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Dopamine and serotonin regulate tumor behavior by affecting angiogenesis

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ABSTRACT

The biogenic amines dopamine and serotonin are neurotransmitters and hormones, which are mainly produced in the central nervous system and in the gastro-intestinal tract. They execute local and systemic functions such as intestinal motility and tissue repair. Dopamine and serotonin are primarily stored in and transported by platelets. This review focuses on the recently recognized role of dopamine and serotonin in the regulation of tumor behavior by affecting angiogenesis and tumor cell proliferation. Preclinical studies demonstrate that dopamine inhibits tumor growth via activation of dopamine receptor D2 on endothelial and tumor cells. Serotonin stimulates tumor growth via activation of serotonin receptor 2B on endothelial cells and serotonin receptors on tumor cells. Drugs that stimulate dopamine receptor D2 or inhibit serotonin receptors are available and therefore clinical intervention studies for cancer patients are within reach.

1. Introduction

Increasingly, it is recognized that apart from tumor cells also the non-tumor cells in the microenvironment participate in tumor behavior (Hanahan and Coussens, 2012; Hanahan and Weinberg, 2011). Endothelial cells are part of this microenvironment and can create new blood vessels, which provide oxygen and nutrients to the tumor, and hence promote tumor growth and metastasis (Carmeliet and Jain, 2000). Besides cells from the microenvironment, also distant host cells are attracted to the tumor and contribute to tumor development. The interaction between tumor microenvironment and distant host cells shows similarities with the process of wound healing, in which immune cells and platelets are attracted to the affected tissue and participate in repair. In tumor development, attracted host cells can have a detrimental effect; they can contribute to tumor growth, invasiveness and metastasis (Schäfer and Werner, 2008). Alike during wound healing, platelets are recruited to the tumor site and adhere to the activated vascular wall (Pinedo et al., 1998). This leads to release of their content consisting of pro- and anti-angiogenic factors such as vascular endothelial growth factor A (VEGF-A) (Holmsen and Weiss, 1979) and dopamine and serotonin (Da Prada and Picotti, 1979).

Dopamine and serotonin are produced in the central nervous system (CNS) and in the gastrointestinal tract, where they play a role in several local and systemic processes (Beaulieu and Gainetdinov, 2011; Mohammad-Zadeh et al., 2008). Moreover, dopamine and serotonin are increasingly recognized to be also involved in tumor behavior by affecting angiogenesis and tumor cell proliferation (Chakroborty et al., 2009; Moreno-Smith et al., 2011; Nocito et al., 2008). This review therefore aims to summarize the available knowledge on the role of dopamine and serotonin as regulators of tumor behavior with a focus on angiogenesis.

2. Dopamine

Dopamine is synthesized in the CNS and the gastrointestinal tract (Eisenhofer et al., 1997; Kopin, 1985; Mezey et al., 1996). It is produced in the cytoplasm from the amino-acid tyrosine by tyrosine hydroxylase (Kopin, 1985). In the blood, ~99% of dopamine is stored in platelets (Da Prada and Picotti, 1979), in plasma ~1% circulates in its free form and the remainder as inactive dopamine sulfate (Eisenhofer et al., 1999).

In the CNS, dopamine is involved in reward mechanisms and limb movement control. In addition, after being transported by sympathetic nerves and platelets it also has peripheral effects

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throughout the body like regulation of vascular tone (Beaulieu and Gainetdinov, 2011). Apart from exhibiting its own function, it is also a precursor of epinephrine and norepinephrine in the CNS and the adrenal glands (Kopin, 1985). Dopamine exerts its function by binding to dopamine receptors (DRs). DRs are located on the cell membrane, and expressed in the brain, heart, kidneys, adrenal cortex, sympathetic nerve terminals, and blood vessels. There are two types of DRs: D1-like DRs and D2-like DRs. D1-like DR consist of subtypes DRD1 and DRD5, and D2-like DR of subtypes DRD2, DRD3, and DRD4. Activation of D1-like DRs stimulates cellular cyclic adenosine monophosphate (cAMP) accumulation, whereas activation of D2-like DRs inhibits this (Beaulieu and Gainetdinov, 2011). Dopamine transporters are located at the plasma membrane. They actively transport dopamine from the synaptic cleft or the blood into cells where it is stored or catabolized. These transporters are expressed in the substantia nigra and ventral tegmental area of the brain, stomach, kidney, pancreatic duct (Torres et al., 2003), and platelets (Frankhauser et al., 2006). Dopamine is predominantly degraded in the liver, kidney and brain by sulfoconjugation, oxidative deamination, and O-methylation (Kopin, 1985).

3. Serotonin

Serotonin, also known as 5-hydroxytryptamine or 5-HT, is produced in the CNS and in enterochromaffin cells of the gastrointestinal tract. It is converted from one amino-acid L-tryptophan by tryptophan hydroxylase. Less than 1% serotonin circulates in its free form in the blood. The remaining serotonin is stored in platelets, presynaptic neurons, and enterochromaffin cells (Da Prada and Picotti, 1979; Mohammad-Zadeh et al., 2008).

Serotonin plays a role in many physiological processes. It modulates heart development (Nebigil et al., 2000), intestinal motility, vascular tone, and platelet aggregation (Mohammad-Zadeh et al., 2008). Serotonin receptors (5-HTRs) are located on the cell membrane, and are present in the CNS, heart, gastro-intestinal tract, blood vessels, and on platelets. There are 7 types of 5-HTRs (5-HTR1-7), some of which are subdivided into for example 5-HTR1A, 5-HTR1B, etc. Activation of 5-HTR1 and 5-HTR5 inhibits intracellular cAMP accumulation, whereas activation of 5-HTR4 and 5-HTR7 stimulates this. 5-HTR2 activation induces intracellular Ca^{2+} release and 5-HTR3 activation stimulates Na^{+}/K^{+} cation channels resulting in membrane depolarization. Serotonin transporters are located at the plasma membrane and actively transport serotonin from the interstitial space and the blood into cells (Mohammad-Zadeh et al., 2008). They are expressed in the brain (Torres et al., 2003), heart (Ni and Watts, 2006), gastro-intestinal tract, adrenal gland (Torres et al., 2003), blood vessels (Ni and Watts, 2006), and on platelets (Torres et al., 2003). Serotonin is metabolized in cells of the brain, gastrointestinal tract, liver, lungs and platelets by monoamine oxidase (MAO), and thereafter excreted by the kidney as 5-hydroxyindoleacetic acid (5-HIAA) (Mohammad-Zadeh et al., 2008).

4. Platelets

Platelets store dopamine and serotonin in dense granules and are their main circulating reservoir (Da Prada and Picotti, 1979; Da Prada and Pletscher, 1969). Platelet activation and content release play a critical role in hemostasis, thrombosis, and angiogenesis (Marcus and Safier, 1993; Pinedo et al., 1998). In cancer, platelets adhere to the activated wall of tumor vessels and release their content, consisting of dopamine and serotonin, but also calcium, factor V, fibrinogen and VEGF-A (Da Prada and Picotti, 1979; Pinedo et al., 1998). VEGF-A is stored in α-granules (Italiano et al., 2008). In this review, we will use VEGF if the articles cited do not specify whether VEGF-A or another isoform is studied.

5. In vitro effects of dopamine on endothelial cells

Dopamine predominantly affects tumor behavior via inhibition of angiogenesis. Many in vitro studies addressed the effect of dopamine on endothelial cells.

Dopamine (1 μM) inhibited VEGF-induced proliferation and migration of human umbilical vein endothelial cells (HUVEC) (Basu et al., 2001) and stimulated early apoptosis in murine mesentery endothelial cells (Moreno-Smith et al., 2011). Furthermore, pretreatment with dopamine (10 μM) abolished VEGF-induced HUVEC permeability in an in vitro permeability assay. Immunoprecipitation showed that this was induced by restabilization of adherent junctions, tight junctions, and occludin (Bhattacharya et al., 2008).

DRD2 agonists had a similar effect as dopamine. In vitro, the DRD2 agonists bromocriptine or quinpirole (50 μM) inhibited HUVEC proliferation and migration, in contrast to DRD1 agonist SKF39393 (50 μM). Quinpirole (10 μM) also inhibited HUVEC permeability (Basu et al., 2001; Bhattacharya et al., 2008). The inhibitory effect of dopamine could be abrogated by the DRD2 antagonist eticlopride (50 μM), but not by the DRD1 antagonist SCH23390 (50 μM). This indicates that dopamine affects HUVEC proliferation and migration via DRD2 activation. Fluorescence activating cell sorting (FACS) analysis revealed that dopamine and DRD2 agonists can induce VEGF receptor type 2 (VEGF-R2) internalization (Basu et al., 2001).

Dopamine not only affects endothelial cells, but also mesenchymal stem cells (MSCs) and endothelial progenitor cells (EPCs) (Shome et al., 2012; Chakroborty et al., 2008), which can be incorporated in newly developing blood vessels (Carmeliet and Jain, 2000; Chakroborty et al., 2008; Shome et al., 2012). For these experiments, MSCs and EPCs were obtained from the bone marrow of healthy mice and expanded in vitro. Dopamine (1 μM) reduced VEGF-induced MSC and EPC migration (Chakroborty et al., 2008; Shome et al., 2012). The effect on EPCs could be abolished by the DRD2 antagonist eticlopride (10 μM). Dopamine also reduced VEGF-A induced extracellular signal-regulated kinase (ERK) 1/2 phosphorylation. Furthermore, the pro-matrix metalloproteinase 9 (MMP-9) level in the supernatant was decreased (Chakroborty et al., 2008). MMP-9 is involved in EPC mobilization from the bone marrow and is under control of the classic mitogen-activated protein kinase (MAPK) pathway (Chakraborti et al., 2003; Heissig et al., 2002) (see Fig. 1).

In summary, dopamine and DRD2 agonists inhibit VEGF-induced endothelial cell proliferation as well as MSC and EPC migration.

6. Dopamine in non-malignant diseases

In non-malignant diseases, the effect of dopamine on angiogenesis has been clearly demonstrated in preclinical and clinical studies. These data support the concept that dopamine also plays a role in tumor behavior.

6.1. Endometriosis

In endometriosis ectopic endometrial tissue is implanted outside the uterus, which is associated with pelvic pain and infertility. Angiogenesis is essential for the maintenance and progression of this disease (Giudice and Kao, 2004).

In mice bearing implanted endometriosis fragments, orally administered DRD2 agonist cabergoline (0.05 and 1 mg/kg/day) decreased VEGF RNA and protein expression (Novella-Maestre

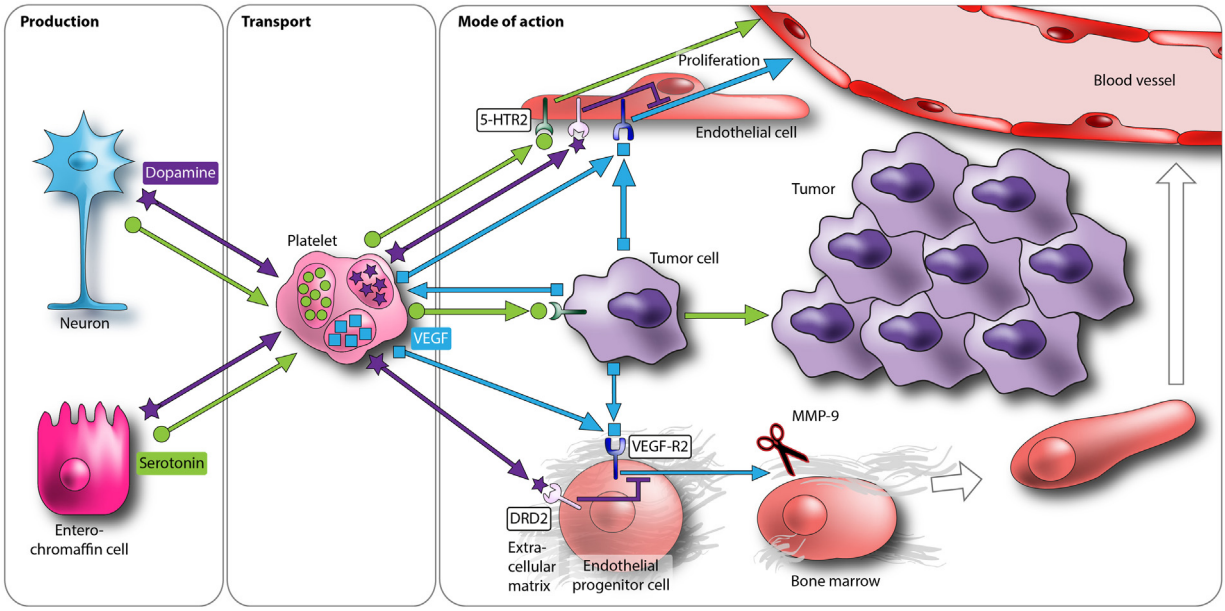

Fig. 1. Dopamine and serotonin are mainly produced in the CNS and enterochromaffin cells of the gastrointestinal tract. Platelets store and release dopamine and serotonin. Serotonin can stimulate tumor cell proliferation by activation of differentially expressed receptors on various tumor types and endothelial cell proliferation and migration via activation of 5-HTR1 and 5-HTR2. Dopamine inhibits VEGF-induced endothelial cell proliferation via activation of DRD2 and VEGF-induced EPC mobilization by diminished production of MMP-9. Hereby, dopamine prevents EPC to transform to endothelial cells at the site of action.

et al., 2009, 2010), VEGF-R2 protein expression (Novella-Maestre et al., 2009), and impaired vascularization in these lesions (Delgado-Rosas et al., 2011; Novella-Maestre et al., 2009).

Endometrial biopsies of patients with endometriosis showed less DRD2 and more VEGF RNA and protein expression than endometrial biopsies of controls. These patients had higher VEGF-R2 RNA expression in the red (active) endometriosis lesions than in white and black (inactive) lesions (Novella-Maestre et al., 2010). These findings led to a clinical trial in nine endometriosis patients. During laparoscopic treatment, one-half of the red endometriosis lesions was removed, while the other lesions were marked with silk sutures. Thereafter, patients received increasing doses DRD2 agonist quinagolide (0.025–0.075 mg/day orally for 18–20 weeks). In a second laparoscopic procedure, the remaining endometriosis lesions were evaluated and removed. Quinagolide treatment reduced the size of the lesions by 69.5% and 35% of the lesions disappeared. VEGF-R2 protein expression was decreased in the remaining lesions (Gómez et al., 2011a). Larger clinical trials have to be conducted to investigate whether DRD2 agonists are a relevant standard treatment for endometriosis, but to our knowledge these are currently not performed.

6.2. Ovarian hyperstimulation syndrome (OHSS)

In 0.5–5% of women undergoing fertilization treatment with gonadotrophins, OHSS occurs as a complication (Delvigne and Rozenberg, 2002). This condition is characterized by swelling of the ovaries and increased vascular permeability resulting in ascites, and is mediated through VEGF-induced VEGF-R2 activation (Gómez et al., 2010).

When HUVECs were treated in vitro with dopamine (2 μM) before exposure to follicular fluid of OHSS patients, phosphorylation of VEGF-R2 and tight and adherent junctions was decreased. Endothelial permeability assay showed that dopamine treatment also reduced HUVEC permeability. HUVEC migration and proliferation however, were only inhibited by a higher dose dopamine (10 μM) (Chen et al., 2010).

In a rat OHSS model, treatment with cabergoline (0.1 or 0.5 mg/kg/day) reduced vascular hyperpermeability. The higher dose however, also disrupted luteal angiogenesis, which is required for follicle maturation and potential subsequent pregnancy development (Gomez et al., 2006).

Women with polycystic ovary syndrome (PCOS) have an increased risk to develop OHSS during ovulation-inducing treatment. Key symptoms of PCOS are hyperandrogenism and chronic anovulation (Franks, 1995). These patients have a lower ovarian and follicular DRD2 protein expression and higher follicular microvessel density than healthy controls (Gómez et al., 2011b).

A meta-analysis of 570 women at high risk of developing OHSS during assisted reproduction showed that cabergoline (0.5 mg/day) reduced this risk with 12% (95% confidence interval (CI) 6.1–18.2%). This treatment decreased ascites and did not adversely affect the ~40% pregnancy rate in these women (Alvarez et al., 2007; Papaleo et al., 2001; Youssef et al., 2010). In a randomized controlled trial with lower doses of cabergoline (0.25 mg/day) a similar absolute risk reduction could be achieved in 100 women at high risk of developing OHSS compared with 100 women not receiving cabergoline (Shaltout et al., 2012).

6.3. Parkinson's disease

Parkinson's disease is characterized by central dopamine depletion due to degeneration of dopamine producing neurons in the substantia nigra. Major symptoms are rigidity, tremor and akinesia (Lang and Lozano, 1998). Parkinson's disease can be treated with the dopamine precursor L-3,4-dihydroxyphenylalanine (L-DOPA), which induces dyskinesia as a side-effect in over half of patients (Chase, 1998).

Rats that developed L-DOPA induced dyskinesia had increased VEGF-A protein levels in the dorsolateral striatum and substantia nigra pars reticulata (Ohlin et al., 2011) and enhanced endothelial cell proliferation and blood vessel length in the basal ganglia (Lindgren et al., 2009; Westin et al., 2006). Signs of dyskinesia and angiogenesis similar as induced by L-DOPA were seen after treatment with the DRD1 agonist SKF38393 (1.5 mg/kg/day), but not

with the DRD2 agonist bromocriptine (2.5 mg/kg/day). The DRD1 antagonist SCH23390 (0.25 mg/kg/day) abolished the effect of L-DOPA, but the DRD2 antagonist eticlopride (0.01 mg/kg/day) did not. The pro-angiogenic effect of L-DOPA in Parkinson's disease thus seems to be mediated through DRD1 (Lindgren et al., 2009).

The mesencephalon of 6 Parkinson patients at autopsy contained more nuclei of endothelial cells than the mesencephalon of 10 non-Parkinson patients. Since it was not reported whether these patients used L-DOPA, it remains unclear whether this phenomenon is a result of L-DOPA treatment or of the disease itself (Faucheux et al., 1999).

6.4. Wound healing

Wound healing partially depends on angiogenesis (Singer and Clark, 1999). Since DRD2 agonists have an anti-angiogenic effect, DRD2 antagonists were evaluated for pro-angiogenic and hence wound healing capacity in mice. In mice with cutaneous wounds, treatment with DRD2 antagonist eticlopride (10 mg/kg/day) did indeed accelerate wound healing and increased microvessel density in the wound compared to saline treatment (Shome et al., 2011). Eticlopride also enhanced the number of circulating MSCs in the peripheral blood compared to saline treatment. The number of bromodeoxyuridine (BrdU) labeled MSCs that were iv injected were also higher in the wound bed after eticlopride treatment (Shome et al., 2012).

7. Dopamine in cancer

Several in vitro experiments indicated that dopamine can directly affect tumor cells. In ovarian cancer cells, dopamine (12.5–50 μM) decreased tumor cell invasion in a membrane invasion culture system and increased apoptosis (Moreno-Smith et al., 2011). Dopamine (5 μM) also diminished proliferation of non-Hodgkin's lymphoma cells. This effect was abolished by the free radical scavenger sodium metabisulfite. The authors suggested dopamine to act via induction of oxidative stress (Meredith et al., 2006). Colon and breast cancer cell proliferation and migration were not affected by dopamine (1.2 μM) (Sarkar et al., 2008). Differences in outcome might be the consequence of different tumor types and dopamine doses used.

Various tumor cell types express DRs and dopamine transporter (Ganguly et al., 2010; Ishibashi et al., 1994; Meredith et al., 2006; Moreno-Smith et al., 2011; Senogles, 2007). Tumor cell behavior can be affected by DRD2 agonists. Clonal growth of human small cell lung cancer cells was inhibited by DRD2 agonist bromocriptine (0.1 nM) (Senogles, 2007). Pretreatment with the DRD2 agonist quinpirole (50 μM) inhibited insulin-like growth factor 1 (IGF1)-induced proliferation of human gastric cancer cells via reduced cellular phosphorylation of IGF1 receptor and its downstream molecule Akt (Ganguly et al., 2010).

In various animal experiments, dopamine's role in cancer was further investigated. In mice, bone marrow dopamine concentrations decreased 7-fold after murine sarcoma transplantation (Chakroborty et al., 2008). In another mouse model, 6-hydroxydopamine injections ablated peripheral dopaminergic nerves and therefore induced dopamine depletion. These mice had larger subcutaneously (sc) injected murine melanomas and sarcomas than mice with intact peripheral dopaminergic nerves. Dopamine depleted mice also had enhanced tumor microvessel density and permeability as well as increased VEGF-R2 phosphorylation of tumor endothelial cells (Basu et al., 2004; Sarkar et al., 2004).

In contrast to dopamine depleted mice, dopamine transporter knockout mice have a hyperdopaminergic system resulting in high systemic dopamine levels. When lung carcinoma cells were sc implanted, these mice had smaller tumors with lower microvessel density compared with wild-type mice (Asada et al., 2008). Apomorphine-susceptible (APO-SUS) rats selected from an outbred population of Wistar rats have a hyperreactive dopaminergic system with a higher amount of cerebral tyrosine hydroxylase mRNA and DRD2 protein (Cools and Gingras, 1998). Seven days after sc implantation, mammary tumors were smaller with a lower tumor microvessel density in APO-SUS rats than in their apomorphine-unsusceptible (APO-UNSUS) counterparts. Furthermore, APO-SUS rats developed fewer lung metastases than APO-UNSUS rats after intravenous (iv) injection of mammary breast cancer cells (Teunis et al., 2002).

Dopamine treatment resulted in decreased tumor growth with a lower microvessel density in several animal models (Basu et al., 2001; Chakroborty et al., 2004; Dasgupta and Lahiri, 1987; Moreno-Smith et al., 2011, 2013; Sarkar et al., 2008). In general, dopamine treatment consisted of intraperitoneal administration of 50 mg/kg/day, resulting in dopamine plasma levels of 1.2 μM in mice and 2.4 μM in rats 1 min after injection. This is 5% of the lethal dose in rodents (Sarkar et al., 2008). Dopamine also reduced vascular permeability in mice bearing human colon and breast tumors (Sarkar et al., 2008) and murine ovarian tumors, resulting in less accumulation of ascites in the latter model (Basu et al., 2001). Tumor endothelial cells of dopamine-treated mice had decreased phosphorylation of VEGF-R2 (Chakroborty et al., 2004) and downstream targets, like focal adhesion kinase (FAK) and MAPK (Sarkar et al., 2008).

In a very elegant study dopamine was shown to decrease EPC mobilization into the peripheral circulation and EPC incorporation in murine sarcoma vasculature. These mice first received a bone marrow transplantation from transgenic Tie2 mice. Four weeks later a murine sarcoma was transplanted, followed by dopamine treatment. $LacZ^+$ EPC from the transgenic mice were then identified by X-gal staining. This staining demonstrated a lower EPC number in sarcoma vasculature of dopamine-treated mice than of untreated mice. MMP-9, involved in EPC mobilization (Chakroborty et al., 2008; Heissig et al., 2002), was also lower in the bone marrow of dopamine-treated mice compared to untreated ones (Chakroborty et al., 2008). In a study with stressed mice bearing human ovarian cancer, it was shown that dopamine treatment increased pericyte coverage of tumor vasculature (Moreno-Smith et al., 2013). Increased pericyte coverage is one of the characteristics of vessel normalization induced by antiangiogenic therapy (Jain, 2005).

The effect of dopamine in combination therapy was investigated in a study in which mice bearing sc human breast tumors received dopamine alone, doxorubicin alone, dopamine and doxorubicin, or vehicle. Dopamine, doxorubicin, and combination of dopamine and doxorubicin resulted in decreased tumor volume (171%, 133%, and 63% of original size respectively) compared with vehicle treatment (413% of original size) and increased life span (with 24%, 38%, and 90% respectively) compared with vehicle treated mice. A similar phenomenon was observed in mice bearing orthotopic human colon tumors treated with dopamine alone, 5-fluorouracil alone, dopamine and 5-fluorouracil, or vehicle (Sarkar et al., 2008). In stressed mice bearing ovarian cancer, dopamine in combination with cisplatin enhanced cisplatin concentration in the tumor as demonstrated by an increased tumor/kidney and tumor/liver cisplatin ratio. This combination treatment resulted in a 6-fold decrease in tumor weight compared to cisplatin only treated animals (Moreno-Smith et al., 2013).

The role of DRD2 was also investigated in animal experiments. DRD2 knockout mice bearing murine sarcoma or melanoma had increased tumor size, microvessel density and permeability compared to wild-type mice (Basu et al., 2004; Chakroborty et al., 2008). Dopamine treatment did not affect EPC mobilization in these mice,

suggesting that DRD2 is necessary for dopamine to execute its function (Chakroborty et al., 2008).

DRD2 agonists bromocriptine and quinpirole (10 mg/kg) inhibited tumor angiogenesis in mice bearing murine ovarian cancer (Basu et al., 2001). DRD2 antagonists eticlopride or domperidon (10 mg/kg/day) administered prior to dopamine treatment, on the other hand, abolished dopamine's inhibitory effect on human gastric and ovarian tumor growth in mice and rats (Chakroborty et al., 2004; Moreno-Smith et al., 2011, 2013). Dopamine-induced pericyte coverage was not affected by DRD2 antagonist eticlopride (10 mg/kg/day) (Moreno-Smith et al., 2013).

There are however also data indicating that DRD2 activation can inhibit tumor cell proliferation as revealed in experiments with siRNA targeting DRD2. In stressed mice bearing human SKOV3ip1 or HeyA8 ovarian tumors, dopamine's inhibitory effect was abolished if it was co-injected with nanoparticles containing siRNA targeting murine DRD2 present on endothelial and other host cells. However, dopamine co-injected with nanoparticles containing siRNA targeting human DRD2 present on tumor cells abolished dopamine's inhibitory effect only on HeyA8 ovarian tumors. As HeyA8 cell viability in vitro is also affected by dopamine treatment, this suggests that DRD2 present on HeyA8 tumor cells is involved in tumor growth. Why SKOV3ip1 tumor cells are not affected by dopamine treatment or siRNA targeting human DRD2 remains puzzling, because this cell line also expresses DRD2 (Moreno-Smith et al., 2011). From these studies, it can be concluded that dopamine inhibits tumor angiogenesis and thereby tumor growth via activation of DRD2; in some tumors also DRD2-mediated inhibition of tumor cell proliferation may play a role.

There is conflicting evidence regarding the influence of DRD1 activation on tumor angiogenesis. One study showed that DRD1 knockout mice bearing murine lung carcinoma had smaller tumors than wild-type mice. In wild-type mice, DRD1 antagonist SCH23390 (0.3 mg/kg/2 days) inhibited tumor growth and microvessel density (Asada et al., 2008). However, in a study in mice bearing murine ovarian tumors neither DRD1 antagonist SCH23390 (10 mg/kg), nor DRD1 agonist SKF38390 (10 mg/kg) affected tumor vascularization or extent of malignant ascites (Basu et al., 2001). Also in stressed mice bearing human SKOV3ip1 and HeyA8 ovarian tumors DRD1 antagonist butaclamol (1.5 mg/kg) did not affect dopamine-induced inhibition of angiogenesis and tumor growth. Butaclamol did however inhibit the increased pericyte coverage of tumor vessels caused by dopamine treatment in these models. In these mice, administration of DRD1 agonist SKF82958 (1 mg/kg) also resulted in increased pericyte coverage of tumor vessels. Combination treatment with cisplatin and DRD1 agonist SKF82958 resulted in two-fold increas in tumor/liver and tumor/kidney cisplatin concentration ratios and a five-fold decrease in tumor growth compared to cisplatin only treated controls (Moreno-Smith et al., 2013). These observations suggest that dopamine-induced DRD1 activation results in vascular normalization.

Dopamine concentrations have also been investigated in cancer patients. In colon cancer tissue of 36 patients, the dopamine level determined by 3[H] dopamine binding assay was 3–10-fold lower than in adjacent healthy colon tissue (Basu and Dasgupta, 1999). Dopamine and tyrosine hydroxylase were not detectable by high performance liquid chromatography in gastric cancer tissue of 22 patients, whereas presence of both was demonstrated in healthy gastric tissue of 22 patients with adenomatous stomach polyps (Chakroborty et al., 2004).

One clinical intervention study was performed, aiming to achieve systemic dopamine levels which could inhibit tumor cell growth. Four patients with metastatic melanoma received dopamine infusion at a maximum dose of 20 μg/kg/min for 48–120 h resulting in plasma dopamine levels between 1 and 10 μM. The study was prematurely terminated due to severe cardiovascular side-effects after the administration of only one treatment cycle (Wick, 1983). An ex vivo proliferation assay of biopsies prior to and immediately after this treatment cycle (Livingston et al., 1974) showed a 10-fold decrease from 1.0–3.0% to 0.1–0.2% radioactive thymidine-labeled tumor cells (Wick, 1983).

DRD2 was expressed in gastric cancer tissue of 65 patients, but was lower in tumors than in benign polyps or normal gastric tissue of 83 controls (Basu and Dasgupta, 1997). Furthermore, the allele frequency of germ line functional single-nucleotide polymorphisms (SNPs) of the *DRD2* gene in cancer patients was investigated in three studies. −141C/del DRD2 SNP allele frequency was higher in 370 colorectal cancer patients than in 327 controls (odds ratio (OR) = 2.28) (Gemignani et al., 2005). In a colon polyp prevention trial with over 2000 participants who underwent polypectomy, this DRD2 SNP and others were evaluated. The −141C/del allele frequency was higher in 673 patients with recurrence of colorectal adenoma (OR = 1.3), and the TaqIA allele frequency was higher in 109 patients with recurrence of advanced colorectal adenoma (OR = 2.40) (Murphy et al., 2009). Another study showed the −141C/del allele to be more frequently present in 335 lung carcinoma patients than in 413 controls (all former or current smokers) (OR = 2.19) (Campa et al., 2007). Since these studies only investigated the DRD2 SNP allele frequency and not mRNA expression, the functional effect of having these SNPs remains unclear.

In summary, dopamine and tyrosine hydroxylase are present in lower concentrations in tumor tissue than in benign tissue. Increasing dopamine levels by dopamine treatment seems to inhibit tumor cell proliferation in melanoma patients, but cannot be used due to toxicity. DRD2 is present in gastric cancer tissue and is an attractive target for therapy with DRD2 agonists.

Surprisingly, there are no data available regarding the relation of dopamine with angiogenesis in paraganglioma and pheochromocytoma, which are neuroendocrine tumors known for their dopamine production (Meijer et al., 2003).

8. In vitro effects of serotonin on endothelial cells

The effect of serotonin on endothelial cells was investigated in several in vitro studies. Serotonin (0.1 μM and 1 μM) enhanced migration, tubule length and proliferation of HUVEC and human aortic endothelial cells (HAEC) (Iwabayashi et al., 2012; Matsusaka and Wakabayashi, 2005; Qin et al., 2013). In a culture of human umbilical cord CD34+ cells together with serotonin (0.2 μM) and thrombopoietin, stem cell factor and FL-3 ligand (TSF), an increased number of endothelial stem cells and EPCs was demonstrated with FACS analysis compared with CD34+ cells cultured with TSF alone. This indicates that serotonin stimulated CD34+ cells to expand the endothelial stem cell and EPC population (Yang et al., 2007). Lastly, HUVEC permeability was increased by serotonin (10 μM) via reduction of adherent and tight junction protein expression (Zhao et al., 2011).

Serotonin exerts its effect on endothelial cells through multiple receptors as shown in experiments with various 5-HTR agonists and antagonists. Serotonin-induced migration of HAEC was inhibited by 5-HTR1 antagonist GR55562 (0.1 μM), but not inhibited by a low dose 5-HTR2 antagonist ketanserin (0.1 μM) (Matsusaka and Wakabayashi, 2005). A higher dose of ketanserin (18 μM) did inhibit migration in HUVEC (Qin et al., 2013). Also serotonin-induced proliferation of HUVEC and dog aortic endothelial cells could be abolished by ketanserin (18 μM) and 5-HTR2B antagonist LY281067 (0.02 μM) (see Fig. 1) (Pakala and Benedict, 1998; Qin et al., 2013). 5-HTR3 antagonist 3-tropanylindole-3-carboxylate methiodide (7 μM) inhibited serotonin-induced HUVEC proliferation and migration (Qin et al., 2013), while for 5-HTR4 opposing results were obtained. 5-HTR4 agonist mosapride citrate (10 μM)

induced arrest of HUVEC in the G0/G1 phase and inhibited its proliferation, migration and tube-like formation (Nishikawa et al., 2010). However, in another study 5-HTR4 antagonist RS39604 (10–30 μM) inhibited HUVEC proliferation, migration and tube-like formation (Profirovic et al., 2013).

Serotonin activates several intracellular second messenger pathways. In the four endothelial cell lines HUVEC, HAEC, human microvascular endothelial cells, and human pulmonary artery endothelial cells the signaling kinases ERK, P70S6K, Src, PI3K, Akt, mTOR, and p38 MAPK were activated upon serotonin stimulation (1 μM). Serotonin induces Akt phosphorylation and upregulation of orphan nuclear transcription factor TR3/Nur77 in HAEC respectively HUVEC (Iwabayashi et al., 2012; Dimmeler et al., 1999; Pakala and Benedict, 1998; Qin et al., 2013; Zamani and Qu, 2012).

Western blot analysis revealed that blocking serotonin with 5-HTR1B antagonist SB316641 (100 nM) inhibited P70S6K, ERK, and the Src/PI3K/Akt/mTOR pathway (Zamani and Qu, 2012).

5-HTR2B antagonist SB2047415 (10 μM) inhibited ERK1/2 and endothelial nitric oxide synthase (eNOS) phosphorylation in HUVEC (Asada et al., 2009). Another 5-HTR2B antagonist, SB206553 (100 nM), and the 5-HTR7 antagonist SB269970 (100 nM) inhibited serotonin-induced activation of p38 MAPK (Zamani and Qu, 2012).

As 5-HTR1B and 5-HTR2B antagonists inhibit ERK phosphorylation and ERK inhibition abolished serotonin-induced HAEC migration (Iwabayashi et al., 2012), these data suggest that serotonin stimulated ERK-induced endothelial cell migration via activation of 5-HTR1B and 5-HTR2B.

Besides endothelial cells, serotonin also affects aortic smooth muscle cells. In vitro, serotonin (1 μM) increased proliferation of bovine aortic smooth muscle cells (Nemecek et al., 1986). Migration of rat aortic smooth muscle cells was enhanced after addition of serotonin (minimum of 1 nM) to smooth muscle cell derived migration factor (25 μm). Pretreatment with 5-HTR2 antagonist MCI-9042 (0.1 μM) abolished serotonin-induced (1 μM) migration (Tamura et al., 1997).

In summary, serotonin in vitro stimulates proliferation of endothelial cells via activation of 5-HTR1, 5-HTR2, and 5-HTR3 and proliferation of aortic smooth muscle cells via 5-HTR2. The role of 5-HTR4 is less clear as opposing results have been found.

9. Serotonin in inflammation

Angiogenesis is not only a hallmark of cancer, but also of inflammation (McDonald, 2001). Preclinical and clinical evidence suggests that serotonin can affect inflammation. In an air-pouch model in rats, inflammation can be induced by sc injection of sterile air and subsequently 1 mL 1% carrageenan solution. Treatment with 5-HTR3 antagonist granisetron (50–200 μM) decreased angiogenesis and inflammation, as shown by reduced hemoglobin levels and leukocytes in the granulation tissue (Maleki-Dizaji et al., 2010). Rheumatoid arthritis and osteoarthritis are examples of chronic inflammation. In a double-blind study in 36 patients with rheumatoid arthritis or osteoarthritis, a single intra-articular injection with 5-HTR3 antagonist tropisetron (10 mg) reduced symptoms with similar efficacy as methylprednisolone (40 mg). Since angiogenic markers were not evaluated after tropisetron treatment, it cannot be confirmed that tropisetron induced symptom reduction via inhibition of angiogenesis (Samborski et al., 2004).

10. Serotonin in cancer

In vitro, serotonin stimulated tumor cell proliferation and prevented cell death in several tumor cell lines (see Fig. 1) (Alpini et al., 2008; Cattaneo et al., 1994; Dizeyi et al., 2005; Drozdov et al., 2009; Liang et al., 2013; Pirozhok et al., 2010; Siddiqui et al., 2006a,b; Soll et al., 2010; Sonier et al., 2006). In contrast, human melanoma cell proliferation was inhibited by serotonin (500 μM) (Müller et al., 2012). In a human cholangiocarcinoma cell line, tryptophan hydroxylase mRNA was 2.5–50-fold higher and MAO-A mRNA was ~2-fold lower compared to non-malignant cholangiocytes. This resulted in increased serotonin production by these tumor cells (Alpini et al., 2008). In the human hepatocellular carcinoma cell line Huh7, serotonin stimulated proliferation in serum deprived medium via upregulation and phosphorylation of FOXO3a. This effect did not occur in two other human hepatocellular carcinoma cell lines HepG2 en Hep3b (Liang et al., 2013).

Tryptophan hydroxylase inhibitors block the conversion of tryptophan to serotonin. In vitro experiments showed reduced proliferation of neuroendocrine tumor cells after treatment with tyrosine hydroxylase inhibitor 7-HTP (1 nM). Cholangiocarcinoma cell proliferation could be blocked by tyrosine hydroxylase inhibitor p-chlorophenylalanine (CPA) (1 mM) (Alpini et al., 2008; Drozdov et al., 2009).

In vitro experiments showed various 5-HTRs to be present on several tumor cell types. Tumor cell growth could be inhibited by specific antagonists targeting the 5HTR expressed on the tumor cell (see Supplementary Table 1). In small cell lung cancer cells, both 5-HTR1A and 5-HTR1D had to be targeted by antagonists (500 nM spiperone respectively GR127935) to achieve maximal inhibition of serotonin-induced cell growth. It was suggested that blocking one 5-HTR leads to increased susceptibility of serotonin-induced activation of the other (Vicentini et al., 1996).

Supplementary table related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drup.2014.09.001.

In animal experiments the effect of serotonin depletion and repletion on tumor behavior was studied. Hepatocellular carcinoma xenografts were not able to grow in tryptophan hydroxylase deficient (and thus serotonin depleted) mice (Soll et al., 2010). Murine colon or lung carcinomas in tryptophan hydroxylase deficient mice were 3-fold respectively 1.5-fold smaller than in wild-type mice. Microvessel density in colon cancers was also decreased in tryptophan hydroxylase deficient mice. Colon and lung carcinoma growth could be restored when 5-hydroxytryptophan (50 mg/kg twice daily) was sc injected 2 days before tumor inoculation. Tryptophan hydroxylase deficient mice had tumor VEGF and VEGF-R2 concentrations similar to wild-type mice, but higher MMP-12 and angiostatin concentrations (Nocito et al., 2008). MMP-12 cleaves plasminogen into angiostatin, which is an endogenous angiogenesis inhibitor (Cornelius et al., 1998). Therefore, it was suggested that serotonin affects the angiostatin-pathway instead of the VEGF-pathway (Nocito et al., 2008). Absence of the serotonin transporter induces lower plasma and tumor serotonin levels. This resulted in smaller tumors in serotonin transporter deficient mice bearing murine lung carcinoma or melanoma compared to wild-type mice. However, tumor microvessel density was not affected. To obtain more insight in the cause of decreased tumor growth, eNOS concentrations were determined and found to be reduced in the tumors of serotonin transporter deficient mice. As eNOS can cause vasodilatation, the authors suggested decreased blood flow to be the cause of the smaller tumors in serotonin transporter deficient mice (Nishikawa et al., 2010). The human cholangiocarcinoma growth reduction in mice after treatment with the tryptophan hydroxylase inhibitor CPA (150 mg/kg trice a week) for ~2 months further supported the evidence that absence of serotonin affects tumor behavior (Alpini et al., 2008).

In mouse studies, research regarding the role of 5-HTR in tumor behavior only focused on the role of 5-HTR2B. Treatment with 5-HTR2B antagonist SB204741 (20 mg/kg) decreased tumor growth and microvessel density in mice bearing murine lung cancer or melanoma (Asada et al., 2009).

In patients immunohistochemistry studies have been performed. Stainings of the neuroendocrine tumor cell markers chromogranin A and serotonin were used to identify neuroendocrine foci in prostate cancer. The presence of serotonin-positive cells was associated with a higher microvessel density (Heinrich et al., 2011) and VEGF expression (Chevalier et al., 2002). 5-HTR was present in several tumor types. 5-HTR1A and 5-HTR1B expression was increased in hepatocellular carcinoma tissue of 109 patients compared to surrounding healthy liver tissue, whereas 5-HTR2B and 5-HTR7 expression was similar in both tissue types. 5-HTR1A, 5-HTR1B and 5-HTR2B expression was associated with a higher proliferation index in tumors of 176 hepatocellular cancer patients. In addition, expression of 5-HTR1B was correlated with tumor size in these patients (Soll et al., 2012). However, in prostate cancer tissue of 25 patients, 5-HTR2B expression was similar among all Gleason grades, whereas 5-HTR4 was only expressed in Gleason grade 3–4 prostate cancer tissue (Dizeyi et al., 2005). In breast cancer tissue of 102 patients, 5-HTR1A, 5-HTR1B, 5-HTR2B and 5-HTR4 were present. In these tumors, receptor expression did not correlate with tumor grade (Kopparapu et al., 2013). In 159 bone metastases of carcinoma and sarcoma patients reverse phase protein microarray analysis showed that expression of serotonin in combination with tumor necrosis factor receptor 1 was associated with a poor survival (Chiechi et al., 2013). Similar to dopamine, there are no data relating serotonin production to angiogenesis in carcinoid tumors (Meijer et al., 2003).

11. Conclusions and perspectives

Based on the available literature it can be concluded that dopamine inhibits tumor growth, whereas serotonin stimulates tumor growth. In vitro and animal studies showed that dopamine inhibits endothelial cell proliferation and tumor growth via activation of DRD2. Treatment with dopamine is not feasible because of severe cardiovascular toxicity. Therefore clinical intervention studies with DRD2 agonists are attractive, especially as these agents are already being used in the clinic for other indications such as Parkinson's disease and hyperprolactinemia (Beaulieu and Gainetdinov, 2011). To our knowledge, no clinical trials with DRD2 agonists in cancer patients are currently performed.

Serotonin's role in tumor behavior has been studied less extensively and data are predominantly derived from in vitro experiments. These experiments showed serotonin to stimulate endothelial cells via activation of 5-HTR1 and 5-HTR2. Tumor cell proliferation could be inhibited by selected 5-HTR antagonists, depending on tumor cell type. Tryptophan hydroxylase inhibitors are currently used in clinical trials in irritable bowel syndrome patients (Brown et al., 2011) and for serotonin-producing carcinoid tumor patients to evaluate the effect on the carcinoid syndrome. However further animal experiments to reveal serotonin's mechanism of action are warranted.

12. Methods

Articles for this review were identified by searches of PubMed and Web of Knowledge using the search terms "dopamine", "serotonin", "5-hydroxytryptamine", "dopamine receptor", "serotonin receptor", "platelets", "angiogenesis", "neovascularization", "neoplasm", and "cancer". Relevant references of found articles were also included. We selected English publications until September 2013. International Clinical Trials Registry Platform (ICTRP) accepted trial registries were searched for ongoing clinical trials.

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Corrigendum

Corrigendum to "Dopamine and serotonin regulate tumor behavior by affecting angiogenesis" [Drug Resist. Updat. 17 (2014) 96–104]

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The authors regret that in paragraph 10 on page 101, the enzyme tyrosine hydroxylase is mentioned where it should have been tryptophan hydroxylase.

The right text is:

Tryptophan hydroxylase inhibitors block the conversion of tryptophan to serotonin. In vitro experiments showed reduced proliferation of neuroendocrine tumor cells after treatment with tryptophan hydroxylase inhibitor 7-HTP (1 nM). Cholangiocarcinoma cell proliferation could be blocked by tryptophan hydroxylase inhibitor p-chlorophenylalanine (CPA) (1 mM) (Alpini et al., 2008; Drozdov et al., 2009).

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