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Neuropeptide Y in neural crest-derived tumors: Effect on growth and vascularization

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Abstract

Neuropeptide Y (NPY) is a sympathetic neurotransmitter recently found to be a potent growth and angiogenic factor. The peptide and its receptors are abundant in neural crest-derived tumors, such as sympathetic neuroblastomas and pheochromocytomas, as well as parasympathetic Ewing's sarcoma family of tumors. NPY regulates their growth directly, by an autocrine activation of tumor cell proliferation or apoptosis, and indirectly, by its angiogenic activity. The overall effect of the peptide on tumor growth depends on a balance between these processes and the type of receptors expressed in the tumor cells. Thus, NPY and its receptors may become targets for the treatment of neural tumors, directed against both tumor cell proliferation and angiogenesis.

Keywords: Neuropeptide Y; Neural crest-derived tumors; Neuroblastoma; Ewing's sarcoma family of tumors; Pheochromocytoma; Angiogenesis

1. NPY system

Neuropeptide Y (NPY) is a 36-amino acid neurotransmitter mainly released from sympathetic nerves, but it is present also in some parasympathetic neurons, as well as extraneuronally, e.g. in endothelium [1,2]. The best known functions of NPY include inhibition of neurotransmitter release, vasoconstriction, and stimulation of food intake [2,3]. Recently, new activities of the peptide as a growth and angiogenic factor have emerged [1,4–6]. The peptide has been shown to stimulate proliferation of a variety of cells, including neuronal precursors, vascular smooth muscle, and endothelial cells [1,5–7]. These findings provide new insight into understanding the role of NPY in the regulation of many physiological and pathophysiological processes, including tumor growth. NPY, as well as the other member of the same family, peptide YY, have already been implicated in prostate, pancreatic and breast cancers [8–12]. This review will be focused on the role of NPY in neural crest-derived tumors.

NPY's actions are mediated by five Gi/o protein-coupled receptors designated as Y1 to Y5 [13–15]. The receptors are differentially expressed in various types of cells and mediate different functions of the peptide. For example, Y1 is the main receptor responsible for NPY-induced vasoconstriction and proliferation of vascular smooth muscle cells and neuronal precursors, while Y2 is a presynaptic receptor involved in neuroinhibition in the central and peripheral nervous system [2,3,5–7]. Actions of NPY are additionally modified by dipeptidyl peptidase IV (DPPIV). This serine protease cleaves the full length $NPY_{1–36}$ to its shorter form, $NPY_{3–36}$, which is no longer able to bind to Y1, but retains affinity to all other receptors [16]. Hence, DPPIV acts as a natural Y1 receptor antagonist and shifts the activities of NPY to those mediated by Y2 and Y5 receptors. Due to its

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proteolytic activity, DPPIV has already been implicated in regulation of tumor growth, including melanoma, non-small lung carcinoma, thyroid and ovarian cancers [17]. The protease can exert growth-stimulatory or-inhibitory effects, depending on the type of tumor and presence of specific catalytic substrates and their receptors. The role of DPPIV in the regulation of NPY's effects on tumor growth will be discussed in this review.

2. NPY as an angiogenic factor

Angiogenesis is a crucial factor in the development of solid tumors, determining their growth and spread. This multi-step process starts with discontinuity and activation of the endothelium, followed by degradation of extracellular matrix, proliferation, and migration of endothelial cells, capillary lumen formation, and finally maturation of new vessels [18]. Recently, NPY has been shown to be a potent, multifunctional angiogenic factor, which stimulates proliferation, migration, and capillary tube formation in endothelial cells [1]. The peptide is involved in re-vascularization of ischemic skeletal muscles, retinopathy, and wound healing [4,19–22]. NPY appears to increase not only capillary angiogenesis but also arteriogenesis or collateral vessel formation in the ischemic tissues [4]. In addition to its effect on endothelial cells, the peptide also promotes the growth of vascular smooth muscle cells, a necessary component for the development of mature blood vessels [1,5]. NPY-induced angiogenesis seems to be mediated mainly by Y2 receptors, since angiogenic functions of the peptide are severely impaired in Y2−/− mice [19,21,23]. NPY-driven neovascularization is additionally enhanced by DPPIV, which converts the peptide to the Y2/Y5-preffereing agonist, $NPY_{3–36}$ [16]. This abundant endothelial protease is up-regulated in ischemic tissues along with NPY and Y2 receptors and is necessary for NPY-induced wound healing [4,20]. Thus, DPPIV and Y2 receptors are essential elements of the NPY angiogenic system. The mechanisms of NPY angiogenic activity also involve interactions with other growth factors. NPY-induced aortic sprouting is completely abolished in mice deficient in endothelial nitric oxide synthetase, indicating that nitric oxide is a critical mediator of the NPY angiogenic effect [4]. In contrast, blocking vascular endothelial growth factor (VEGF) inhibits NPY-driven formation of capillaries while not affecting endothelial cell migration stimulated by the peptide. Hence, VEGF is involved in some, but not all, steps of the NPY angiogenic activity [4]. These data indicate that NPY is a factor acting upstream from several angiogenic pathways. Activation of these secondary mediators, as well as the direct effect of NPY on endothelial and vascular smooth muscle cells are involved in the multi-step process of vascularization resulting in the formation of capillaries and mature arterial vessels.

3. Expression of NPY in neural crest-derived tumors

NPY is one of the most abundant neuropeptides in the brain, where it exerts systemic effects, including regulation of food intake, energy balance, and pituitary secretion. In the periphery, NPY is released mainly from sympathetic nerves, but is also expressed in some of the parasympathetic neurons. Additionally, high levels of NPY are found in the adrenal medulla [2]. As a sympathetic neurotransmitter, NPY is also often expressed in neural crest-derived tumors, particularly those originating in the autonomic nervous system. The peptide and its receptors are abundant in sympathetic neuroblastomas and pheochromocytomas, but is present also in Ewing's sarcoma family of tumors (ESFT) of the parasympathetic origin [24–30]. In tumors of the central nervous system, expression of NPY is significantly lower than in those originating in the peripheral neurons. Low levels of the peptide have been found in pituitary adenomas and glioblastomas, whereas it is almost not detectable in astrocytomas and prolactinomas [31]. Moreover, lack of NPY distinguishes central primitive neuroectodermal tumors (cPNET) from their NPY-rich peripheral counterparts (pPNET) belonging to the ESFT [31].

Due to the abundance of NPY and its receptors, tumors of the autonomic nervous system have been widely used to study the regulation of peptide expression, its signaling, and functions of the receptors [32–34]. However, till now, NPY was considered merely a marker of neuronal differentiation and nothing was known about its actual function in these tumors. Yet, recent studies on in vitro and in vivo models indicate that, due to its growth-promoting and angiogenic activities, the peptide might be an active regulator of neural crest-derived tumors [28].

4. NPY as an autocrine stimulator of neuroblastoma growth

Neuroblastoma is a childhood tumor originating from the precursors of sympathetic neurons, often arising in the adrenal glands or sympathetic ganglia [35,36]. The phenotype of the disease varies significantly and highly depends on the age of the patients.