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Potential Use of Dopamine and Dopamine Agonists as Angiogenesis Inhibitors in the Treatment of Cancer

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Objectives

After completion of this program, the reader should be able to:

1. Explain the processes of angiogenesis and tumorigenesis and the role of each in cancer metastasis.
2. Describe the actions of dopamine on tumorigenesis and its relationship with vascular endothelial growth factor.
3. Discuss the methodology and results of the initial trials suggesting the use of dopamine and dopamine agonists in cancer treatment.
4. Evaluate the potential use of dopamine for cancer treatment in regard to side effect profiles and cost of therapy in comparison to current angiogenesis inhibitors.

Abstract

In recent years, there have been numerous developments in monoclonal antibodies used as anticancer drugs with a focus on reducing the ability of cancers to metastasize and produce new vasculature. These agents are called angiogenesis inhibitors and although these agents have been proven effective in treating certain types of cancers, production and administration of monoclonal antibodies comes at a steep cost with a severe side effect profile. Under normal physiologic conditions, angiogenesis is an important mechanism to create new blood vessels from preexisting vessels, usually occurring in adults. Tumor cells can hijack the angiogenesis pathway to produce new distant tumors sites, which may lead to poor prognosis. In an ongoing effort to discover alternative therapeutic options for cancer treatment, researchers have discovered that dopamine (DA) is able to inhibit angiogenesis through a mechanism involving vascular endothelial growth factor (VEGF) and the D_2 receptors. When the D_2 receptor is activated, this causes the VEGF receptor 2 (VEGFR2) to undergo endocytosis thereby preventing VEGF binding and stopping the creation of new vessels. Endocrine and gastrointestinal cancers have a high expression of D_2 and VEGF receptors and therefore are potential targets of therapy. Although DA may provide better tolerability and cost benefits, future studies in humans must be conducted to clearly determine its safety and efficacy as a treatment for cancer.

Key Terms

Angiogenesis Inhibitors; Antineoplastic Agents; Dopamine; Endothelial Growth Factor A; Gastrointestinal; Neoplasms; Pathologic Neovascularization; Vascular Endothelial Growth Factor A

Introduction

Angiogenesis is a natural process used by our bodies to produce new vasculature to increase blood flow to certain areas which have need of additional oxygenation.[1] When cancers proliferate, an increased demand for energy emerges. Cancers utilize the process of angiogenesis to increase blood flow to the area to allow for continued growth of a tumor in a process known as tumorigenesis. Inhibiting this action is one strategy of therapy used today to prevent further growth of the cancer. Due to high costs of traditional angiogenic inhibitor therapy for cancer, other options are a welcome sight. One option currently being studied is dopamine.

Angiogenesis and Tumorigenesis

Angiogenesis occurs in a four-step process: cellular injury, migration, proliferation and survival. The first step can be induced by a number of stimuli, including hypoxia.[1] A hypoxic environment can be caused by lack of perfusion to a local area, leading to a decrease in available oxygen and nutrients, which in turn stimulates Hypoxia-Inducible Factor 1 (HIF-1), a heterodimer consisting of an alpha and beta subunit. Hypoxia-Inducible Factor 1 is stabilized by the hypoxic environment and binds to gene sequences that allow for the upregulation of glucose transporters, erythropoietin and vascular endothelial growth factor (VEGF). Hypoxia-Inducible Factor 1 also induces upregulation of the VEGF receptor (VEGFR), namely VEGFR2, which is involved in the process of angiogenesis. The VEGF/VEGFR complex is an important activator of endothelial cell function by a number of signal transduction pathways, allowing for an increase in proliferation, permeability, migration and survival.

The VEGF/VEGFR complex also regulates the release of matrix metalloproteinases (MMPs), which degrade the basement membrane of the endothelial cells, enabling cellular migration toward chemicals secreted from the hypoxic areas through the process known as chemotaxis.[2] A key agent in angiogenic chemotaxis is VEGF. Cells are able to move by using membrane projections consisting of actin-sensing chemoattractants (filopodia) and the formation of a leading edge of the cell by cytoplasmic actin (lamellipodia). Finally, through a complex mechanism, endothelial cells arrive at the hypoxic site and form a tubule stabilized by pericytes from surrounding vasculature and differentiated mural cells[1].

In tumorigenesis, the initial neoplastic lesion can only grow between 2 to 3 mm^3 because of the lack of vascularity and the diffusion barrier of oxygen.[1] To overcome this limitation, the tumor must find a way to obtain access to vasculature in order to continue its proliferation. The tumor is able to grow through activation of the "angiogenic switch," occurring when the inhibitory factors are outnumbered by the positive factors, leading to development of new vascularization. The p53 tumor suppressor gene normally works to inhibit excessive angiogenesis by blocking the expression of the necessary growth factors, including VEGF; however, p53 is mutated and inactivated in almost 50 percent of cancer, rendering this inhibitory pathway futile. Additionally, because the environment of tumors is likely hypoxic, there is often an overexpression of HIF-1 stimulating the release of VEGF-A, an isoform of VEGF, and leading to the angiogenic sequences described above. Because of the hyperexpression of VEGF-A, Bcl-2 is also overexpressed in cancers and inhibits apoptosis by maintaining mitochondrial membrane integrity by overwhelming the effects of Bax, which normally induces apoptosis.[3] Additionally, survivin, usually a negligible protein in healthy individuals, is overexpressed due to elevated VEGF-A levels in cancers.[1] Survivin is thought to inhibit caspase activity, an apoptosis inducing protease, adding a second mechanism for endothelial cell survival and tumorigenesis.

Introduction to Dopamine

Dopamine, also known as 3-hydroxytyramine, is a monoamine metabolic product of the amino acid tyrosine.[4] It is stored in vesicles located in the presynaptic terminals of neurons after being taken in from the cytosol through the vesicular monoamine transporter 2 (VMAT2).[5] Dopamine is released into the synaptic cleft and exerts its actions by binding to postsynaptic G-protein coupled receptors (GPCR) of two different classes, which are differentiated based on their biochemical effects and gene sequencing.[6] It should also be mentioned that DA has different affinities (nanomolar to micromolar) for each receptor subtype which in turn has implications on receptor subtype sensitivity to DA agonists and antagonists.[4] Remaining DA in the synapse can undergo reuptake via the dopamine active transporter (DAT) back into the presynaptic neuron or undergo enzymatic degradation by either monoamine oxidase (MAO) or catechol-o-methyltransferase (COMT).

The D_1 receptor class consists of the postsynaptic D_1 and D_5 receptors and activates the $G\alpha_{s/olf}$ protein family to increase adenylate cyclase activation to produce cAMP. In contrast, the D_2 receptor class includes the D_2, D_3 and D_4 receptors, with D_2 and D_3 located both presynaptically and postsynaptically.[5] These are coupled to the $G\alpha_{i/o}$ protein family that inhibit adenylate cyclase to decrease cAMP.[4] By altering the levels of cAMP, the activity of various downstream signaling molecules are regulated.[6] Additionally, there are routes of dopamine receptor signaling that are independent of cAMP. In fact, many intracellular signaling pathways can be mediated through various enzymes, such as ERK, Epac 1 and GRK 2.

In terms of expression, DA receptors are found both in the central nervous system (CNS) and peripheral areas of the body.[5] Within the brain, dopaminergic neurons project to four major DA pathways associated with learning, cognition and motor function. In peripheral areas, the different subtypes are found on vascular smooth muscle, on various renal and mesenteric arteries and in the endocrine system.[7] Many actions may result from DA binding, such as diuresis and natriuresis in the kidneys and regulation of norepinephrine release. Dopamine receptors may play a role in the immune system with nervous and renal inflammation and autoimmune reactions. Lastly, another important result of receptor activation is the downstream effect of altering glutamate signaling.

Currently, DA and other agents that work by agonizing or antagonizing its receptors are used to treat a variety of conditions, especially within the CNS. Dopamine precursors and agonists are indicated in Parkinson's disease (PD) therapy while DA antagonists are used as atypical antipsychotics for schizophrenia.[4] Other uses include the treatment of endocrine disorders, hypertensive crisis and as prokinetic agents.

Additionally, DA is utilized for its effect on alpha-receptors and beta-receptors in the cardiovascular system for vasodilation and its inotropic effect on the heart.[8] This counteracts its ability to induce NE release in the periphery for vasoconstriction. It is indicated for hypotension with bradycardia and may be used in combination with other agents to treat post-resuscitation shock. At higher doses, DA will cause systemic and splanchnic constriction of the arteries. It may therefore be used to increase renal blood flow for acute oliguric renal failure and low cardiac output in critically ill patients.[9] However, it has not been supported in trials for renal insufficiency prevention or to decrease mortality or morbidity.[10]

More recently, the potential anticancer effect of DA has been discovered and its role in treatment is being researched.[6] Therefore, with the various existing therapeutic indications for DA, it is widely available and determining its anticancer effects may be useful in terms of costs, therapy management and side effects.

Dopamine and VEGF

While already acknowledged as an important neurotransmitter in the CNS, it has been suggested that DA, acting through the D_2 receptor, can inhibit tumor growth by a number of different pathways. One mechanism shows that DA increased association between the D_2 receptor and Sarcoma Homology Phosphatase-2 (SHP-2) at the surface of the cell.[11] The association stimulates the phosphorylation of SHP-2, inhibiting activation of the VEGFR-2. Another theory suggests that DA stimulation of the D_2 receptor actually causes the endocytosis of the VEGFR-2, which prevents VEGF from binding and causing its associated effects.[12] This demonstrates an association between the nervous system and angiogenesis that was previously unknown. This allows for D_2 receptor agonists that are already in existence to be used in other clinical settings.

Evidence for the Use of Dopamine

The connection between DA and VEGF to the associated effects on angiogenesis and tumorigenesis has prompted

researchers to consider DA as a potential agent to target these mechanisms which cancer cells use to thrive. It has been found that DA selectively inhibits the actions of VEGF by acting on the D_2 receptor and/or causing endocytosis of VEGFR-2. However, since this is a selective inhibition, other modulators of angiogenesis are still promoting angiogenesis, and the process is not completely inhibited.[12,13] This selective inhibition means there is room to study DA and D_2 agonists (since they both activate the DA receptors and have the similar effects) to see if its use can be successful in the treatment of cancers.

Both an animal study utilizing rats and a small human study were conducted to compare the outcome of treating ovarian hyperstimulation syndrome (OHSS) when using cabergoline, a long-acting D_2 receptor agonist. Ovarian hyperstimulation syndrome is caused when there is ovarian hypersecretion of VEGF which activates VEGFR-2.[14] The results of the study showed a decrease in the incidence of OHSS in rats treated with cabergoline (100 μg/kg/day) and, with the limited side effects seen in the rodent trial, the researchers decided to do a small trial on humans as well. For humans, cabergoline treatment was given only to individuals who were oocyte donors at high risk for developing the syndrome. The human test subjects were being treated with prophylactic doses of 5 to 10 μg/kg/day of cabergoline. Results on humans showed a 65 percent occurrence of OHSS in the control group compared with 25 percent in the treatment group. Since OHSS is dependent upon high concentrations of VEGF, these results show that activating the D_2 receptor may possibly have beneficial effects to decrease the rate of angiogenesis and tumorigenesis in humans suffering from cancer. However, the specifics about how the researchers performed this study, the sample size and other parameters were not available at the time of publication.

Another animal study showed that rats with a hyperactive dopaminergic system had decreased tumor angiogenesis.[15] The researchers bred rats to have hyperactive dopaminergic systems, a requirement for the study, and then implanted rat adenocarcinoma cells into the rats in order to observe the tumor growth. It was discovered that rats with hyperactive dopaminergic systems had about 35 percent smaller tumors compared to the placebo rats. Fewer lung metastases were observed in the experimental group (hyperactive dopaminergic system rats) compared to the control group (nonhyperactive dopaminergic system rats) macroscopically after all test rats had died. On the 24th day after implanting the cancerous cells into the rats with either hyperactive or nonhyperactive dopaminergic systems, all rats with nonhyperactive dopaminergic systems had died and none of the rats with hyperactive dopaminergic systems had died. Most importantly, it was found that rats with hyperactive dopaminergic systems had decreased tumor angiogenesis by determining hemoglobin content in tumors from both groups of rats. Hemoglobin content in tumors were significantly lower in rats with hyperactive dopaminergic systems compared to those with nonhyperactive dopaminergic systems (hyperactive: 40.6±7.6 mg/dL; nonhyperactive: 76.9±13 mg/dL, $P<0.05$). The lower hemoglobin content in the tumor corresponded to decreased tumor growth. No medication was used in this study. The data gathered was based upon the premise that rats with hyperactive dopaminergic systems would have increased levels of DA in their system, allowing for the effects of naturally produced DA to show its action. This further suggests that DA has a mechanism by which angiogenesis is inhibited.

A study was conducted on gastric cancerous tissue in rats and mice.[16] Gastric cancer is known to require increased angiogenesis activity to survive and the possibility of using doses of DA to inhibit the growth of this cancerous tissue was being examined. In the study, some rats and mice were pretreated with domeperidone, a D_2 receptor antagonist, to confirm that the actions of DA were through the D_2 receptor. The researchers found that when rats or mice were pretreated with domeperidone followed by treatment with DA, there was no effect, confirming that the D_2 receptor is responsible for the effects shown in the study. The results showed that even low doses of DA (50 mg/kg/day or about 5 percent of the median lethal dose in rodents) would inhibit the growth of the cancer tumor substantially (tumor size: 311.5 ± 11.9mm^3 in placebo group, 106.0 ± 7.4 mm^3 in treatment group, $P<0.05$). What is even more interesting is that in all of the samples of tissue examined, the concentrations of endogenous DA were very low, almost negligible, and the concentrations of VEGF were increased. Cancers deplete the stores of DA in the tissue, allowing for the growth of the cancer with increased expression of VEGF. This explains why even low doses of DA would inhibit the growth of the cancer; the DA administered to the site would be able to act on every receptor available since all or most of the endogenous DA was gone. The DA would be able to endocytose many of the VEGFR-2 and thereby decrease the angiogenic properties of the gastric cancer.

Since human cancers utilize this same mechanism of angiogenesis to provide their sustenance, animal studies can provide a good basis for comparison. Human studies will need to be conducted to confirm that this effect can be mirrored in the human physiology and allow for this to be a treatment option for those with cancers and tumors sensitive to DA therapy, such as endocrine tumors.[17,18] Human studies will need to be used to determine the dose of DA that may be administered in treating cancers, as this is not known at this time.

A study was conducted to evaluate the prevalence of the D_2 receptors and VEGF in various pituitary adenomas.[19] Knowing this information would be beneficial in the plan to treat patients with certain kinds of cancers, as it could tailor the therapy to target a specific receptor if it is known to have increased expression in that cancer. The study examined 197 tissue samples from patients with various types of pituitary adenomas. A streptavidin-peroxidase method was used for staining the samples of cancerous tissue obtained from the patients. These stains were then scored on a 0 to 7 scale which accounted for the strength of the stain (0 to 3, where 0 is negative, 1 is weak, 2 is medium, 3 is a strong stain) and the extent of the stain (0 to 4, where a percentage of the staining area compared to the whole carcinoma sample was

evaluated; 0 (0 percent), 1 (1 to 25 percent), 2 (26 to 50 percent), 3 (51 to 75 percent), 4 (76 to 100 percent)). Any score above 3 was considered a high expression stain. Results showed that 64.9 percent of the pituitary adenomas had a high expression of D_2 receptors and 58.9 percent had a high expression of VEGF. From this data, it can be inferred that over half of pituitary adenomas could potentially benefit from DA therapy to decrease the cost of treatment and help reduce tumor size, since these tumors would be more sensitive to treatment with DA due to high D_2 receptor expression.

Side Effects

Side effects associated with the costly VEGF inhibitors can include bleeding, clots that can lead to a stroke or heart attack, high blood pressure, proteinuria and gastrointestinal disturbances. Rarer side effects can include GI perforation, fistulas of the bile duct and even certain cancers. Birth defects have been seen in animal models, but have yet to be seen in humans. Generally, VEGF inhibitors carry a larger, more severe side effect profile that occurs more often than with an agent like dopamine.[20] Furthermore, because both dopamine and VEGF inhibitors work via similar mechanisms, treatment will require concurrent therapies with chemotherapeutic agents, like 5-Fluorouracil.[21] The use of VEGF inhibitors could be problematic in patients suffering from cardiovascular conditions in addition to cancer, whereas DA or D_2 agonists could be a safer option in patients with or at risk for cardiovascular complications.

While DA agonists may be considered as an anticancer treatment, the severity of side effects must be postulated from their current indications in other therapies. Dopamine agonists have been observed to cause peripheral edema, orthostatic hypotension, hallucinations, sudden-onset of sleeping ("sleep attacks") and impulse control disorders (ICDs).[22] Characteristics of ICDs include hypersexuality and compulsive eating, gambling and buying. This particular adverse effect has been found in 17 percent of PD patients taking DA agonists and may eventually have other negative consequences relating to finance, behavior and social relationships. Addressing these effects includes either discontinuing or tapering DA therapy. Strategies for tapering may include substituting other medications such as L-dopa; however, this may worsen the disease being treated. Furthermore, tapering may be ineffective in some patients and can result in dose-dependent dopamine agonist withdrawal syndrome (DAWS). Dopamine agonist withdrawal syndrome has been characterized by both psychological and physical symptoms including anxiety, panic attacks, depression, agitation, fatigue, flushing, nausea and vomiting. These symptoms are similar to withdrawal from other psychostimulants. Additionally, there is currently no treatment for the syndrome and the only way to alleviate DAWS is by restarting or increasing the DA agonist therapy. Therefore, to prevent DAWS, prevention strategies must be in place before beginning therapy. It is recommended to remain cautious with patients with a high risk of ICD because this side effect is highly associated with DAWS. Additionally, patients should avoid using high doses of DA agonists for long periods of time as this is a risk factor for ICD. Therefore, patients must provide informed consent and become educated on the potential consequence of DAWS. They also should be screened for ICD risk during therapy and report any ICD and DAWS symptoms right away.

An animal model examining endometrial angiogenesis used DA agonist cabergoline and observed reduced neoangiogenesis.[23] It was noted that DA safety considerations needed to be studied in the future since DA therapy may interfere with pregnancy. Researchers noted that lower doses of 0.05 mg/kg cabergoline were as effective as higher doses of 0.1 mg/kg, implying that using the lowest effective dose may help lower the incidence of side effects if used in humans. Although dosing has not yet been established for DA in anticancer treatments in humans, this may be a dosing consideration in terms of maximizing efficacy while minimizing side effects.

Even with the concern for DAWS, DA agonists have already been used for a length of time, making their side effects well known and manageable, and can be generally considered safe.[24] However, addressing side effects by tapering therapy may not be practical in cancer treatment. Therefore, the risk of DA side effects must be sufficiently studied when DA is used at anticancer doses in humans.

Cost Implications

One of the major barriers of utilizing newer anticancer treatments, especially monoclonal antibodies, is the price associated with them. For example, one study looked into the cost of three angiogenesis inhibitors: the VEGF inhibitor bevacizumab (Avastin) and two protein kinase inhibitors, sunitinib (Sutent) and sorafenib (Nexavar). It found that the per-patient per-month cost associated with these three medications was: $5,639 for sunitinib, $5,214 for sorafenib and $13,664 for bevacizumab.[25] These prices do not include the costs of additional procedures and/or the treatments related to the adverse events. However, for a vial of 400mg/5mL DA the hospital cost is around 50 cents per vial, which is 10,000 times less expensive than the angiogenesis inhibitors.[26] For the D_2 agonist cabergoline, the daily cost is between $10 and $15, so the cost per month would be roughly $300 to $450.[27] With the significant cost differences between DA and VEGF inhibitors, this provides an added benefit to its potential anticancer effects.

Conclusion

From the limited number of animal studies currently published, it seems that treatment with DA and D_2 agonists potentially has a great benefit in patients with cancers known to have high expression of D_2 receptors, such as endocrine tumors and gastrointestinal tumors. While large human studies have yet to be performed, there is strong evidence from the animal studies and the small human study that DA and D_2 agonists decrease the effects of the VEGFR-2 and inhibit angiogenesis and tumorigenesis. Applying this to cancer treatment regimens could lead to decreased costs for health care systems and reduced adverse events, as DA and D_2 agonists are less expensive and potentially safer options compared to the conventional angiogenesis inhibiting regimens. Since the first priority of health care is the safety and well-being of the

patient, despite the initial promise of using DA and D_2 agonists for cancer treatment, it cannot be fully recommended until additional research is completed. Future trials with humans must be conducted to determine the full spectrum of safety, dosing and efficacy of utilizing DA as a potential new anticancer treatment.

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Assessment Questions

1. Referring to OHSS, which of the following doses were used in humans who were oocyte donors at high risk for developing the syndrome?
   A. 100 µg/kg/day
   B. 150 µg/kg/day
   C. Prophylactic doses of 5-10 µg/kg/day
   D. Prophylactic doses of 50-100 µg/kg/day

2. Rats with hyperactive dopaminergic systems had tumors which were what percent smaller in size compared to the nonhyperactive dopaminergic system rats?
   A. 12%
   B. 30%
   C. 56%
   D. 35%

3. Which two types of cancer have shown to have a high expression of D_2 receptor density?
   A. Lung and Prostate
   B. Endocrine and Gastrointestinal
   C. Breast and Testicular
   D. Pancreatic and Gastrointestinal

4. Angiogenesis involves which of the following steps:
   A. Migration
   B. Proliferation
   C. Cellular injury
   D. Survival
   E. All of the Above

5. The overexpression of which growth factor is primarily behind angiogenesis?
   A. Growth Differentiation Factor 9
   B. Vascular Endothelial Growth Factor
   C. Transforming Growth Factor Alpha
   D. Migration Stimulating Factor

6. VEGF inhibitors carry no cardiovascular side effects.
   A. True
   B. False

7. The mechanisms in which dopamine inhibits VEGF receptors include:
   A. SHP-2
   B. Receptor Endocytosis
   C. A and B
   D. None of the above

8. Which of the following drugs may be used to block the D_2 receptor?
   A. Dopamine
   B. Cabergoline
   C. Domeperidone
   D. All of the above

9. The treatment for DAWS includes:
   A. Antidopamine therapies
   B. Risperidone
   C. Apomorphine
   D. Currently no treatment is available

10. Dopamine's effects are mostly observed in:
    A. The central nervous system
    B. The cardiovascular system
    C. The pancreas
    D. Both A and B

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Program Content:	Strongly Disagree				Strongly Agree
The program objectives were clear.	1	2	3	4	5
The program met the stated goals and objectives:					
Explain the processes of angiogenesis and tumorigenesis and the role of each in cancer metastasis.	1	2	3	4	5
Describe the actions of dopamine on tumorigenesis and its relationship with vascular endothelial growth factor.	1	2	3	4	5
Discuss the methodology and results of the initial trials suggesting the use of dopamine and dopamine agonists in cancer treatment.	1	2	3	4	5
Evaluate the potential use of dopamine for cancer treatment in regard to side effect profiles and cost of therapy in comparison to current angiogenesis inhibitors.	1	2	3	4	5
The program met your educational needs.	1	2	3	4	5
Content of the program was interesting.	1	2	3	4	5
Material presented was relevant to my practice.	1	2	3	4	5

Comments/Suggestions for future programs:

Thank you!

Answers to Assessment Questions—Please Circle Your Answer

1. **A B C D**
2. **A B C D**
3. **A B C D**
4. **A B C D E**
5. **A B C D**
6. **A B**
7. **A B C D**
8. **A B C D**
9. **A B C D**
10. **A B C D**

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