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Importance of the Pharmacological Synergism in Modern Concept of Anti-Ischemic Therapy

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Research Article

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ABSTRACT

Nowadays, the increase of therapy efficacy of ischemic conditions in cardiology and neurology is one of the top trends in clinical, pharmaceutical and pharmacological studies on a global scale. In this article the issues of anti-ischemic therapy optimization by the example of the combined use of precursors and carnitine analogues – trimethylhydrasine propionate (TMHP) and γ-butyrobetaine (GBB) are reviewed. The pharmacodynamic advantages of this combined use are characterized by the occurrence of the synergistic phenomenon in the form of a mutual potentiation of its effects. TMHP is a famous cardio- and neuroprotector; in the binary mechanism of its action the metabolic component is more significant than vasodilatation one and its combination with GBB makes up for this shortcoming. Adding GBB, on the background of inhibiting its conversion into carnitine under the impact of TMHP, leads to its quick accumulation in the ischemic tissues, to reinforcement of nitrogen oxide synthesis and to vasodilatation high-speed development of, which, in turn, substantially enhances the pharmacodynamic metabolic component of the given combination. The present concept has underlaid the development of the original regulator of the vascular endothelial function – the drug "Capicor", which has unified the advantages of metabolic and endothelial cytoprotector TMHP, as well as endothelial corrector of GBB

INTRODUCTION

Cardiovascular system diseases hold the first place in the structure of total mortality both in Europe and all over the world [1-3]. Thus, in 2012 according to the WHO, 17.5 million people died from cardiovascular diseases, representing 31% of all premature deaths in the world [3, 4]. Out of this number, 7.4 million people died from coronary heart diseases and 6.7 million died due to strokes. More than 75% of deaths from this group of diseases occur in countries with low- and middle-income rates [1, 4, 5].

In this connection, the effective prevention and treatment of ischemic conditions is currently one of the priority areas of research in the field of Clinical Pharmacy, as well as Clinical and Experimental Pharmacology.

MODERN PRINCIPLES OF THE THERAPY OF ISCHEMIC CONDITIONS

The basic principles of anti-ischemic therapy used in current clinical practice can be reflected in the form of a scheme **(Figure 1)**. It is based on a combination of two complementary concepts – hemodynamic and metabolic ones, which are realized through different mechanisms of drug action [6-8].

Thus, the hemodynamic concept includes measures that are directed at correcting endothelial dysfunction, compensating impaired circulation and increasing oxygen delivery and energy substrates to the ischemic tissue [1, 6]. The metabolic therapy means improving energy metabolism of cells by pharmacological control of the energy formation and its transfer to cell organelles

in order to improve the efficiency of energy production without affecting the organ perfusion and hemodynamic parameters as, for example, in the case of cardiac muscle - the frequency and force of heart pre- and afterload, etc. [7, 8].

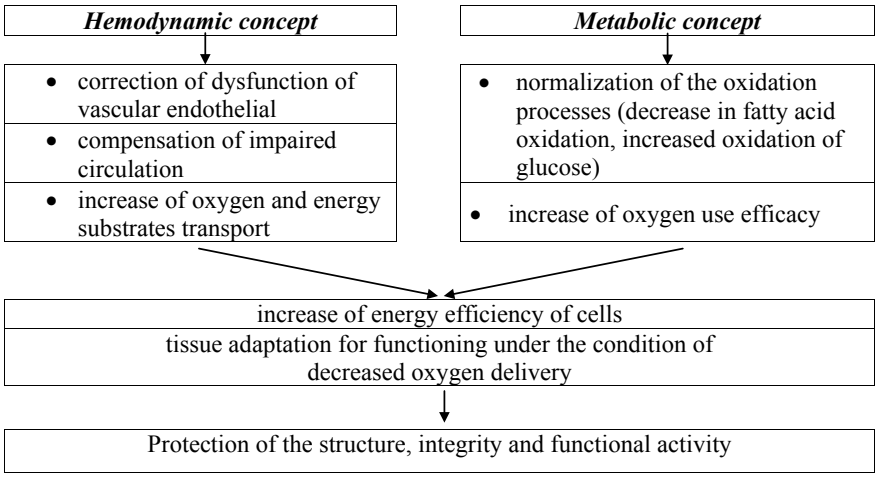

Figure 1. Modern principles of ischemic conditions therapy

An endothelial dysfunction plays a special role in the development of hemodynamic disturbances . Today there is no doubt that the vascular endothelium proves itself an important and independent in the development and progression of ischemic conditions, being the main factor of microcirculation [9, 10]. Endothelium is a huge paracrine organ distributed over the entire inner surface of the cardiovascular system of the human body in the form of a thin semipermeable membrane lining the inside of the heart and vessels and continuously generating a great number of important biologically active substances [11]. In a convenient form for human consciousness endothelium is an organ with a mass of five hearts with normal cell count - 1 trillion and a total surface area that equals to the area of 6 tennis courts [9].

Furthermore, the metabolic concept is essential in the treatment of cardiovascular diseases as it is related to the physiological features of the cardiovascular system. Hence, in order to ensure its effective functioning it requires uninterrupted power supply to the myocardial tissue, which is carried out by anaerobic oxidation of glucose 2%, aerobic - by 20-40% and the β-oxidation of fatty acids - by 60-80% under the condition of a physiologically normal state. Thus, the oxidation of fatty acids requires considerably more oxygen [1, 8, 12, 13].

In case of ischemia the glycolysis processes are inhibited in the myocardium: aerobic glycolysis is nearly completely suppressed (up to 10%), and the oxidation of fatty acids is mostly activated. This phenomenon has a "vicious cycle" nature since the use of fatty acids as a primary energy substrate leads to reduced glucose utilization, increased production of acyl-CoA, and, as a result, increased synthesis of fatty acids, which in turn increases the processes of their recurring oxidation. At the same time, there is 12-17% an increase in oxygen consumption. Moreover, there is an accumulation of fatty acid oxidation product – acyl-CoA, which causes an increase of acidosis in cardiomyocytes, calcium ion concentration, decreased ATP synthesis, increased activity of the processes of free radical oxidation, and, as a result, cell dysfunction. The above-mentioned determines the necessity of cell preconditioning, i.e. their readiness for hypoxic conditions, optimization of their enzymatic systems, as well as more efficient use of oxygen, etc. [6, 12, 14].

It should also be noted that after ischemia the hemodynamic recovery period inevitably leads to the development of the syndrome of "reperfusion". This phenomenon is due to cell inability to dispose of the rush flow of oxygen (for which it is necessary to restore the original metabolic processes within cell) [6, 1]. This results in a rapid formation of reactive oxygen species, free radicals, activated processes of lipid peroxidation, with a destruction of cell membrane structures (especially endothelial cells) and the tissue involved in oxidative stress [10, 11]. In this regard, it is evident that in the complex therapy of ischemic conditions along with agents reducing hemodynamic and endothelial dysfunction, metabolic drugs must be included in order to ensure cytoprotection in case of oxidative stress [7, 8, 12, 15-17].

BRIEF COMPARATIVE PHARMACODYNAMIC CHARACTERISTICS OF METABOLIC CYTOPROTECTORS

Taking into consideration the multi-vector nature of the pathogenesis of ischemic conditions, recently the attention of specialists has been focused on drugs of polytropic action that can provide cytoprotection in case of pathophysiological conditions.

Most drugs in this class have a metabolic nature of the effects on the ischemic tissue. Today trimetazidine (TMHP) and trimethylhydrasine propionate, also known as meldonium, are the best known among them [12, 18-21].

Both of the drugs reduce the rate of oxidation of fatty acids, enhance glycolysis and improve, thereby, the efficiency of energy production in cells under ischemic conditions [14, 19, 22, 23]. However,the comparative analysis of the mechanisms of their actions hasrevealed several distinct advantages for TMHP **(Figure. 2.)** [18].

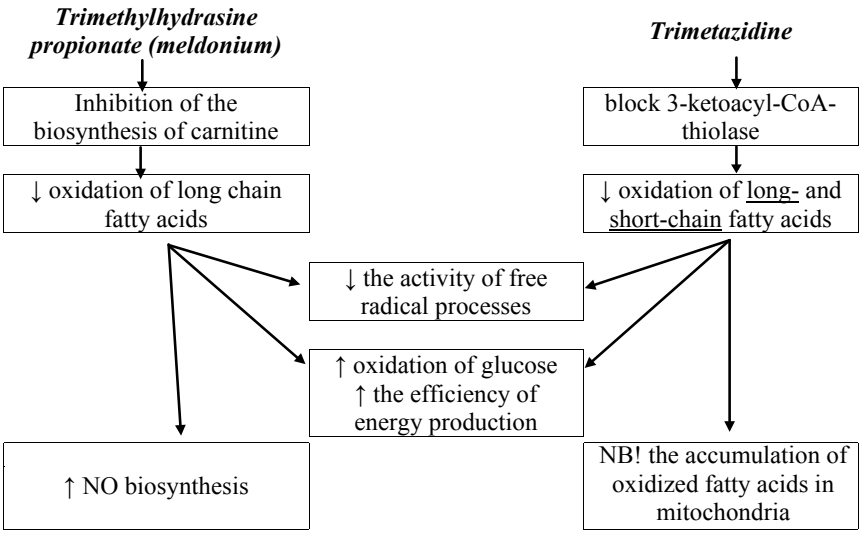

Figure 2. Comparative elements and pharmacodynamics of TMHP and trimetazidine

First of all, while only reducing oxidation of long chain fatty acids, TMHP does not lead to the accumulation of oxidized fatty acids in mitochondria and, therefore, does not exert the toxic effectson their breath, unlike trimetazidine [13, 14, 18, 19]. TMHP also promotes activation of the biosynthesis of nitrogen oxide (NO) and related vasodilation [12, 25, 26]. It should be noted that the rate of occurrence of this effect, and its degree is not high enough [13, 24].

CARNITINE ANALOGUES AND PRECURSORS: THEIR ROLE IN THE TREATMENT OF ISCHEMIC CONDITIONS

In the connection with the above, the approach to the correction of ischemic conditions, and certain disadvantages of monodrugs of TMHP (low speed and severity of vasodilation) the modification of the pharmacological properties by the substance of γ-butyrobetaine (GBB) is becoming the focus of scientific interest that underlies the development of the drug "Capicor" **(Figure 3.)**.

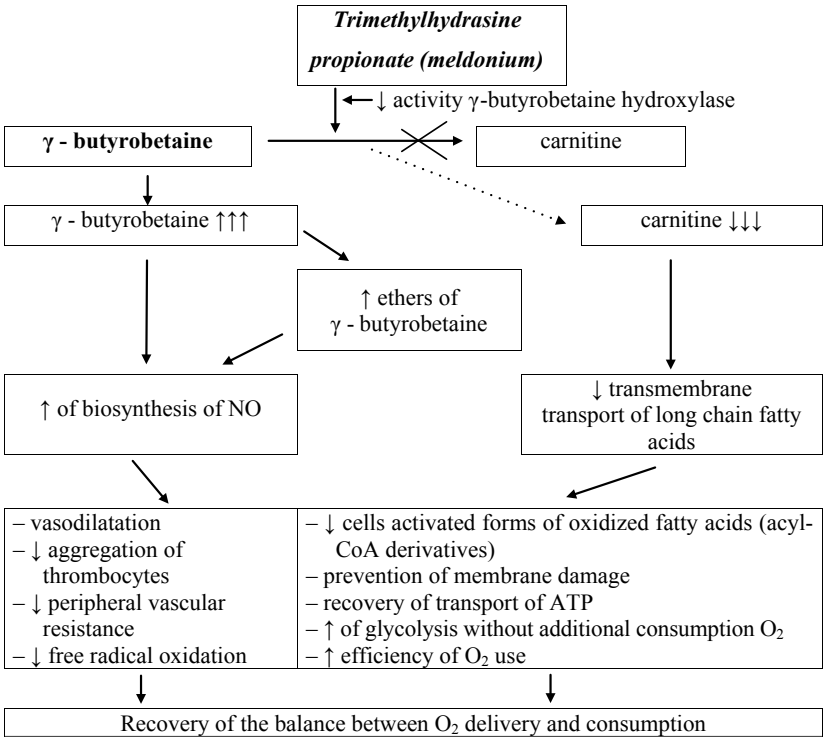

Figure 3. The main constituent elements of pharmacodynamic synergy of carnitine analogues and precursors

In itself TMHP is a structural analogue of carnitine providing in the cells transport of long-chain fatty acids across the mitochondrial membrane and their utilization in the process of energy production [28, 29, 30]. Due to this structural similarity TMHP inhibits γ-butyrobetaine hydroxylase – an enzyme that converts GBB into carnitine by its hydroxylation [12, 31, 30]. Thus, TMHP reduces the synthesis of carnitine and contributes to the accumulation of its predecessor - GBB in the tissues [13, 25, 32-34]. On the one hand,

this leads to a reduction of transport of long chain fatty acids across mitochondrial membranes, prevents the accumulation in cells of the activated forms of oxidized fatty acids, increases glycolysis and the efficiency of oxygen utilization [29, 33, 35]. On the other hand, it causes an accumulation of GBB in tissues, which potentiate endothelial biosynthesis of nitrogen oxide and, as a consequence, cause vasodilatation [13, 19, 36].

However, the metabolic component is more significant in the binary mechanism of action of TMHP than vazodilatation one and its combining with the GBB compensates this drawback. Adding of GBB on the background of suppression of its transformation into carnitine, which is caused by the influence of TMHP, leads to its quick accumulation in the tissues, increased synthesis of NO and high-speed development of vazodilatation effect [22]. It should be noted that this effect can be achieved by means of unmodified substrate of GBB but also with the help of its metabolites - ethers (methyl and ethyl), which are significantly more potent than GBB itself [28, 31, 35, 37]. The research results show that esterified GBB metabolites have a high structural similarity with acetylcholine, thereby enhance the activity of NO-synthase in natural physiological way - through the activation of acetylcholine receptor endotheliocytes [13, 37]. A number of publications, which have appeared in recent years, proved the high potential of these compounds in the treatment of atherosclerosis, ischemic heart disease, disorders of cerebral hemodynamics and other cardiovascular diseases associated with dysfunction of vascular endothelium [38-40].

A clear demonstration of the value of GBB and its metabolites in terms of speed and severity of the vasodilatation effect in pharmacodynamic profile of carnitine analogues and precursors are the study results of the effect of TMHP, GBB and its ethers in the synthesis of nitrogen oxide in blood serum and myocardial tissue in animals [21] **(Figure. 4)**.

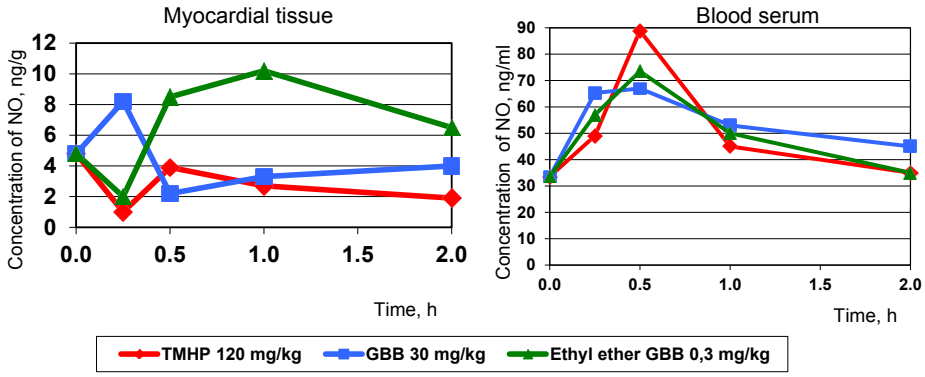

Figure 4. Effect TMHP, GBB and its ethers on the synthesis of nitrogen oxide.

In this study, it was shown that both in myocardium and blood serum the maximum concentration of NO at 15 minutes point was originated from GBB influence. Further, ethyl ether of GBB shows the greatest activity in the myocardial tissues and TMHP – in blood. It should be noted that ethyl ether of GBB was used in a 100-fold lower dose than the GBB itself and at the same time it was not only inferior to GBB by efficacy, but was even significantly effective in the myocardium. Consequently, just the etherified metabolites of GBB among the carnitine analogues and precursors provide the highest rate and extent of exposure to nitrogen oxide synthesis and vasodilatation [40-42].

Based on the above considerations, the Latvian scientists developed the drug "Capicor" (JSC "Olainfarm", Olaine, Latvija), which is a combination of TMHP and GBB in the ratio 3: 1. Summarizing the elements of its pharmacodynamics, the most significant can be identified as following [13]:

- cardioprotective effect;
- reducing the size of the necrotic zone, shortening rehabilitation period in the acute myocardial ischemia;
- heart failure - increased myocardial contractility and physical stress tolerance, reduce the frequency of angina attacks;
- cerebroprotective action;
- patients with ischemic cerebrovascular circulation – strengthening the cerebral circulation, blood redistribution in favor of the ischemic area;
- increasing of efficiency;
- reduction of symptoms of mental and physical stress.

CONCLUSIONS

Taking into account the available types of pharmacodynamic synergy and on the basis of the above, we have concluded that the synergistic combination of a polytropic pharmacological action of TMHP and GBB has been achieved by mutual potentiation of these analogues and precursors of carnitine, which have different mechanisms of action, providing the same effect. Thus, the combined drug "Capicor" is an original and worthy alternative to the existing metabolic cytoprotectors in clinical practice being a

drug with multivector elements of pharmacodynamics, whose use will optimize the treatment of ischemic conditions in modern cardiovascular and neurological practice and, consequently, improve patients' compliance to their treatment and intensifies the awareness of professionals in the field of Medicine and Pharmacy within the framework of pharmaceutical care doctors grant their patients.

The authors have no financial interest with the manufacturer of Capicor.

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