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# Betahistine: Targeting on Vascular Wall Aging

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## Abstract

Betahistine are routine drug in neurological practice, which is used to correct vertigo. The clinical efficacy of this drug can be caused not only by neuro-, but also by endotheliotropic action. In this review, the main information on the potential mechanisms for the implementation of vasoprotection, including metabolic, NO-ergic, anti-inflammatory and other components of the action are discussed. Betahistine as histamine receptors type 3 antagonist and histamine receptors type 1 and 2 agonist has a positive effect on cerebral and systemic hemodynamics, and due to anorexigenic action and the ability to stimulate lipolysis can ameliorate dyslipidemia as well as suppress the synthesis of pro-inflammatory cytokines and increase the expression of endothelial NO synthase.

**Keywords:** Betahistine, Endothelial Dysfunction, Atherosclerosis, Histamine, Vertigo.

## Introduction

Neurological disorders such as vertigo, attention deficit, cognitive decline, and fatigue are among the most common symptoms in women of menopausal age. The etiology of this kind of symptoms is different, but the most obvious cause is dyscirculatory cerebral blood flow disorders, associated, among other, with endocrinological alterations and endothelial dysfunction typical of this age [1].

The close coherence of endothelial function (ED) with cerebral hemodynamic abnormalities allows us to consider the endothelium as an important target of therapeutic effects. Widely known that the endothelial monolayer is the largest endocrine organ and its functional activity is associated with the regulation of hemodynamics, coagulation, local inflammation, angiogenesis and many other processes. Endothelial dysfunction leads to hypertension, impaired normal tissue perfusion, the appearance of a tendency to thrombosis and pathological changes in the vascular network anatomy. Changes in the spectrum of molecules secreted and expressed by the endothelium and a violation of its barrier function ultimately lead to infiltration of the vascular wall with atheromatous masses and the formation of atherosclerotic plaques [2].

With the aim to improve the effectiveness of underlying disease treating and reduce the risk of developing life-threatening vascular complications, pharmacological correction of neurological symptoms associated with impaired brain blood supply should be carried out using drugs that have not only neuro-, but also endothelium-protective activity. Since betahistine is one of the most commonly prescribed drugs in neurological practice (Fig. 1), it seems appropriate to evaluate its pharmacodynamics from the point of view of the effect on endothelium function.

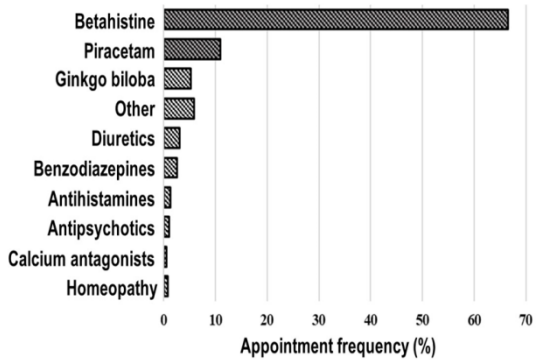


**Figure -1:** The structure of drugs for the vertigo treatment [3]

## Betahistine, Histamine and Endothelium

At the beginning of the 20th century, the future Nobel laureate from London, Henry Dale (Henry Dale) worked on the detection of compounds responsible for improving uterine tone when using an extract of ergot [5]. In 1910, the search led to the discover of histamine, and the description of its phenotypic effects, such as vasodilation, increased tone of the smooth muscles of the internal organs, as well as a positive chrono-and inotropic effect [6].

After another 10 years, Popelsky in experiments on dogs discovered the ability of histamine to increase the secretion of hydrochloric acid in the stomach [7]. Finally, in 1937, William Feldberg and staff provided compelling evidence that histamine is a mediator of experimental anaphylaxis [8, 9]. Studies of the second half of the 20th century were marked by the identification of histamine molecular targets — histamine receptors (HR) of types 1, 2, 3, cloning of their genes, and the synthesis and study of a wide range of compounds having chemical affinity for them, mainly antagonists [10]. Then, already in the 21st century, using the bioinformatics screening, histamine receptor of type 4 was discovered, whose functions are mainly limited to immune regulation [10-12]. H3R are predominantly expressed in the brain, where they provide modulation processes for synaptic transmission. They are characterized by high spontaneous activity and the ability to inhibit the neuronal liberation of histamine. The therapeutic potential of this type of blockade, receptors, includes the treatment of vertigo, narcolepsy, attention deficit, Alzheimer's disease, allergic rhinitis, and some other pathologies [13].

Betahistine was registered in 1970 as a drug for the treatment of Meniere's disease. He is a selective H3 antagonist and an H1 and H2 receptor agonist. While the blockade of H3R causes mainly vestibulotropic effects, effects on H1R and H2R can cause endothelioprotective action.

### Hemodynamic Effects of Betahistine

Violation of the endothelium vasoregulatory function leads to the appearance of permanent vasoconstriction. At the same time, hypertension is a factor contributing to damage to the endothelial monolayer. As a result, a kind of vicious circle is created, the gap of which is one of the important tasks of pharmacotherapy.

Histamine receptors are widely expressed in the endothelium, responding mainly to controlling vascular tone and permeability. The H1 and H2 receptors are involved in endothelium-dependent vasodilation, which is prevented by prior administration of the blocker of the endothelial NO synthase L-NAME [14].

A particularly important role is played by histamine receptors in the regulation of cerebral blood flow, where their activation may be accompanied by both contraction and relaxation of blood vessels. At the same time, vasodilation is a more stereotypical response and is also mediated by endothelium [15]. Following the histamine infusion, a two-phase drop in blood pressure occurs, which is implemented initially through the H1 and then through the H2 receptors. The hemodynamic effect of the H1R and H2R agonists with respect to the small steep circulation has the opposite direction and is expressed in an increase in pulmonary pressure [16].

### Betahistine and Inflammation

Acute or permanent inflammation, leading to cytokinemia and reactive oxygen species increased production is one of the factors contributing to the development and progression of ED [17]. The ability of drugs to reduce the excess activity of the adaptive and innate parts of the immune system can be considered as part of the endothelioprotective action.

Although the histaminergic system is classically associated with a proinflammatory focus, experimental studies in animal models have shown that phlogogenic potential mainly has H1R, while the action of other subtypes of histamine receptors is not so clear. Thus, the inflammatory infiltration of the brain by neutrophils after the simulation of focal ischemia is reduced almost 2 times against the background of the introduction of L-histidine [18]. This effect is due to the ability of histamine to reduce the production of IL-12 through H2R and is prevented by the introduction of ranitidine [19, 20]. Histamine, as a classic edemogenic agent, after intra-arterial injection into the carotid artery increases transcapillary penetration of albumin into brain tissue (again through H2R) [21, 22]. However, against the background of the already existing edema, activation of the histaminergic system leads to a decrease in the content of transudate in the affected areas [23]. This phenomenon may be due to both a decrease in capillary permeability and the ability of histamine to reduce neuronal excitotoxicity [24].

In vitro treated by with a histamine solution (from $10^{-5}$ to $10^{-7}$ M) macrophages showed a decrease in chemotaxis, production of superoxide anions, and macrophage phagocytic activity. In addition, histamine and the H2R agonist dimaprit inhibited TNF-α and IL-12 production induced by lipopolysaccharide, as well as the expression of the ICAM-1 molecule on monocytes (Fig. 3) [25, 26].

In animal models of local inflammation, betahistine reduces the severity of arthritis and levels of pro-inflammatory cytokines, including TNF-α, IL-6, IL-23, and IL-17 in mouse paw tissues. Lymph node cells in mice treated with betahistine are characterized by a decrease in proliferation, as well as a lower Th17 content [27].

### Metabolic Effects of Betahistine

The endothelium is one of the most vulnerable organs experiencing the damaging effects of dysmetabolic disorders. Improving the metabolic profile is considered as one of the promising strategies for the correction of endothelial dysfunction [28-31].

In this regard, the fact that betahistine has anorexigenic properties and the ability to stimulate lipolysis is especially intriguing.

Numerous experiments have shown that the brain histaminergic system plays a role in the pathogenesis of obesity. Intracerebral administration of histamine, systemic use of its precursor L-histidine and H3-R blockade reduce food intake, body weight and improve the rodent lipid profile [32-35]. In contrast, administration of the alpha-fluoromethylhistidine, histidine-decarboxylase inhibitor and intraventricular injection of H1-R antagonists increase food intake in rodents [36]. Similarly, transgenic mice with reduced H1-R and histidine carboxylase expression develop hyperphagia, obesity, and diabetes [37–40]. These data are confirmed in clinical studies. So, one of the side effects of the drug for the treatment of schizophrenia olanzapine is obesity [41]. This effect is presumably associated with the presence of histaminergic action in it and is leveled with simultaneous use with betahistine [42-45].

The positive metabolic effects of H1R agonists are also due to the peripheral component of the action. Thus, the use of betahistine enhances the expression of enzymes involved in lipolysis and inhibition of lipogenesis in the liver by activating the receptor activated by peroxisome proliferator (PPAR-α) (Fig. 3) [46].

PPAR-α is known to be the target of antidiabetic drugs of the thiazolidinediones group and associated with an increase in glucose utilization, normalization of energy metabolism and contributes to an increase in eNOS activity in endothelial cells [47, 48].

## Conclusion and Perspectives

Thus, betahistine has a large range of potential ways to achieve endothelioprotective action, which include an improvement in the metabolic profile, a positive effect on hemodynamics, a decrease in pro-inflammatory activation and NO-ergic activity.

Accumulated clinical experience indicates that betahistine has a positive effect on cerebral blood flow, but its effect on peripheral hemodynamics and atherothrombogenesis processes may be a subject of further study.

Search and study of drugs that improve endothelial function is an important task of modern pharmacology [49-57]. Special attention should be paid to remedies that, along with the treatment of the underlying disease, reduce the risk of other pathologies and improve the long-term prognosis of patients.

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