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Sympathetic Neurotransmitters in Neuroblastoma – Between Physiology and Pathology

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1. Introduction

Neuroblastomas arise from precursors of sympathetic neurons due to defects in their normal development (Edsjo et al., 2007). Consequently, the tumors exhibit various degrees of neuronal differentiation manifested by expression of markers characteristic for sympathetic neurons and release of their physiological neurotransmitters (Bourdeaut et al., 2009). Since the levels of neuroblastoma cell differentiation determines clinical phenotype of the disease and its outcome, the factors regulating this process have been extensively studied and recently introduced to the clinic (Edsjo et al., 2007; Maris, 2010). Surprisingly, however, little attention has been paid to the role the sympathetic neurotransmitters excessively released from neuroblastoma cells play in this pathological condition. Despite their known role in the regulation of proliferation and survival of other cell types, in the neuroblastoma field those factors have been treated merely as markers of neuronal differentiation. Very often, even if studies on functional effects of neurotransmitters on neuroblastoma cells have been performed, these cells have been considered purely as a neuronal model (Laifenfeld et al., 2002; Lopes et al., 2010). Therefore, the results of such studies have been interpreted in the context of other neurological disorders, but not assessed in terms of their implications for neuroblastoma biology and therapy. Research conducted in our laboratory focuses on growth-promoting functions of one of such neurotransmitters, neuropeptide Y (NPY). We were able to show that this physiological peptide acts as a crucial mitogenic and angiogenic factor for neuroblastomas and significantly contributes to their progression (Kitlinska et al., 2005; Lu et al., 2010). However, the role of other sympathetic neurotransmitters in biology of these tumors remains understudied. This chapter summarizes our current knowledge on the role these molecules play in the regulation of neuroblastoma growth, and identifies problems which thus far have not been addressed.

2. Sympathetic neuron differentiation

The sympathetic nervous system consists of two major components - sympathetic neurons organized in ganglia and neuroendocrine chromaffin cells, which form the adrenal gland (Huber, 2006). Even though neuroblastomas often develop in adrenals, they are believed to

arise from precursors of sympathetic neurons, which are also present in immature adrenal glands (Edsjo et al., 2007; Hoehner et al., 1996).

The sympathetic nervous system is the major derivative of the neural crest and develops in a process tightly controlled by local microenvironments encountered by neural crest cells during their migration within an embryo (Huber, 2006). The essential factors involved in this process are bone morphogenic proteins (BMPs) released from dorsal aorta, which initiate the differentiation of neural crest cells toward sympathoadrenal lineage (Huber, 2006) (Fig. 1). The subsequent development of sympathoneural phenotype is triggered by induction of multiple transcription factors, such as Phox2B, MASH-1, GATA3, Hand2 and MYCN (Huber, 2006). During this process, immature sympathetic neurons acquire expression of TrkA receptor and become dependent on its ligand, nerve growth factor (NGF), for their survival (Glebova & Ginty, 2005). The mature sympathetic neurons attain the adrenergic phenotype associated with the ability to synthesize and release in a controllable manner their main neurotransmitter - norepinephrine (Huber, 2006). Consequently, the enzymes involved in the synthesis of this catecholamine, tyrosine hydroxylase (TH) and dopamine β -hydroxylase (DBH), are considered as the most characteristic sympathetic markers (Fig. 1, 2) (Glebova & Ginty, 2005; Huber, 2006). However, other neurotransmitters released from sympathetic neurons, such as NPY, are also frequently used for their identification (Bowden & Gibbins, 1992; Damon, 2008; Pahlman et al., 1991).

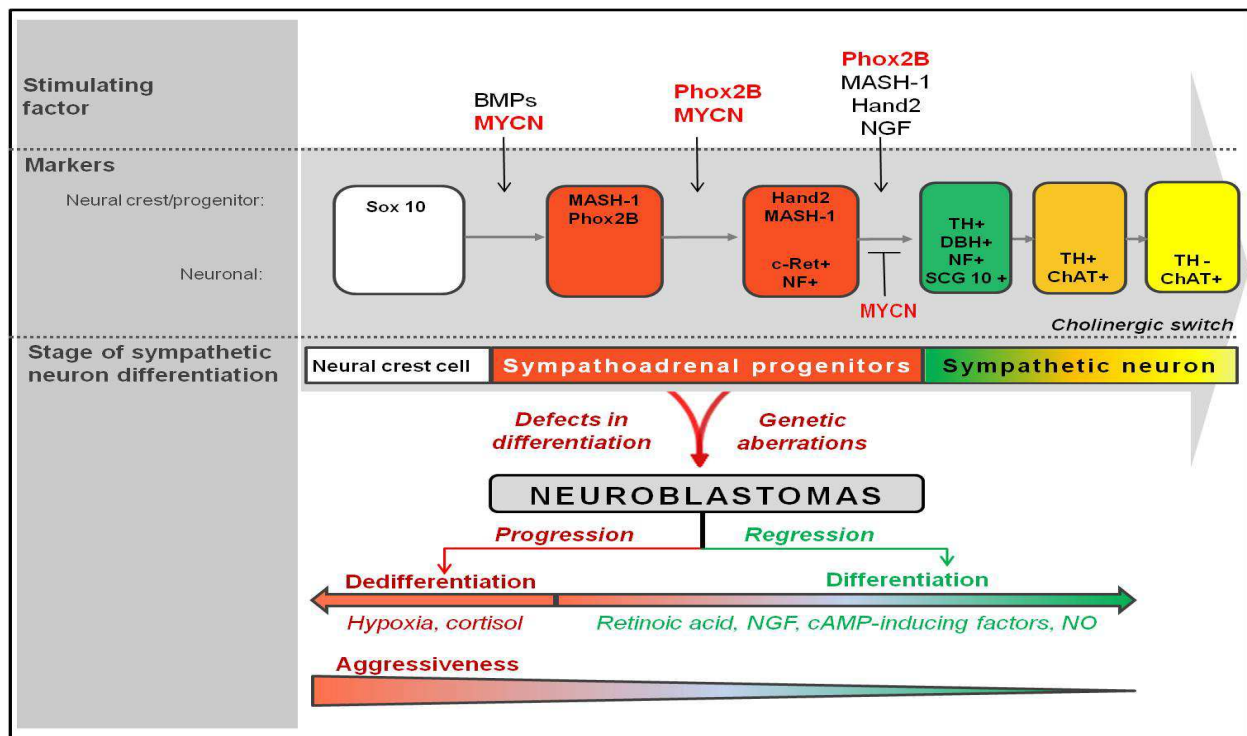


Fig. 1. Sympathetic neuron differentiation and neuroblastoma development.

Even though development of the adrenergic phenotype is considered as the end stage of sympathetic neuron differentiation, in their small subset innervating sweat glands, periosteum and skeletal muscle vasculature, this process proceeds further and the neurons undergo a “cholinergic switch” (Glebova & Ginty, 2005). In this process, the adrenergic

neurons acquire additional cholinergic features, such as expression of the enzyme involved in acetylcholine synthesis, choline acetyltransferase (ChAT), and the ability to release this neurotransmitter (Fig. 1) (Glebova & Ginty, 2005). In this transient stage, the neurons have both adrenergic and cholinergic characteristics. Subsequently, however, their adrenergic properties are lost and the neurons become purely cholinergic (Glebova & Ginty, 2005). Interestingly, all these stages of sympathetic differentiation are reflected in various phenotypes of neuroblastomas (Bourdeaut et al., 2009).

3. Neuroblastoma as a disorder of neuronal differentiation

Neuroblastoma is an extremely heterogeneous disease with phenotypes ranging from spontaneously regressing to highly metastatic, aggressive tumors (Janoueix-Lerosey et al., 2010). This phenotypical diversity is attributed to the fact that neuroblastomas arise at different stages of sympathetic neuron development. Consequently, the diverse clinical features of the disease are strongly associated with different levels of neuronal differentiation observed within tumor tissue (Fig. 1) (Bourdeaut et al., 2009). The undifferentiated neuroblastomas, which represent the most aggressive tumors, lack morphological features of mature neurons and do not exhibit adrenergic properties, such as expression of enzymes involved in catecholamine synthesis – TH and DBH. Instead, they are characterized by high expression of genes normally active in sympathetic precursors, such as Phox2B (Bourdeaut et al., 2009). In contrast, poorly differentiated neuroblastomas preserve some neuronal morphology and in the vast majority are highly adrenergic, with elevated expression of TH, DBH and with catecholamine synthesis. In some, however, the adrenergic properties are accompanied by expression of cholinergic markers, which corresponds to the transient state of dual adrenergic and cholinergic properties observed in sympathetic neurons undergoing the “cholinergic switch” (Bourdeaut et al., 2009). In line with this, the differentiating tumors with the least malignant clinical features are characterized by down-regulation of adrenergic properties and enhanced cholinergic phenotype (Bourdeaut et al., 2009).

Neuroblastoma tumorigenesis is associated with genetic aberrations targeting crucial factors involved in the regulation of normal sympathetic differentiation. The most aggressive neuroblastomas are often associated with amplification of MYCN, while the hereditary form of the disease is driven by mutations in the genes encoding transcription factor, Phox2B or the direct target of its transcriptional regulation, anaplastic lymphoma kinase (ALK) (Bachetti et al. 2010; Bourdeaut et al., 2005; Janoueix-Lerosey et al., ; Mosse et al., 2008). ALK mutations are also present in sporadic neuroblastomas (Chen et al., 2008; George et al., 2008). Interestingly, despite the genetic nature of the disease, differentiating factors are able to inhibit growth of already existing neuroblastomas and induce their maturation even in the presence of oncogenic mutations (Edsjo et al., 2007). Such a differentiation is also believed to contribute to spontaneous regression observed in stage 4S neuroblastomas and incomplete penetrance of the familial disease. Thus, the deregulation of normal sympathetic differentiation is indispensable for neuroblastoma development and may be, at least partially, independent of genetic aberrations (Edsjo et al., 2007; Prasad et al., 2003).

Neuroblastoma cell differentiation, manifested by morphological changes, up-regulation of neuronal markers and down-regulation of oncogenes, can be triggered *in vitro* by a variety

of factors (Fig. 1) (Edsjo et al., 2007). The most extensively studied is retinoic acid and its derivatives, which have been recently introduced to the clinic as a routine treatment following chemotherapy (Handler et al., 2000; Maris, 2010; Sidell, 1982). Similar effects, however, can also be achieved with other factors, such as NGF in neuroblastoma cells with induced TrkA receptor expression, nitric oxide and cyclic AMP (cAMP) -stimulating factors, such as prostaglandins and pituitary adenylate cyclase activating polypeptide (PACAP), as well as a stable analog of cAMP, dibutyryl cAMP (Kume et al., 2008; Matsushima & Bogenmann, 1990; Monaghan et al., 2008; Prasad et al., 2003; Revoltella & Butler, 1980; Reynolds & Perez-Polo, 1981; Rodriguez-Martin et al., 2000) (Fig. 1). Depending on the type of differentiation factor and cell line used, such a morphological differentiation is associated with augmenting the adrenergic features of the cells manifested by increase in norepinephrine synthesis or, conversely, in down-regulation of adrenergic markers and enhancement of cholinergic properties (Handler et al., 2000; Kume et al., 2008; Pahlman et al., 1981). In some cases, stimulation of the mixed adrenergic and cholinergic phenotype has been observed (Monaghan et al., 2008). Thus, the differentiation factors shift the neuroblastoma cells toward more mature phenotype, with the cholinergic phenotype representing the most mature cells, mimicking the final stage of differentiation observed in sympathetic neurons and human neuroblastomas. In contrast, there are several factors, such as glucocorticoids and hypoxia, known to induce dedifferentiation of neuroblastoma cells associated with down-regulation of neuronal markers (Fig. 1) (Jogi et al., 2003; Yaniv et al., 2008).

4. Catecholamines – the physiological neurotransmitters in pathological condition

Due to their origin, sympathetic neurotransmitters are an integral part of neuroblastoma biology. The levels of catecholamines and/or their metabolites are elevated in over 90% of neuroblastoma patients and their plasma and urinary levels are utilized as a diagnostic tool (Monsaingeon et al., 2003) (Fig. 2). The pattern of catecholamine secretion reflects the level of neuroblastoma differentiation. The differentiating tumors release a relatively high amount of actual sympathetic neurotransmitters, norepinephrine and epinephrine (Zambrano & Reyes-Mugica, 2002). Paradoxically, however, systemic levels of these catecholamines are rarely elevated in neuroblastoma patients, while concentrations of their metabolites - free normetanephrine and vanillylmandelic acid - are significantly higher than normal (Davidson et al., 2011). This phenomenon is attributed to the fact that poorly differentiated neuroblastomas lack catecholamine storing mechanisms, which leads to an uncontrolled release of norepinephrine and its rapid metabolism (Itoh & Omori, 1973).

In contrast, patients with undifferentiated neuroblastomas are characterized by relatively high levels of dopamine and its metabolite, homovanilic acid (Zambrano & Reyes-Mugica, 2002). These dopaminergic features of aggressive tumors result from their immature adrenergic phenotype manifested by a decreased ability to convert dopamine to norepinephrine. Consequently, the high ratio of dopamine to norepinephrine and/or its metabolites has been postulated as an unfavorable prognostic factor (Strenger et al., 2007; Zambrano & Reyes-Mugica, 2002). Thus, measurement of multiple catecholamines and their metabolites appear to be necessary for proper diagnosis and stratification of neuroblastoma (Fig. 2) (Monsaingeon et al., 2003).

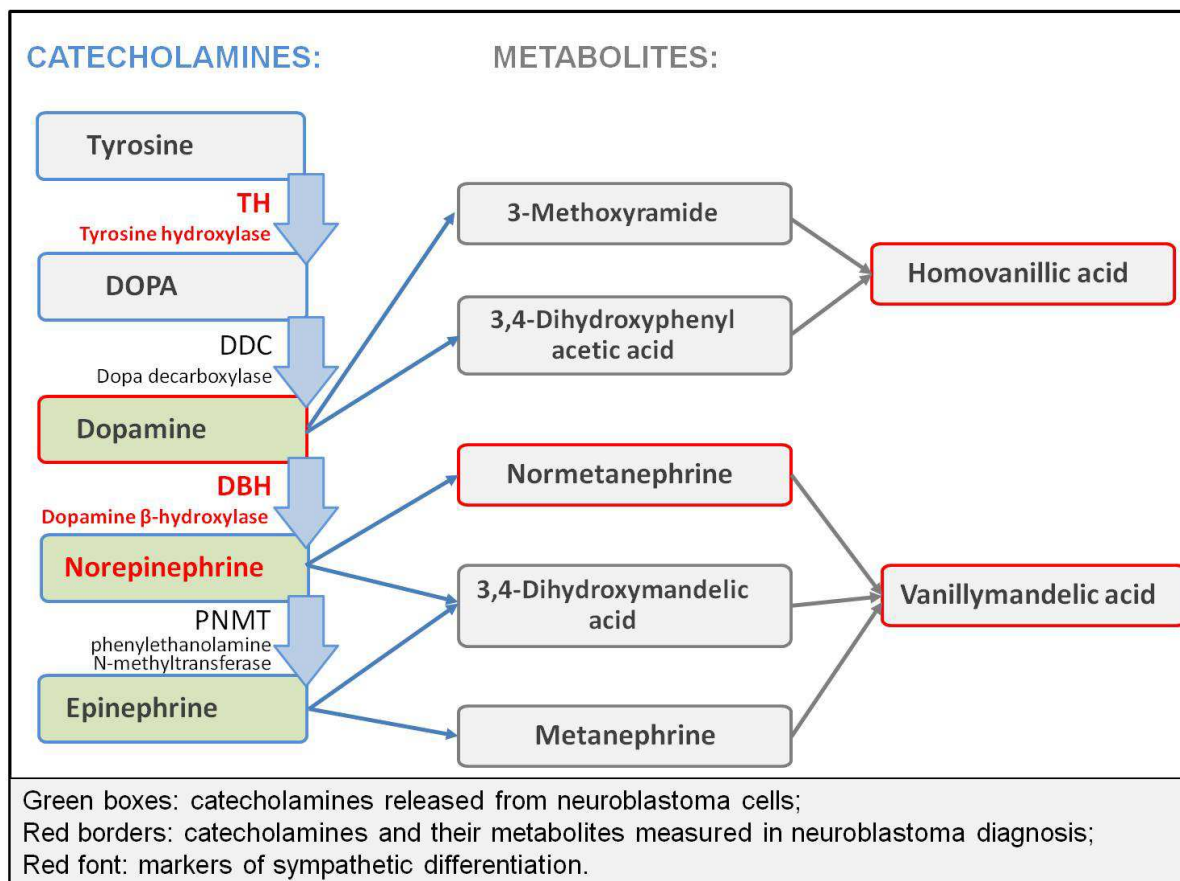


Fig. 2. Catecholamines and their metabolites in neuroblastoma

4.1 Functions of norepinephrine and epinephrine

Aside from releasing catecholamines, neuroblastoma cells also express their receptors – most often α 2-adrenergic receptors (AR), but in some cell lines additionally β 2-AR (Bawa-Khalfe et al., 2007; Parsley et al., 1999). Consequently, norepinephrine has been found to exert significant effects on neuroblastoma cell physiology. Treatment with exogenous norepinephrine inhibited neuroblastoma cell proliferation, while promoting their survival and inducing morphological differentiation manifested by neurite outgrowth comparable to this observed upon retinoic acid stimulation (Fig. 3) (Laifenfeld et al., 2002; Yaniv et al., 2008). These changes were accompanied by the decrease in expression of a marker of pluripotency, Oct4 and up-regulation of neuronal markers, such as growth-associated protein 43 (GAP-43). The norepinephrine-induced neuronal differentiation of neuroblastoma cells was mediated by α 2-AR and p44/42 mitogen-activated protein kinase (MAPK) pathway (Yaniv et al., 2008; Yaniv et al., 2010). However, in the studies described above, neuroblastoma cells have been used solely as models of neuronal cells and the data interpreted in the context of neuronal plasticity. Thus, the role of endogenous norepinephrine in regulation of neuroblastoma cell proliferation and differentiation, as well its effect on neuroblastoma tumor growth have never been explored.

As sympathetic neurotransmitters, norepinephrine and epinephrine are highly released during stress. Therefore, their stimulatory effect on the growth of various tumor types has been proposed as a mechanism of stress-induced augmentation of cancer progression. Further studies revealed that these catecholamines act mainly by increasing tumor

vascularization. This effect is driven by β -ARs present on cancer cells, the stimulation of which results in an increased release of angiogenic factors – vascular endothelial growth factor (VEGF) and interleukins 6 and 8 (IL-6 and IL-8) (Fig. 3) (Nilsson et al., 2007; Thaker et al., 2006; Wong et al., 2007; Yang et al., 2009; Yang et al., 2006; Yang & Chou, 2004). Adrenergic stimulation has also been shown to increase the secretion of metalloproteases, MMP-2 and MMP-9, which further augments angiogenic and metastatic processes (Yang et al., 2006). In addition to those indirect activities, catecholamines can also exert direct effects on endothelial cells through α -ARs (Fig. 3). Phenylephrine, a non-vasoconstrictive α -AR agonist, has been shown to induce endothelial cell proliferation and migration, as well as promote capillary formation. These effects were potentiated by hypoxia (Vinci et al., 2007), which is also a known stimulator of norepinephrine release from the sympathetic nerves (Borovsky et al., 1998). Thus, the direct angiogenic effect of norepinephrine can be particularly pronounced in hypoxic areas of tumors. However, as mentioned before, all of the above studies on the angiogenic effects of norepinephrine and epinephrine have been performed on tumors developing in adults, in the context of the stress response. The role of their angiogenic effects in the growth of catecholamine-rich neuroblastomas has never been directly tested.

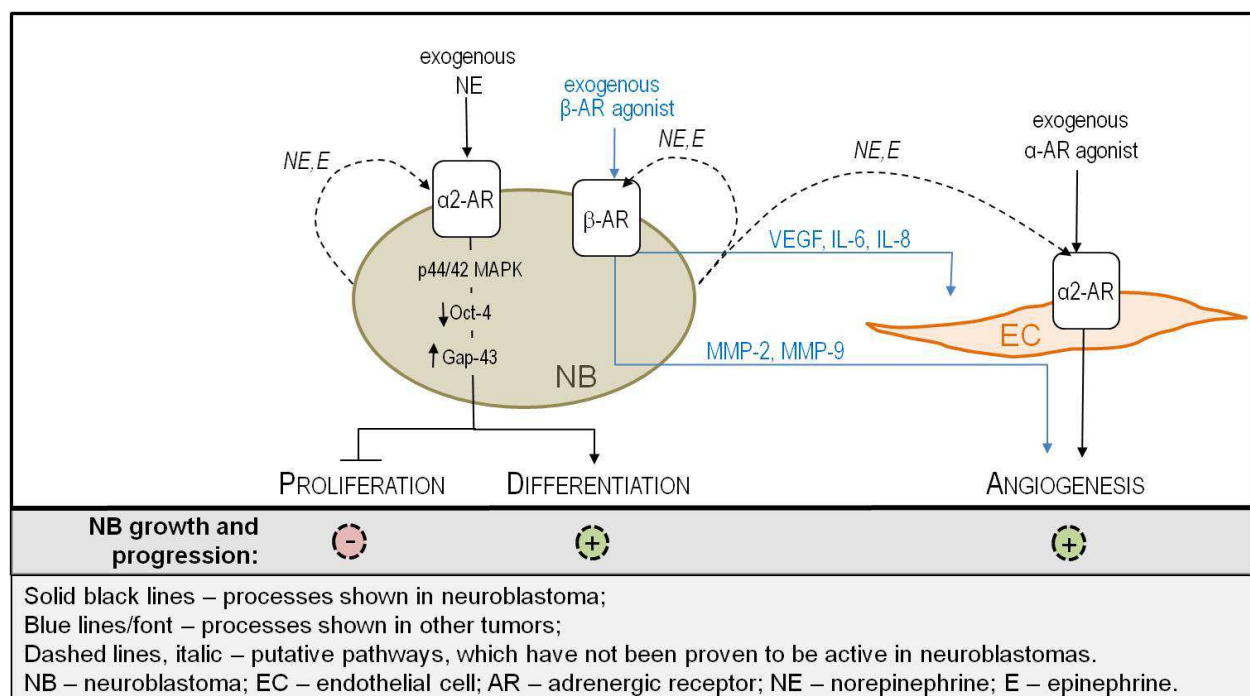


Fig. 3. Potential effects of norepinephrine and epinephrine on neuroblastoma growth and progression

4.2 Dopamine

Another catecholamine which is highly released from neuroblastomas is dopamine. Under physiological conditions, this catecholamine serves mainly as a brain neurotransmitter. However, it can also be released from peripheral sympathetic neurons and chromaffin cells, despite the fact that in these cells most of it is converted to norepinephrine or epinephrine (Fig. 2) (Goldstein, 2003). A similar phenomenon is observed with neuroblastomas, particularly the undifferentiated tumors that are characterized by an “immature adrenergic

system” and low levels of enzymes converting dopamine to norepinephrine (Zambrano & Reyes-Mugica, 2002). As in case of other catecholamines, the role of the endogenous dopamine in the regulation of neuroblastoma growth has not been explored. However, the studies designed to test the potential role of dopamine in the development of neurodegenerative diseases have shown that this catecholamine, if given at high concentrations (100-500 μ M), becomes toxic for neuroblastoma cells (Fig. 4). This effect is driven by intracellular dopamine, the oxidation of which creates reactive oxygen species (ROS) and triggers apoptosis and autophagy (Bisaglia et al., 2010; Gimenez-Xavier et al., 2009; Junn & Mouradian, 2001). Whether or not endogenous dopamine is present in neuroblastoma cells at these toxic concentrations and, if not, what are its effects at the levels present locally in the tumor tissue remains to be elucidated.

As previously shown for other catecholamines, dopamine is also involved in the regulation of tumor angiogenesis. However, in contrast to norepinephrine and epinephrine, dopamine decreases vascularization in a variety of tumor types and animal models (Fig. 4) (Asada et al., 2008; Chakroborty et al., 2004; Sarkar et al., 2008). The mechanism underlying this effect involves blocking VEGF-induced proliferation and migration of mature endothelial cells and their progenitors (Chakroborty et al., 2008). This effect is mediated by endothelial D2 receptors, which upon dopamine stimulation enhance endocytosis of VEGF receptor 2 (VEGF-R2) and decrease its membrane expression. This, in turn, interferes with VEGF signaling by reducing VEGF-induced phosphorylation of VEGF-R2 and preventing the activation of downstream kinases – focal adhesion kinase (FAK) and p42/44 MAPK (Basu et al., 2001; Sarkar et al., 2004).

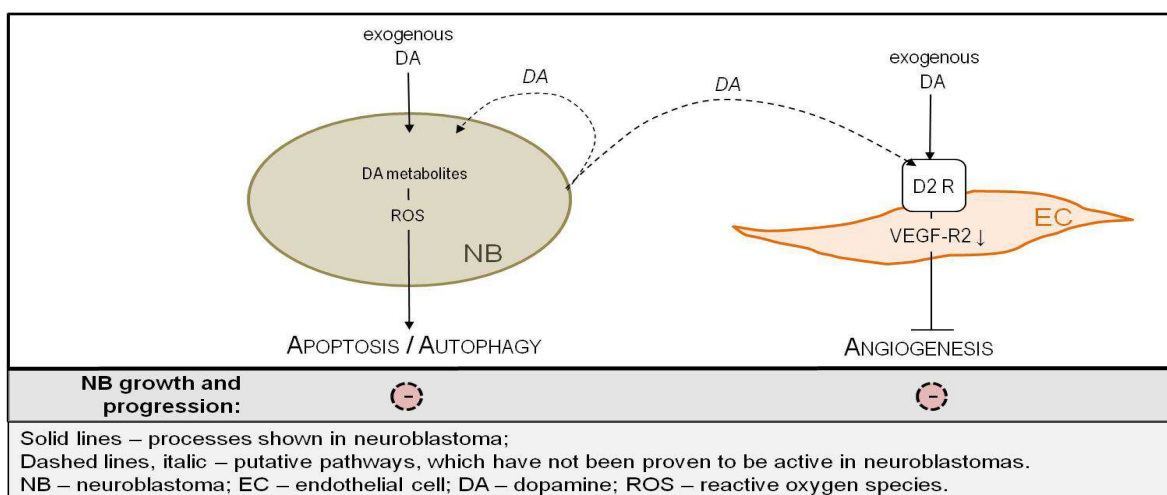


Fig. 4. Potential functions of dopamine in neuroblastoma.

In contrast to D2 receptor-mediated anti-angiogenic effects, stimulation of D1 dopamine receptors has been shown to increase endothelial cell proliferation and angiogenesis (Lindgren et al., 2009). This effect, however, has been shown mainly for brain microvascular endothelial cells stimulated by selective D1 receptor agonists (Bacic et al., 1991; Lindgren et al., 2009; Lu et al., 2008). On the contrary, in cancer models, the inhibitory effect of D2 receptor-preferring dopamine prevails, reducing tumor vascularization and growth (Asada et al., 2008; Chakroborty et al., 2004; Sarkar et al., 2008). The specific effects of endogenous dopamine on neuroblastoma vascularization, as well as their biological and clinical relevance, have yet to be determined.

5. Neuropeptide Y – neuronal marker or growth factor?

Neuropeptide Y (NPY) is a 36-amino acid peptide, which is normally co-released with norepinephrine from mature sympathetic nerves. Consequently, as shown for catecholamines, the elevated plasma levels of NPY have been reported in neuroblastoma patients (Grouzmann et al., 1989). However, early attempts to use it as a general diagnostic marker failed due to high variability of the peptide's concentrations. More detailed analyses revealed that release of NPY is elevated in stage 3/4 and stage 4s neuroblastomas, but not in stage 1/2 (Dotsch et al., 1998; Kogner et al., 1994). Also, among patients with advanced disease, the NPY levels were diverse, with many cases comparable to healthy controls. However, the increased plasma concentrations of NPY in patients from this group strongly correlated with poor clinical outcome of the disease (death and relapse) and MYCN amplification (Dotsch et al., 1998; Kogner et al., 1994). Interestingly, in advanced neuroblastomas, the elevated levels of NPY in a patient's plasma did not correlate with its high mRNA levels in the tumor tissue (Cohen et al., 1990; Dotsch et al., 1998). Similarly, based on the data from the Oncogenomics data base, high mRNA levels of NPY in tumor tissues correlated with better survival (Wei et al., 2004). This observation is in agreement with NPY being a sympathetic marker up-regulated by numerous differentiation factors (Bowden & Gibbins, 1992; Damon, 2008; Edsjo et al., 2007; Pahlman et al., 1991). The discrepancies between NPY mRNA levels and its release can be explained by a defect in neurotransmitter storage mechanisms observed in neuroblastoma (Itoh & Omori, 1973). It is plausible that despite high expression of NPY in differentiating tumors, the release of the peptide is tightly controlled and needs certain stimulation to occur, as observed in mature sympathetic neurons. In contrast, undifferentiated tumors synthesize less NPY, but release it in an uncontrolled manner, which leads to elevated systemic levels of the peptide in neuroblastoma patients, as well as further depletion of the peptide in neuroblastoma tissue. Such an uncontrolled secretion has been already described for catecholamines (Davidson et al., 2011; Itoh & Omori, 1973).

The clinical reports associating elevated plasma NPY levels with poor prognosis of neuroblastoma suggested that the peptide can be a growth factor for these tumors. Indeed, neuroblastoma cells express not only NPY, but also its G protein-coupled receptors – mainly Y2 receptors (Y2Rs), with low levels of Y5R co-expression in some cell lines (Kitlinska et al., 2005; Korner et al., 2004). We have shown that this autocrine loop stimulates neuroblastoma cell proliferation via p44/42 MAPK pathway (Fig. 5) (Kitlinska et al., 2005). More importantly, blocking the NPY/Y2R mitogenic signaling reduces basal levels of p44/42 MAPK activity in neuroblastoma cells and significantly inhibits their proliferation (Lu et al., 2010). This effect is associated with an increase in neuroblastoma cell apoptosis mediated by the Bim pathway, known to be activated upon growth factor withdrawal (Lu et al., 2010). Altogether, these observations suggest that the NPY/Y2R autocrine loop is essential to maintain neuroblastoma in their proliferative state

Aside from being a mitogenic factor for neuroblastomas, NPY is also known to stimulate angiogenesis via its direct proliferative and pro-migratory effect on endothelial cells (Lee et al., 2003b; Movafagh et al., 2006; Zukowska-Grojec et al., 1998). Strikingly, the angiogenic effect of NPY is also mediated by Y2Rs, which are expressed in activated endothelial cells (Lee et al., 2003a; Movafagh et al., 2006). Therefore, *in vivo*, NPY stimulates neuroblastoma

tumor growth via two independent mechanisms – a direct proliferative effect on neuroblastoma cells and indirectly, via increasing tumor vascularization (Fig. 5). Since both of these actions are mediated by Y2Rs, blocking Y2Rs in neuroblastoma xenografts leads to substantial inhibition in tumor growth associated with reduced proliferation levels, increased apoptosis, decreased tumor vascularization and marked focal fibrosis (Lu et al., 2010). Thus, the above data gathered in our laboratory indicate that NPY and its Y2Rs are promising new targets in neuroblastoma therapy. However, further studies are required to increase the efficiency of Y2R blockage, as well as to elucidate the role of NPY in other processes involved in regulation of tumor progression, such as chemoresistance and metastases.

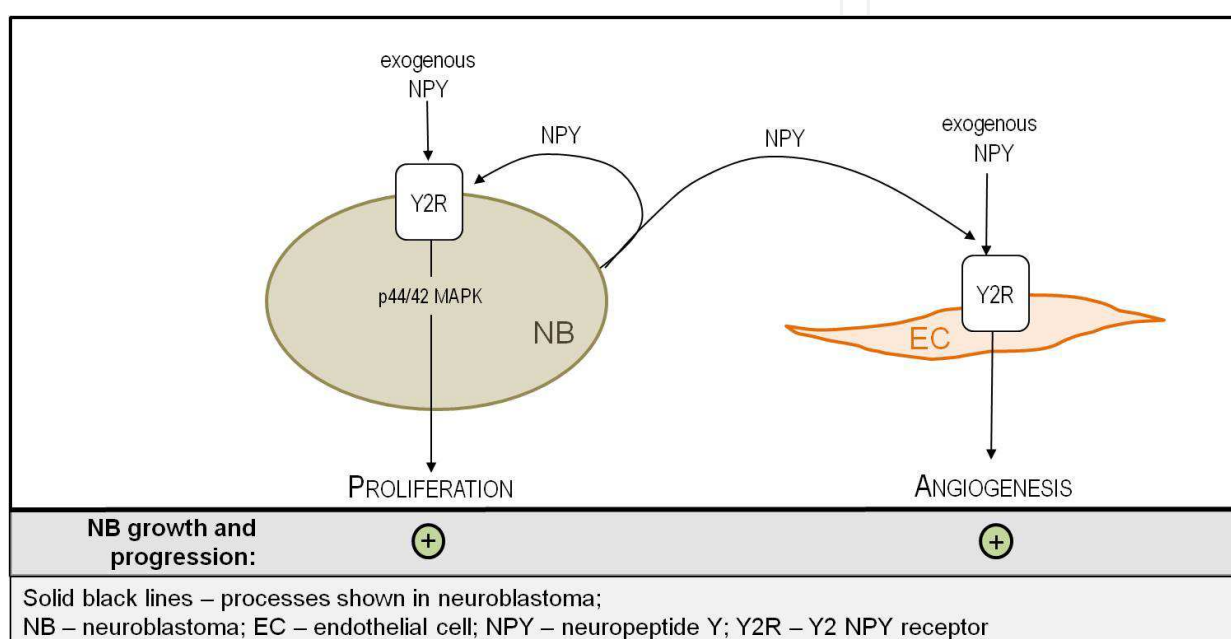


Fig. 5. Growth-promoting actions of NPY in neuroblastoma

6. Acetylcholine – the end stage of neuroblastoma differentiation

As described above, the most differentiated neuroblastomas exhibit cholinergic properties manifested by the expression of the proteins involved in synthesis and release of acetylcholine (Bourdeaut et al., 2009). Similar cholinergic features are acquired by neuroblastoma cells differentiated with retinoic acid (Handler et al., 2000). Neuroblastoma cells have also been shown to express functional muscarinic receptors of acetylcholine (M_1 - M_5) (Baumgartner et al., 1993). Stimulation of serum-starved neuroblastoma cells with a non-specific muscarinic agonist, carbochol, resulted in an increase in their survival. This effect was mediated by M_3 muscarinic receptors and the p44/42 MAPK pathway (Fig. 6) (Greenwood & Draganow, 2010). The pro-survival activity of muscarinic receptors can be further augmented by their ligand-dependent cross-talk with VEGFR2, which augments PI3K/Akt/mTOR pathway activation (Fig. 6) (Edelstein et al., 2011). Again, whether or not endogenous acetylcholine also serves as a survival factor for differentiating neuroblastomas and the role of other muscarinic receptors present in neuroblastoma cells, remains to be elucidated.

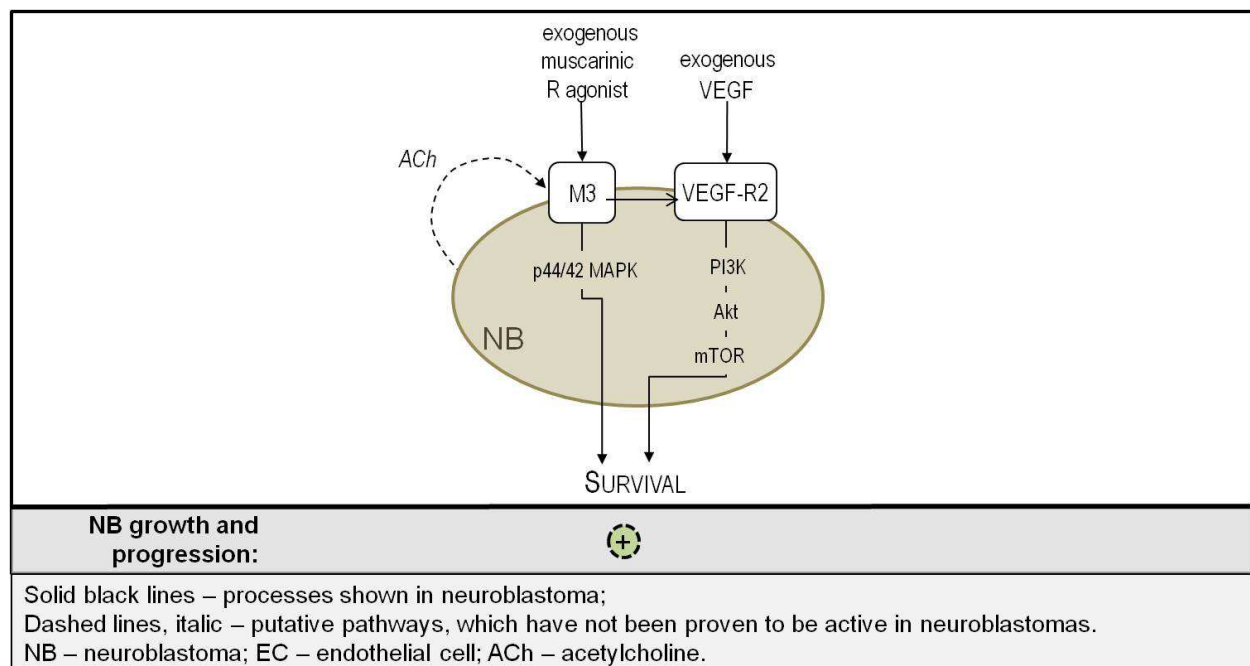


Fig. 6. Potential effects of cholinergic stimulation on neuroblastoma growth

7. Conclusions

Neuroblastomas, along with pheochromocytomas, sympathetic nervous system-derived tumors of adulthood, are extremely rich in sympathetic neurotransmitters (Bourdeaut et al., 2009; Cohen et al., 1990; Dotsch et al., 1998; Grouzmann et al., 1989). They are also known to express their receptors, which creates functional autocrine loops (Baumgartner et al., 1993; Bawa-Khalfe et al., 2007; Kitlinska et al., 2005; Parsley et al., 1999). Sympathetic neurotransmitters, in turn, are known to be potent regulators of many processes involved in the regulation of tumor growth, such as cell proliferation, survival, migration and angiogenesis (Greenwood & Dragunow, 2010; Kitlinska et al., 2005; Laifenfeld et al., 2002; Lee et al., 2003b; Tilan & Kitlinska, 2010; Yaniv et al., 2008). Their involvement in the pathogenesis of neurological disorders and stress-induced exacerbation of various diseases has been well characterized (Thaker & Sood, 2008). Surprisingly, however, despite highly elevated levels of these neurotransmitters in sympathetic tumors, their functions in these malignancies have been underappreciated. Our recent studies on NPY and its growth-promoting effects brought the first definitive data proving the crucial role of endogenous sympathetic neurotransmitters in neuroblastoma biology and their potential value as targets in its therapy (Lu et al., 2010). Nevertheless, many seemingly obvious connections, such as the potential role of angiogenic activity of norepinephrine in neuroblastoma progression, have not been made.

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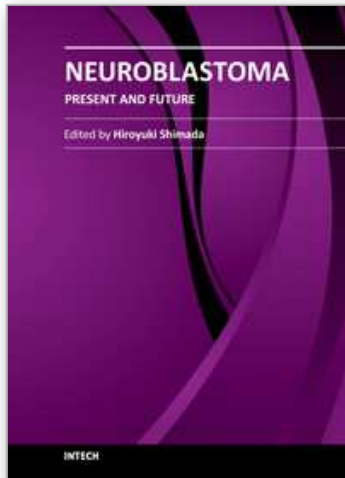
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Neuroblastoma - Present and Future

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Neuroblastoma, once called "enigmatic", due to "unpredictable" clinical behaviors, is composed of biologically diverse tumors. Molecular/genomic properties unique to the individual tumors closely link to the clinical outcomes of patients. Establishing risk stratification models after analyzing biologic characteristics of each case has made a great success in patient management. However, the trend of improving survival rates in neuroblastoma over the last 30 years has started to level off, and currently available treatment modalities have almost reached to their maximized intensity. Furthermore, aggressive treatment causes significant long-term morbidities to the survivors. We really need to make the next step to the level of personalized medicine with more precise understanding of neuroblastoma biology. This book includes useful data and insights from the world's experts in this field. I believe this book can make an excellent contribution to all the investigators working hard and fighting for the children stricken by this disease.

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