DOI: 10.24292/01.OT.310320.05

The potential usage of D2 dopaminergic agonists in the treatment of VEGF-related eye diseases

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HIGHLIGHTS

Dopamine and D_2 dopaminergic agonists inhibit vascular endothelial growth factor (VEGF) and are potential drugs for the treatment of exudative AMD, diabetic macular edema and proliferative diabetic retinopathy.

ABSTRACT

Dopamine and D_2 dopaminergic agonists inhibit endothelial growth factor (VEGF). This effect has been proven in many types of cancer and in ovarian hyperstimulation syndrome. Experimental studies indicate the potential use of these substances in the treatment of eye diseases with increased VEGF release, such as exudative AMD, diabetic macular edema and proliferative diabetic retinopathy. This paper presents a review of the latest literature on the potential use of D_2 dopaminergic agonists in the treatment of vascular endothelial growth factor (VEGF) related diseases.

Key words: VEGF, AMD, diabetic retinopathy, dopamine, D_2 dopaminergic agonists

Dopamine and D2 dopaminergic agonists inhibit activity of endothelial growth factor (VEGF). This effect has been demonstrated in many neoplastic diseases and ovarian hyperstimulation syndrome. The studies carried out so far indicate the potential use of these substances also in the treatment of ocular diseases with increased release of vascular endothelial growth factor, such as: exudative (wet) age-related macular degeneration (AMD), diabetic macular edema (DME) or proliferative diabetic retinopathy (PDR).

Vascular endothelial growth factor (VEGF) is a protein that stimulates developmental and pathological angiogenesis and increases vascular permeability. The increase in the concentration of this protein underlies many pathological processes within the retina. In the proliferative diabetic retinopathy, the concentration of VEGF increases in response to growing hypoxia caused by the retinal inflammatory process. The occurrence of diabetic macular edema, which is the main cause of visual impairment in diabetic patients, is also associated with the increase of VEGF. In the exudative form of age-related macular degeneration (AMD), an increase in VEGF-A concentration and proliferation and growth of blood vessels under the retinal pigment epithelium layer (type I AMD) or in subretinal space (type II) were observed. The increase in VEGF concentration, which is produced in response to retinal ischemia, also the main reason of macular edema occurring during retinal vein thrombosis. Currently, injections of substances blocking the effect of VEGF and/or its receptor (anti-VEGF medications) are used in the treatment of these diseases. However, due to the complicated procedure of application, varied efficacy and observed side effects of anti-VEGF preparations, a search is going on for substances that would complement or substitute the current treatment. Dopamine and D2 dopamine receptor agonists are a very interesting group of drugs with potential use in ophthalmology.

Dopamine is the main neurotransmitter in the central nervous system (CNS), next to adrenaline, noradrenaline and acetylcholine. It was discovered over 60 years ago by Dr. Arvid Carlsson, who, together with Eric Kandel and Paul Greengard, received the Nobel Prize in Physiology and Medicine in 2000 for this discovery, and for demonstrating the role of dopamine in the development of schizophrenia. Dopamine acts through specific, chemical membrane receptors, which increase (D1 receptors) or inhibit (D2 receptors) the activity of the adenyl cyclase [1]

In the 60s and 70s of the 20th century, several epidemiological studies were carried out, showing a reduced risk of cancer and death from cancer in patients diagnosed with schizophrenia [2]. Due to the fact that in the course of schizophrenia and mania there is an increase in dopamine activity in the CNS [3], it was concluded that the change in cancer risk may indicate an important role of dopamine in inhibiting the development of neoplastic diseases [4]. The above observations were confirmed by the results of experimental studies. In rats with increased dopaminergic activity, slower growth of tumors, lower number of metastatic foci and increased survival were found compared to animals with lower dopaminergic activity [5].

Experimental studies have shown that dopamine inhibits VEGF-stimulated angiogenesis, and therefore inhibits tumor growth. It was found that this effect is associated with the activation of dopaminergic D2 receptors and inhibition of VEGF- VEGFR-2 receptor phosphorylation (vascular endothelial growth factor receptor 2) [6].

The anticancer effect of dopamine and D2 dopamine receptor agonists has been proven in many models of cancer, such as gastric cancer [7], colorectal cancer [8], malignant melanoma [9], multiple myeloma [10], ovarian cancer [11], endometriosis [12], small cell lung cancer [13], non-small cell lung cancer [14], prostate cancer [15] and pituitary tumor [16]. Under the influence of administered dopamine or D2 dopaminergic receptor agonists, the number and permeability of blood vessels in the neoplastic tissue, the size and number of neoplastic foci and the number of metastases were reduced and the survival rate of the examined animals increased.

It was also found that dopamine increases the effectiveness of anticancer drugs, such as doxorubicin and 5-fluorouracyl [17]. Moreover, the experimental studies on colorectal and pulmonary cancer models have shown that the efficacy of dopamine is comparable to that of sunitinib, a tyrosine kinase inhibitor, e.g. VEGFR-1, VEGFR-2 and VEGFR-3. At the same time, it has been demonstrated that dopamine has a more favorable safety profile, does not significantly affect the arterial blood pressure values or change the liver and renal parameters [18].

The anti-edematous effect of dopamine and D2 dopamine receptor agonists is used in the treatment of ovarian hyperstimulation syndrome (OHSS). OHSS is a life-threatening gynecological condition, and occurs in women who are induced to ovulate for the purpose of taking their ova for external fertilization. OHSS is characterized by ovarian enlargement, increased permeability of blood vessels and penetration of fluid into the peritoneum and pleura. Increased Blood density, decreased renal flow and increased risk of thrombosis:is also observed. The main role in the etiopathogenesis of OHSS is played by VEGF released by granular cells of maturing Graff's follicles. The agonists of dopaminergic D2 receptors, cabergoline and bromocrip-

tine, have proven their efficacy in the treatment of OHSS by inhibiting the VEGF – VEGFR-2 receptor activity [19].

The results of epidemiological studies published in recent years indicate an increased risk of AMD or exudative (neovascular) age-related macular degeneration and diabetic retinopathy in patients with Parkinson's disease [20, 21]. Moreover, it has been observed that AMD occurs at a later age in people treated with dopamine precursors or dopamine receptor agonists [22]. The above data may indicate an important role of dopamine in the etiopathogenesis of VEGF-dependent neovascularization and increased vascular permeability.

SUMMARY

So far, it has been found that selected dopaminergic D2 receptor agonists inhibit stimulated angiogenesis and gene expression for VEGF [23-25]. The above results set a new direction of research aimed at developing an effective and safe group of drugs used to treat nAMD, diabetic macular edema and proliferative form of diabetic retinopathy. The authors of this paper plan to conduct research to check the antiangiogenic action of dopaminergic receptor agonists D2.

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Authors' contributions:
Maciej Osęka: idea of using D_2 agonists in inhibiting neoangiogenesis in eye diseases, preparation of this work.
Katarzyna Saładziak: idea of research, conducting research and developing their results.
Agnieszka Jamrozy-Witkowska: substantive consultation and preparation of this work.
Jacek Dziedziak: substantive consultation and preparation of this work.
Agnieszka Cudnoch-Jędrzejewska: substantive consultation and preparation of this work.
Anna Święch: developing the concept of the study, conducting the research and developing their results.

Conflict of interest:
Maciej Osęka: three patents/patent applications covering the presented area of knowledge.
Other autors: none.

Financial support:
None.

Ethics:
The content presented in the article complies with the principles of the Helsinki Declaration, EU directives and harmonized requirements for biomedical journals.