not increase urinary bradykinin excretion. Furthermore, intrarenal infusion of bradykinin did not alter the urine flow rate or sodium excretion [49]. Other potential mediators of the tubular action of are the cyclooxygenase-derived vasodilatory/natriuretic prostaglandins. It has been reported that treatment with indomethacin did not affect NPY-induced alterations in systemic and renovascular hemodynamics, but completely abolished NPY- and PYY_{3-36}-induced diuresis and natriuresis, indicating that cyclooxygenase derivatives may be involved in this action [50]. Finally, although initial studies did not report an increase in potassium excretion following NPY administration, analysis of the data demonstrated a kaliuretic response under several experimental conditions [45]. Both kaliuresis and diuresis were slow in onset (requiring > 45 min to develop fully) and blocked by the cyclooxygenase inhibitor indomethacin [45].

In summary, in addition to its potent renal vasoconstrictor effect, NPY may exert distinct tubular actions. These are species dependent and in the rat are characterized by a slow onset natriuresis, diuresis, calciuresis and kaliuresis. The cellular mechanisms of, as well as the nephron sites at which the tubular actions of NPY are exerted have not been thoroughly elucidated and remain to be determined.

Effects of NPY on renin secretion

The juxtaglomerular apparatus is richly supplied by nerve endings containing immunoreactive NPY [11]. In addition, Y_1 receptor mRNA was detected in the juxtaglomerular apparatus of murine kidney by *in situ* hybridization [21]. However, in a more recent study, Y_1-immunoreactive staining was detected by immunohistochemistry in the juxtaglomerular apparatus of the mouse but not in rats [51]. Indeed, several studies in the past have suggested that NPY may negatively regulate renin secretion via a pressure-independent, pertussis-sensitive mechanism, involving the Y_1-receptor [23, 34, 38, 52–54]. Such an inhibitory effect was reported in the rat, cat, and humans, but not in dogs or primates [40, 44]. Moreover, NPY was able to lower plasma renin in pathophysiological situations characterized by increased activity of renin-angiotensin system, such as renal artery stenosis and postmyocardial infaction [54, 55]. Further support for an inhibitory action of NPY on renin release emerged from recent reports in Y_1 receptor knockout mice. Thus, plasma renin concentrations were significantly increased in Y_1 knockout mice [56]. Furthermore, using the 2 kidney 1 clip (2K1C) model of renovascular hypertension in mice, it was shown that renin secretion was higher in Y_1-deficient mice than in wild type controls [56]. These findings provide further evidence that renin secretion is controlled in part by NPY via the Y_1 receptor subtype, and that this receptor acts preferentially as an inhibitor of renin release. It is possible that such an NPY-related decrease in plasma renin activity may mediate in part the natriuretic/diuretic effect of the peptide in the rat [9].

Miscellaneous renal effects

In 1989 Dillingham and Anderson demonstrated that NPY significantly decreased arginine vasopressin (AVP)-stimulated water transport in perfused rat cortical collecting tubules [57]. Either α-2-adrenergic receptor blockade (yohimbine) or pretreatment of CCT with pertussis toxin abolished the NPY action on AVP-stimulated water transport, suggesting that NPY acts via an α-2-adrenergic receptor coupled to a pertussis toxin-sensitive protein to inhibit AVP-stimulated cAMP formation and water permeability in the collecting duct [57]. It is possible that such an interaction could contribute to the diuretic effect of NPY in the rat.

Studies by Ohtomo and co-workers [58, 59], using isolated permeabilized rat renal proximal convoluted tubule cells, demonstrated that NPY was able to stimulate Na^+, K^+,-ATPase activity. Removal of extracellular Ca^{2+}, addition of nifedipine the L-type Ca^{2+} blocker, or CaMKII-Ala286[281–302] a blocker of Ca^{2+}/calmodulin-dependent protein kinase II, inhibited the NPY-stimulated Na^+, K^+,-ATPase activity, indicating that this effect was Ca^{2+}-dependent [59]. Additional data from this laboratory suggest that NPY may modulate the renal sympathetic tone by shifting the equilibrium between the α- and β-adrenergic

tonus in the regulation of Na^+, K^+,-ATPase activity [60]. The physiological relevance of this phenomenon remains controversial since in the rat NPY has been shown to exert a natriuretic rather than an antinatriuretic effect.

Studies in genetically-manipulated animals

In recent years, studies using genetic approaches in which the gene of NPY or its receptors were deleted or overexpressed have been published. These investigations, in knockout mice and transgenic mice and rats, provided exciting information unraveling novel biological activities of NPY and its receptors [56, 61, 62]. Interestingly, no major impairments or alterations in renal function have been reported in these genetically-modified models [61]. With the exception of the data of Pedrazzini [56] on the elevated plasma renin activity in Y_1 receptor knockout mice, alluded to in the previous section, noticeable alterations in renal hemodynamics or electrolyte excretion have not been reported. It might be argued that renal function has not been thoroughly and specifically studied in these models. However, given the complex and redundant control of renal hemodynamics and sodium excretion, it is also possible that additional regulatory pathways are activated to compensate for the missing renal action of NPY.

Summary

The presence in the mammalian kidney of NPY and at least one of its receptor subtypes has been proven by several independent methodologies. Also, numerous studies using physiological and pharmacological approaches indicated that this peptide has the capacity to alter renal function. In particular, these studies suggest that NPY may exert renal vasoconstrictor and tubular actions that are species dependent, and may also influence renin secretion by the kidney. The question whether NPY plays an important role in the physiological regulation of renal hemodynamics and electrolyte excretion, remains largely unanswered at present. No major impairments in renal function have been reported in genetically models deficient in NPY or its Y_1 receptor. Thus, additional studies are required to elucidate the role of NPY in the physiological and pathophysiological regulation of renal function.

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