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Beta-Oxybutyrates: Biological and Pharmacological Effects

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ABSTRACT
Current knowledge of the biological and pharmacological effects of beta-hydroxybutyrates obtained by various methods was presented in a review. Antidiabetic, neuroprotective, renoprotective and antiepileptic effects, anticonvulsant and anti-inflammatory activity, as well as numerous other aspects of the biological activity of the studied substances, have been shown. The main directions for the development of the pharmacological use of beta-hydroxybutyrates have been identified.

Keywords: β-hydroxybutyrate, biological activity, pharmacological effects.

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INTRODUCTION
β-hydroxybutyrates (or 3-hydroxybutyrates, hereinafter β-OHB) are salts of β-hydroxybutyric acid (Fig. 1). This acid belongs to the hydroxycarboxylic acid group; these acids contain carboxyl and hydroxyl groups. Therefore, they are capable of exhibiting both the properties of acids and the properties of alcohols. β-hydroxybutyric acid is a chiral compound and exists in the form of D- and L-enantiomers; in the human body, only the D-enantiomer is synthesized [1].

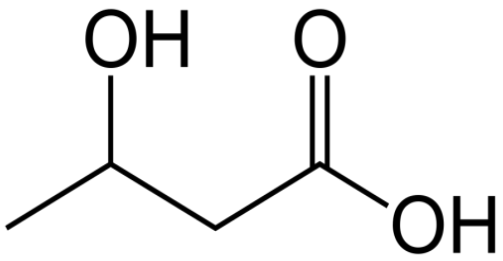

Figure 1. Skeletal formula of beta-hydroxybutyric acid.

In industry, β-hydroxybutyric acid is obtained during one-stage fermentation by genetically modified *Corynebacterium glutamicum* strain [2]. Sodium, calcium, and magnesium β-hydroxybutyrates are found in food in milk and dairy products [3]. All salts exhibit a similar effect regardless of the cation nature.
In industry, β-hydroxybutyric acid can be used as a precursor substrate in the biotechnological production of a biodegradable polymer – poly-β-hydroxybutyrate; a genetically modified *E. coli* strain is used as a producer [4].

MATERIALS AND METHODS
Content analysis of various sources of information was carried out; electronic search engines (Google, Google Scholar), scientific literature, electronic databases (Pubmed, Scopus, Web of Science) were used.

RESULTS AND DISCUSSION
β-OHB belongs to ketone bodies. Ketone bodies are normally present in the blood at a concentration of 1-3 mg/dl. The synthesis of ketone bodies is normal during starvation, prolonged intense physical activity, and the consumption of foods high in fat and low in carbohydrates (with the so-called ketogenic diet). Synthesis is regulated by glucagon during starvation or adrenaline during exercise; as a result of the action of these hormones, lipolysis is activated, and fatty acids in combination with albumin are transported to the liver and in it are β-oxidized to acetyl-CoA. Acetyl-CoA is subsequently synthesized from acetoacetate, from which β-OHB is synthesized by β-hydroxybutyrate dehydrogenase. Acetoacetate and β-OHB have a broad spectrum of action and are reserve sources of energy for the brain, heart, and skeletal muscles [5].
Energy and signaling functions. β-hydroxybutyrate supports the energy requirement during starvation and has signaling functions [6]. β-OHB is an endogenous histone deacetylase (HDAC) inhibitor and a ligand for at least two cell surface receptors. Downstream products of β-OHB metabolism, including acetyl-CoA, succinyl-CoA, and NAD^+, themselves have signaling activity. These regulatory functions of β-OHB serve to link the external environment with cellular function and gene expression and have important implications for the pathogenesis and treatment of metabolic diseases, including type 2 diabetes [7].
The protective effect of β-OHB in hypoglycemic conditions is associated with its ability to reverse the production of reactive oxygen species and reduce the phosphorylation of the ERK and SK3β enzymes, and, therefore, to reverse the accompanying cytotoxicity [8, 9]. In persistent hyperinsulinemic hypoglycemia in two infants, oral administration of β-hydroxybutyrate (0.8-1.0 g per kg of body weight) reduced the incidence of

hypoglycemic episodes in which generalized seizures developed. This suggests that the administration of β-OHB may become an additional approach to persistent hyperinsulinemic hypoglycemia of infancy (PHHI) therapy [10].

Neuroprotective and antiepileptic effect. It is known that β-hydroxybutyrate increases the synthesis of kynurenic acid (KYNA); this substance is an endogenous antagonist of glutamatergic and α7-nicotinic receptors. Subsequent attenuation of excessive excitatory glutamate-mediated neurotransmission may, at least in part, explain the neuroprotective effects of β-OHB [11].

Also, the neuroprotective effect of β-OHB is based on an increase in cerebral blood flow, which is not accompanied by an increase in oxygen consumption [12]. Astrocyte ketogenesis can have a neuroprotective effect, both by removing unesterified fatty acids that negatively affect brain cell function and by forming ketone bodies that act as cellular substrates [13].

The neuroprotective effect in Parkinson's disease. This effect has been studied in dopaminergic neuroblastoma cells using rotenone as a neurotoxin; pretreatment of cells with β-OHB provided significant cell protection. Rotenone caused a loss of mitochondrial membrane potential, released cytochrome C (Cytc) into the cytosol, and decreased the content of Cytc in mitochondria; however, the addition of β-OHB blocked this toxic effect. β-OHB also attenuated rotenone-induced activation of caspase-9 and caspase-3 [14].

A protective role in Huntington's disease (HD). Protective role of β-OHB has been noted in mouse models of HD. β-OHB infusion prolongs lifespan, alleviates motor deficits, and prevents deacetylation of histones in the striatum. This suggests that β-OHB may be a valuable therapeutic agent for HD [15].

The neuroprotective effect of β-OHB in Alzheimer's disease. Alzheimer's disease is a neurodegenerative disease; it is associated with the deposition of amyloid-beta (Aβ) peptides in the senile plaques and vasculature of the brain. The neurotoxic mechanisms of this condition are associated with apoptosis; apoptosis is caused by oxidative stress resulting in the loss of neurons. It was established that the administration of exogenous β-OHB effectively prevents Aβ deposition and neuronal apoptosis. Pretreatment of PC-12 cells with β-OHB also relieves oxidative stress after administration of Aβ; this is evidenced by a decrease in intracellular reactive oxygen species and Ca^{2+} levels, activation of the transcription factor NRF2, and reduction of superoxide dismutase and catalase [16].

Increasing plasma ketones through oral administration of medium-chain triglycerides (MCTs) may improve cognitive function in older adults with memory impairments. This is due to the fact that ketone bodies (and in particular β-OHB) are an effective alternative energy substrate for brain activity [17].

The anticonvulsant activity of β-OHB is manifested in a model of seizures induced by pilocarpine – when β-OHB is administered, the latency to the onset of seizures is prolonged [18]. **The anti-inflammatory activity of β-OHB** is due to its action as a signaling molecule that affects the opening of K^+ channels and the regulation of Ca^{2+} channels. β-OHB is a histone deacetylase inhibitor; it increases the expression of genes involved in the regulation of metabolism and in protection against oxidative stress. β-OHB acts on immunocompetent cells and reduces the production of inflammatory cytokines; thus reduces inflammation [19]. Mechanistically, β-OHB inhibits NLRP3 inflammasome by preventing K^+ efflux and reducing ASC oligomerization and speck formation. The inhibitory effect of β-OHB on NLRP3 is independent of chirality or starvation-regulated mechanisms such as AMP-activated protein kinase (AMPK), reactive oxygen species (ROS), autophagy, or glycolytic inhibition [20]. The anti-inflammatory effect of β-OHB against neuroinflammation is manifested by stimulating the ramification of microglia [21]. The ability of β-OHB to suppress the development of endoplasmic reticulum stress-induced inflammation has also been noted. [22].

Application for cerebral ischemia. In cerebral ischemia, β-OHB can be used as an energy source that does not cause lactate accumulation and therefore does not worsen brain damage [23].

The renoprotective effect of β-OHB was noted for paraquat-induced kidney injury. In this case, injury is associated with oxidative stress, which can be measured by increased lipid peroxidation and decreased intracellular anti-oxidative abilities. β-OHB pretreatment significantly attenuated these effects and inhibited caspases-mediated apoptosis [24]. β-hydroxybutyrate attenuates renal ischemia-reperfusion injury through its anti-pyroptotic effects [25].

The treatment of multiple acyl-CoA dehydrogenase deficiency (MADD). The use of ketone bodies is often discussed in connection with rare metabolic diseases such as MADD. There are no alternative treatments for such kind of diseases. A number of clinical cases show positive results of therapy with ketone bodies [26].

Application in ophthalmology. β-OHB was applied in eye drops in a rat dry eye model. In the course of the experiment, it was found that β-OHB significantly reduces the number of puncture lesions on the cornea. This indicates the potential clinical use of β-OHB in corneal surface epithelial disorders in patients with moderate to mild dry eye [27, 28].

Application for therapeutic starvation. Both intravenous and oral β-OHB supplementation significantly reduced total body protein loss during therapeutic starvation in obese patients. Administration of β-OHB did not significantly affect the rate of weight loss but seemed to increase the fat to lean ratio of tissue loss. Patients taking β-OHB did not experience any untoward effects and did not complain of hunger [29].

Suppression of post-traumatic protein catabolism. β-OHB and sodium lactate were administered to two groups of patients with injury severity scores (ISS) greater than 20. A decrease in the release of alanine from muscles during β-OHB infusion was observed in injured patients. This suggests that β-OHB and other ketone bodies have a suppressing effect on post-traumatic protein catabolism [30].

Role in cancer. β-OHB plays both metabolic and epigenetic roles in cancer. In several studies, it, like other ketone bodies, showed an anti-cancer effect via inhibition of histone deacetylases; however, other studies observed faster tumour growth. Apparently, this is due to two factors – the presence of the Warburg effect and the concentration of ketone bodies. At low concentration and no Warburg effect, β-OHB possesses a metabolic role and has no anti-cancer effect [31].

Effect on the heart. It has been noted that ketone bodies in healthy people reduce myocardial glucose uptake and increase myocardial blood flow. These observations indicate that ketone bodies are important cardiac fuel source and vasodilators that may have the therapeutic potential [32].

The role of β-OHB in type 2 diabetes mellitus (T2DM). The negative effects of high doses of β-OHB have been noted in animal studies. Often, high concentrations are associated with or can lead to diabetic conditions. For example, high concentrations of β-OHB typical of untreated diabetes mellitus may have embryotoxic and teratogenic effects in rat embryos [33]. Continuously increasing doses of β-OHB when administered to rabbits can cause hypoglycemia and then persistent hyperglycemia; this may be due to continued stimulation of pancreatic B-cells, leading to their atrophy and hypoinsulinism [34]. It has also been noted that prolonged exposure to ketone bodies alters the action of insulin in cardiomyocytes, and it is suggested that this substrate may play a role in the development of insulin resistance in the heart [35]. However, in T2DM, the ketogenic diet appears to have significant benefits. A long-term prospective study involving two groups of patients was performed. The first group received standard treatment, the second group received remote support from healthcare professionals and a ketogenic diet. In the second group of patients, a significant decrease in systolic and diastolic blood pressure and body weight was noted; in the blood picture, a decrease in small LDL-P and triglycerides, the level of highly sensitive C-reactive protein and the number of leukocytes was observed. A significant decrease in the overall use of antihypertensive drugs and diuretics has also been noted. Thus, such therapy significantly reduces the risks of cardiovascular complications, which are the leading cause of death. The data obtained allow us to judge the positive effect of a ketogenic diet (and, consequently, ketone bodies, including β-OHB) on the duration and quality of life of patients with type 2 diabetes (Fig. 2) [36].

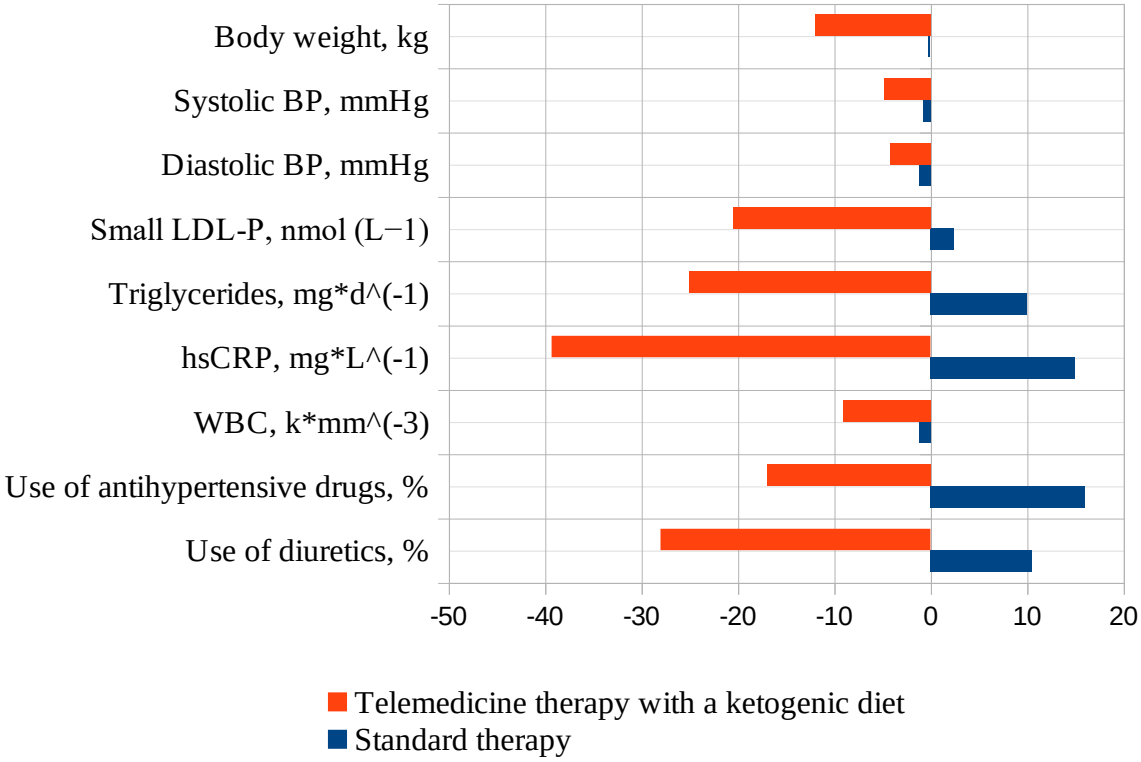

Figure 2. Changes in biomarkers with standard T2DM therapy and telemedicine therapy with a ketogenic diet.

The pharmacological effects of β-OHB in various conditions are presented in Table 1.

Table 1. The pharmacological effects of β-OHB in various conditions.

Condition	Pathogenesis	Effect of β-OHB
Starvation	Lack of glucose in the bloodstream and therefore in the organs, which leads to a lack of energy.	β-OHB serves as an energy source for the brain, heart, and skeletal muscles.
Hypoglycemia	Cytotoxicity is due to the production of reactive oxygen species and an increase in phosphorylation of the ERK (extracellular-signal regulated kinase) and SK3β enzymes.	β-OHB has a protective effect due to its ability to reverse the production of reactive oxygen species and to decrease the phosphorylation of the ERK and SK3β enzymes.
Epilepsy	The pathological activity of neurons spreads uncontrollably and leads to a	β-OHB increases kynurenic acid synthesis, which attenuates excessive

	seizure.	excitatory glutamate-mediated neurotransmission, resulting in lower seizure rates.
Parkinson's disease	Rotenone and similar pesticides are able to penetrate the blood-brain barrier (BBB), cause a loss of mitochondrial membrane potential, promote the release of cytochrome c into the cytosol and, thereby disrupt the respiratory chain, which leads to cell death.	β-OHB blocks the described toxic effect of rotenone and attenuates rotenone-induced caspase activation.
Huntington's disease	The mutant huntingtin protein affects the striatum through several mechanisms, including influence on gene expression; this leads to movement disorders.	β-OHB infusion prolongs lifespan, alleviates motor deficits, and prevents deacetylation of histones in the striatum.
Alzheimer's disease	Deposition of beta-amyloid peptides in the senile plaques and blood vessels of the brain, which leads to apoptosis as a result of oxidative stress.	β-OHB infusion effectively prevents Aβ deposition and neuronal apoptosis, also relieves oxidative stress after Aβ administration, and improves cognitive function in patients.
Inflammation	Inflammation develops due to the action of pro-inflammatory cytokines secreted by inflammosomes.	β-OHB inhibits NLRP3-inflammasome and increases the expression of genes involved in protection against oxidative stress. β-OHB acts on immunocompetent cells, reduces the production of inflammatory cytokines, and reduces inflammation.
Consequences of cerebral ischemia	In the course of glucose metabolism, lactate is formed and exacerbates brain damage during ischemia.	Lactate is not produced during β-OHB metabolism.
Multiple Acyl-CoA Dehydrogenase Deficiency (MADD)	As a result of acyl-CoA dehydrogenase deficiency, a metabolic crisis occurs; it manifests itself in the form of hypoketotic hypoglycemia, paroxysm, and coma.	β-OHB provides energy for the brain, heart, and skeletal muscles, thereby helping to relieve symptoms.
Therapeutic starvation	The problem of therapeutic starvation is the loss of not only fat but also protein, as well as the development of untoward effects and the feeling of hunger.	β-OHB reduces overall protein loss and suppresses hunger and untoward effects.
Cardiovascular complications in type 2 diabetes mellitus (T2DM)	Risk factors for CVD in T2DM are, inter alia, abdominal obesity, atherogenic dyslipidemia (characterized by high triglyceride levels, an increase in small LDL and a decrease in HDL-C), and inflammation assessed by C-reactive protein and leukocyte count.	When using the ketogenic diet, there was a significant decrease in systolic and diastolic blood pressure, and body weight was noted; in the blood picture, a decrease in small LDL-P and triglycerides, the level of highly sensitive C-reactive protein, and the number of leukocytes was observed.

CONCLUSION

Taking into account the above data we can suggest that the production of dietary supplements based on β-OHB in the form of sodium, potassium, and magnesium salts is relevant, as well as the use of β-OHB in the future as a medicine.

β-OHB supplements can serve a number of important functions:

- serve as an additional source of energy for brain activity.
- help the body to more easily cope with hypoxic and ischemic conditions, as well as facilitate recovery from injuries that caused muscle damage (including sports injuries);
- ease the feeling of hunger when switching to a lower-calorie diet or during therapeutic starvation, while reducing protein loss. This application is especially relevant in connection with the global problem of obesity.
- delay the development of neurodegenerative diseases or reduce the severity of their symptoms.

The use of β-OHB allows us to get the positive effects of a ketogenic diet without the stress of changing the usual diet and possible digestive disorders as a result of changing the diet. Most patients easily tolerate oral β-OHB dosage forms, which is its separate advantage. At the same time, the negative effects of β-OHB are relatively rare and can manifest themselves in chronic overdose (hypoinsulinism, insulin resistance) or when taken during pregnancy (teratogenicity).

CONFLICTS OF INTEREST

None.

AUTHOR'S CONTRIBUTIONS

All authors contributed equally to this work.

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