

Pharmacokinetics and Pharmacodynamics of Phenibut: Their Potential Dependence on Endogenous Hydrogen Sulfide : A Literature Review

ABSTRACT

Aims: The aim of the study was to analyze the current literature data on the pharmacokinetics and pharmacodynamics of phenibut, as well as to evaluate their potential dependence on endogenous hydrogen sulfide.

Material and Methods: Retrospective analysis of literature data was carried out on the basis of data from Scopus, Web of science, PubMed, ScienceDirect, UpToDate databases, as well as using the Google search service. When searching for information on the investigated problem, various combinations of keywords in Ukrainian and English were used: "phenibut", "pharmacokinetics", "pharmacodynamics", "pharmacology", "hydrogen sulfide", "H₂S", "mechanism of action", "physiology", "pathophysiology". During the processing the search results, either the most recent publications (for the last 10 years) or the latest publications on this issue (regardless of the age) were selected. After studying the data of the search results, 38 scientific sources were selected that met the terms of the request.

Results: Despite its promising profile, phenibut is not without certain limitations and problems. Its effectiveness in the treatment of anxiety disorders is considered moderate compared to traditional anxiolytics such as benzodiazepines. In addition, due to the limited number of studies, its safety and potential side effects with long-term use require further study. Overall, phenibut is an interesting and promising drug that deserves further investigation, but limitations of its use may be related to individual characteristics of pharmacokinetics and pharmacodynamics. In our opinion, the cause of such individual characteristics may be certain endogenous factors that vary among different people. One of these endogenous modulators includes hydrogen sulfide, which regulates a wide range of biochemical and physiological processes.

Conclusion: The broad and diverse influence of endogenous hydrogen sulfide on the course of biochemical and physiological processes in the body prompts the study of its potential modulating influence on the pharmacological properties of drugs. A preclinical study of the pharmacokinetics and pharmacodynamics of drugs (in particular, phenibut) taking into account the level of hydrogen sulfide in the body will allow further optimization of therapeutic schemes by adjusting the background level of this transmitter.

Keywords: phenibut, pharmacokinetics, pharmacodynamics, hydrogen sulfide.

1. INTRODUCTION

Phenibut (beta-phenyl-gamma-aminobutyric acid) is a synthetic drug that exhibits anxiolytic, nootropic and neuroprotective properties [1].

The mechanism of action of phenibut is related to the modulation of the level of gamma-aminobutyric acid in the central nervous system [1, 2, 3]. Unlike classic benzodiazepine anxiolytics, phenibut does not interact directly with GABA

receptors, but instead stimulates GABA metabolism through activation of the vitamin B6-dependent GABA transaminase enzyme. This helps to increase the level of GABA in the synaptic cleft, which, in turn, leads to a calming effect.

In addition to anxiolytic effects, phenibut also has nootropic properties [1, 2, 3, 4]. It can improve cognitive functions such as attention, memory and learning ability by modulating neurotransmitter systems and reducing oxidative stress in the brain. This feature makes it potentially useful for the treatment of cognitive impairment associated with various neurological disorders such as Alzheimer's disease, traumatic brain injury, and cerebrovascular disease.

The neuroprotective potential of phenibut also attracts the attention of researchers [5]. It can prevent neuronal damage by inhibiting glutamate excitotoxicity and reducing oxidative stress. These properties may be useful in the treatment of neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease, as well as in the prevention of brain damage due to ischemia or trauma.

Despite its promising profile, phenibut is not without certain limitations and problems. Its effectiveness in the treatment of anxiety disorders is considered moderate compared to traditional anxiolytics such as benzodiazepines [6, 7]. In addition, due to the limited number of studies, its safety and potential side effects with long-term use require further study.

Overall, phenibut is an interesting and promising drug that deserves further investigation, but limitations of its use may be related to individual characteristics of pharmacokinetics and pharmacodynamics. In our opinion, the cause of such individual characteristics may be certain endogenous factors that vary among different people. One of these endogenous modulators includes hydrogen sulfide, which regulates a wide range of biochemical and physiological processes [8].

The aim of the study was to analyze the current literature data on the pharmacokinetics and pharmacodynamics of phenibut, as well as to evaluate their potential dependence on endogenous hydrogen sulfide.

2. MATERIAL AND METHODS

Retrospective analysis of literature data was carried out on the basis of data from Scopus, Web of science, PubMed, ScienceDirect, UpToDate databases, as well as using the Google search service. When searching for information on the investigated problem, various combinations of keywords in Ukrainian and English were used: "phenibut", "pharmacokinetics", "pharmacodynamics", "pharmacology", "hydrogen sulfide", "H₂S", "mechanism of action", "physiology", "pathophysiology". During the processing the search results, either the most recent publications (for the last 10 years) or the latest publications on this issue (regardless of the age) were selected. After studying the data of the search results, 38 scientific sources were selected that met the terms of the request. Below is an overview and detailed analysis of scientific publications on the researched problem.

3. RESULTS AND DISCUSSION

Pharmacokinetics of phenibut

Available information on the pharmacokinetics of phenibut is quite limited.

Lapin in his review reports that phenibut is not metabolized after intravenous administration to rabbits or rats [9]. It is also reported that the drug is largely excreted unmetabolized in the urine by glomerular filtration in rats, rabbits, cats, and dogs. In addition, it is noted that phenibut was detected in the liver, kidneys, brain, blood and urine after intravenous administration, with dissipation to trace levels 3 hours after injection.

In humans, 65% of a 250 mg oral dose of phenibut was reported to be unmetabolized and excreted in the urine, and its clearance mimicked that of creatinine. It was established that the half-life from plasma is 5.3 hours.

In the review published by Lapin, none of these statements are referenced, which precludes consideration of primary research [9]. All other literature discussing any of these effects cites the Lapin publication.

In the publication of Grinberg et al. It contains information that phenibut is detected in the brain tissue of rats 1 hour after intraperitoneal administration of 100 mg/kg daily for 3 days [10].

Patients report the onset of effects of phenibut within 2-4 hours after oral administration, with a peak "high" occurring approximately 6 hours after administration and a duration of 15 to 24 hours [11].

Pharmacodynamics of phenibut

Phenibut is structurally and functionally similar to the GABA derivatives, gabapentin and baclofen. Phenibut is a GABA agonist that crosses the brain blood barrier more readily than GABA itself. This is due to the presence of a phenyl group on the beta carbon [12]. The affinity of phenibut for the GABA B receptor is approximately 15 times lower than the GABA B agonist, baclofen [13].

Baclofen is used to treat anxiety, alcohol dependence and muscle spasticity [14], while gabapentin is used as an anti-epileptic and also to treat neuropathic pain [15]. Like its structural analog baclofen, evidence shows that phenibut acts as a GABA B receptor agonist [16], and thus some of its actions are thought to reflect its interactions at the GABA B metabotropic G protein-coupled receptor, the primary means of inhibitory neurotransmission within the brain. Similarly to GABA and its analogs, phenibut was shown to reversibly reduce the firing rate of isolated cat neurons [17].

In a comprehensive set of experiments conducted in rodents Dambrova et al. examined the comparative pharmacological activity of optical isomers of phenibut [13]. Administration of racemic phenibut and its R-enantiomer showed dose-dependent decreases in open field activity, increased analgesia in the antinociception test and decreased immobility during the forced swim test. Pretreatment with a GABA B antagonist blocked these effects. The S-enantiomer showed low to no effects. Results are congruent with the antidepressant and anxiolytic properties of phenibut. GABA B agonists such as baclofen are used to treat spasticity however, much higher doses (30- fold higher) of phenibut were needed to impact muscle function than were needed to affect open field behavior. Given its minimal effect on muscle function, the authors hypothesize that an unexplored potential clinical avenue for phenibut may be in treating disorders wherein muscle relaxation is not required

Radioligand binding studies conducted within the same set of experiments as above showed that baclofen, racemic phenibut and R-phenibut demonstrated an affinity for GABA B receptors, with K_i constants of 6 ± 1 , 177 ± 2 and 92 ± 3 μM , respectively, while the S-enantiomer did not bind to GABA B receptors [13]. Phenibut's actions on GABA B receptors have been shown to activate an outward-rectifying potassium current, suppressing the generation of action potentials [18], highlighting its depressant properties.

Importantly however, **although phenibut binds directly to the GABA B receptor** [13], phenibut also has high affinity for the $\alpha 2\text{-}\delta$ subunit of voltage dependent calcium channels (VDCCs) [19], which is the same mechanism associated with the anti-nociceptive properties of gabapentin. Data show that the binding affinity of R-phenibut for the $\alpha 2\text{-}\delta$ subunit of the VDCC is 4 times higher than its affinity for the GABA B receptor. Calculated K_i values of 23 ± 6 μM , 39 ± 5 μM and 156 ± 40 μM were observed for R and S-phenibut and baclofen, respectively. Further, in rodent models testing the anti-nociceptive effects of R-phenibut, it was shown that antagonism of the $\alpha 2\text{-}\delta$ subunit of the VDCC blocked the anti-nociceptive effects of phenibut while GABA B antagonism did not [19]. In other words the anti-nociceptive effects were not mediated by phenibut's activity at the GABA B receptor, rather its effects at the $\alpha 2\text{-}\delta$ subunit of the VDCC. Thus, in line with its structural similarity to gabapentin, phenibut also behaves in a functionally similar manner and may be a suitable candidate to treat neuropathic pain.

Lapin discusses actions of phenibut at the GABA A receptor, which is a major mechanism of action of benzodiazepines [9]. However, there is no available literature showing that phenibut has actions at the GABA A receptor. In other literature discussing phenibut's actions at the GABA A receptor Lapin is cited, however, the primary study cited by Lapin was not accessible.

Hydrogen sulfide

Hydrogen sulfide (H_2S) was first synthesized in 1777 by the Swedish chemist Carl Wilhelm Scheele.

Hydrogen sulfide is widely distributed in the environment and is a flammable, colorless gas with a sharp "rotten egg" smell. In nature, this gas is formed during the breakdown of proteins that contain sulfur-containing amino acids. Hydrogen sulfide is a highly toxic compound, 5 times more toxic than CO. Entering the body in high concentrations, this compound can inhibit the processes of tissue respiration, inhibiting cytochrome c oxidase [10]. However, more than 30 years ago it became known that hydrogen sulfide is synthesized by almost all living organisms. Since the end of the 80s of the 20th century, interest in hydrogen sulfide has increased significantly due to the establishment of its involvement in the regulation of physiological functions in animals and humans. Today, this compound belongs to the family of gas transmitters, which includes nitrogen monoxide (NO) and carbon monoxide (CO). Hydrogen sulfide is involved in the regulation of vascular tone, neuromodulation, cytoprotection, inflammation, apoptosis, and other processes [11, 12, 13].

Hydrogen sulfide is a short-lived molecule with a half-life of several minutes. In aqueous solutions at pH 7.4, 20-30% of hydrogen sulfide exists in an undissociated form and 70-80% – in the form of hydrogen sulfide anion ($\text{H}_2\text{S} \leftrightarrow \text{H}^+ + \text{HS}^-$; $\text{pK}_a=6.89$), which is partially transformed into sulfide-anion (S^{2-}). H_2S has high lipophilicity and dissolves twice as easily in lipid membranes (partition coefficient – 2.06) than in water [14].

The main substrates for endogenous hydrogen sulfide in tissues are sulfur-containing amino acids – L-cysteine and L-homocysteine, the main enzymes producing it are the pyridoxal phosphate-dependent enzymes cystathionine- β -synthase, cystathionine- γ -lyase, as well as cysteine aminotransferase.

The main reactions that ensure the formation of hydrogen sulfide in animal and human tissues include [15]:

- 1) Desulfurization of L-cysteine to pyruvate with the participation of cystathionine- γ -lyase.
- 2) Condensation of L-homocysteine with L-cysteine and desulfurization of L-cysteine to L-serine with the participation of cystathionine- β -synthase.
- 3) Transamination of L-cysteine with α -ketoglutarate with the participation of cysteine aminotransferase with the formation of 3-mercaptopyruvate, from which H_2S is further released with the participation of 3-mercaptopyruvate sulfurtransferase.

In the body, hydrogen sulfide acts as a signaling molecule, a gas transmitter, for which no specific receptors have been found. The molecular targets of H_2S are various ion channels, receptors, enzymes and proteins that regulate a wide range of biochemical and physiological processes [8].

The content of H_2S in the blood plasma of animals (rats) and humans is about 50-80 μM [13], while H_2S is contained in larger amounts in tissues, and its concentration in different organs varies quite a lot. Various pathological conditions are associated with disturbances in the content and production of H_2S in tissues. A decrease in the basal content of H_2S in the blood plasma is noted in patients with arterial hypertension, coronary heart disease, deep vein thrombosis of the lower extremities, Alzheimer's disease, and hyperhomocysteinemia [16, 17, 18]. In contrast, in many cases, the level of hydrogen sulfide increases, for example, in diabetes, pancreatitis, peritonitis, and shock states [18, 19].

Equally interesting is the ability of hydrogen sulfide to modulate the body's response to inflammation (reduction of swelling, reduction of pain intensity, reduction of neutrophil infiltration in the center of inflammation) [20] and to stimulate angiogenesis (stimulation of endothelial cell proliferation) [13, 21].

It is also known about the participation of hydrogen sulfide in the course of neurotrauma and a number of psychiatric and neurodegenerative diseases, in particular, anxiety disorders, depression, and manic-depressive psychosis [22, 23, 24, 25, 26].

Thus, by modulating the course of many physiological processes in the body both by direct activation or modulation of channels, receptors and enzymes, and by modulating the activity of enzymes with the help of intracellular signaling, hydrogen sulfide changes the conditions in which drugs act, and, therefore, their pharmacokinetic features and pharmacological effects [27, 28]. In our opinion, the study of the pharmacological features of drugs depending on the background level of hydrogen sulfide in the body is promising both from a scientific and a practical point of view.

4. CONCLUSION

The broad and diverse influence of endogenous hydrogen sulfide on the course of biochemical and physiological processes in the body prompts the study of its potential modulating influence on the pharmacological properties of drugs. A preclinical study of the pharmacokinetics and pharmacodynamics of drugs (in particular, phenibut) taking into account the level of hydrogen sulfide in the body will allow further optimization of therapeutic schemes by adjusting the background level of this transmitter.

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