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INVOLVEMENT OF THE SEROTONIN SYSTEM IN THE DEVELOPMENT OF PULMONARY ARTERIAL HYPERTENSION

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Abstract

Pulmonary arterial hypertension is a multifactorial disease characterized by vasoconstriction and pulmonary vascular remodeling, inflammation and thrombosis. Remodeling of the pulmonary vascular wall leads to an increase in pressure in the pulmonary artery, which increases the load on the right heart and ultimately leads to right ventricular failure [7, 10].

Despite significant progress in treatment, the prognosis of the disease remains unfavorable - in pediatric practice mortality within five years after diagnosis ranges from 25 to 60% [63]. Due to the frequent late diagnosis of pulmonary arterial hypertension and the severe consequences of this condition, the issue of identifying and studying biological markers of pulmonary arterial hypertension is actual problem.

Although a growing body of research confirms that pulmonary artery smooth muscle endothelial cells, as well as platelets, play a role in the pathogenesis of pulmonary arterial hypertension, it is still unclear what these factors have in common. Platelets, releasing a wide variety of chemokines, can actively influence the pathogenesis and development of pulmonary arterial hypertension. The effect of platelet serotonin on the endothelium is mediated through vascular constriction and an increase in vascular resistance [9]. Currently, the role of serotonin and its metabolism in the pathogenesis of pulmonary arterial hypertension is widely discussed.

This article presents a literature review, the purpose of which is to demonstrate the role of the serotonin system in the development of pulmonary arterial hypertension. The review includes data from articles (original clinical trials and literature reviews) found in the Scopus, Web of Science, Pubmed databases according to keywords. Sources published from 2012 to 2023 were used.

Keywords: *pulmonary arterial hypertension, congenital heart disease, platelets, hemostasis, serotonin, serotonin metabolism, 5-HIAA, SERT, serotonin receptors.*

Резюме

УЧАСТИЕ СЕРОТОНИНОВОЙ СИСТЕМЫ В РАЗВИТИИ ЛЕГОЧНОЙ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ

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Легочная артериальная гипертензия — многофакторное заболевание, которое характеризуется вазоконстрикцией и ремоделированием легочных сосудов, воспалением и тромбозом. Ремоделирование легочной сосудистой стенки приводит к повышению давления в легочной артерии, что увеличивает нагрузку на правые отделы сердца и в конечном итоге приводит к правожелудочковой недостаточности [7, 10]. Несмотря на значительный прогресс в лечении, прогноз заболевания остается неблагоприятным, в педиатрической практике смертность в течение пяти лет после постановки диагноза составляет от 25 до 60% [23]. В связи с частой поздней диагностикой легочной артериальной гипертензии и тяжелыми последствиями данного состояния, остро стоит вопрос о выявлении и изучении биологических маркеров легочной артериальной гипертензии.

Хотя все больше исследований подтверждают, что эндотелиальные клетки гладкой мускулатуры легочных артерий, а также тромбоциты играют определенную роль в патогенезе легочной артериальной гипертензии, до сих пор неясно, что объединяет эти факторы. Тромбоциты, высвобождая большое разнообразие хемокинов, могут активно воздействовать на патогенез и развитие легочной артериальной гипертензии. Влияние тромбоцитарного серотонина на эндотелий осуществляется через сосудистую констрикцию и увеличение сосудистого сопротивления [9]. В настоящее время широко обсуждается роль серотонина и его метаболизм в патогенезе легочной артериальной гипертензии.

В данной статье представлен литературный обзор, целью которого является демонстрация роли серотониновой системы в развитии легочной артериальной гипертензии. В обзор включены данные статей (оригинальные клинические исследования и литературные обзоры), найденные в базах данных Scopus, Web of Science, Pubmed согласно ключевым словам. Использованы источники, опубликованные с 2012 по 2023 год.

Ключевые слова: *легочная артериальная гипертензия, врожденные пороки сердца, тромбоциты, гемостаз, серотонин, метаболизм серотонина, 5-ГИУК, SERT, рецепторы к сеоротонину.*

Түйіндеме

ӨКПЕ АРТЕРИЯЛЫҚ ГИПЕРТЕНЗИЯСЫНЫҢ ДАМУЫНА СЕРОТОНИН ЖҮЙЕСІНІҢ ҚАТЫСУЫ

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Өкпе артериялық гипертензиясы – тамырлардың тарылуымен және өкпе тамырларының қайта құрылуымен, қабынуымен және тромбозымен сипатталатын көп факторлы ауру. Өкпе тамырларының қабырғасының қайта құрылуы өкпе артериясындағы қысымның жоғарылауына әкеледі, бұл оң жүрекке жүктемені арттырады және соңында оң жақ қарыншаның жеткіліксіздігіне әкеледі [7, 10]. Емдеудегі елеулі прогреске қарамастан, аурудың болжамы қолайсыз болып қала береді, педиатриялық тәжірибеде диагноз қойылғаннан кейін бес жыл ішінде өлім 25-тен 60% -ға дейін жетеді [63]. Өкпе артериялық гипертензиясының жиі кеш диагностикалануына және осы жағдайдың ауыр зардаптарына байланысты өкпелік артериялық гипертензияның биологиялық маркерлерін анықтау және зерттеу мәселесі өткір тұр.

Өсіп келе жатқан зерттеулер тобы өкпе артериясының тегіс бұлшықетінің эндотелий жасушалары, сондай-ақ тромбоциттер өкпе артериялық гипертензиясының патогенезінде рөл атқаратынын растайды, бірақ бұл факторлардың ортақтығы әлі белгісіз. Әртүрлі химокиндерді шығаратын тромбоциттер өкпе артериялық патогенезі мен дамуына белсенді әсер етуі мүмкін. Тромбоциттік серотониннің эндотелийге әсері қан тамырларының тарылуы және тамырлардың кедергісінің жоғарылауы арқылы жүзеге асады [9]. Қазіргі уақытта өкпелік артериялық гипертензияның патогенезіндегі серотониннің рөлі және оның метаболизмі кеңінен талқылануда.

Бұл мақалада өкпелік артериялық гипертензияның дамуындағы серотонин жүйесінің рөлін көрсету мақсаты болып табылатын әдебиеттерге шолу ұсынылады. Шолу кілт сөздерге сәйкес Scopus, Web of Science, Pubmed дерекқорларында табылған мақалалардың деректерін қамтиды (түпнұсқа клиникалық сынақтар және әдебиеттерге шолулар). 2012 жылдан 2023 жылға дейін жарияланған пайдаланылған дереккөздер.

***Түйінді сөздер**: өкпе артериялық гипертензиясы, туа біткен жүрек ақауы, тромбоциттер, қан тоқтату, серотонин, серотонин алмасуы, 5-ГИСҚ, SERT, серотонин рецепторлары.*

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Introduction

Pulmonary hypertension (PH) is characterized by an increase in mean pressure in the pulmonary artery trunk of more than 20 mmHg during cardiac catheterization at rest. Precapillary pulmonary hypertension (pulmonary arterial hypertension, PAH) is a condition in which mean pulmonary artery pressure is ≥20 mmHg, pulmonary artery wedge pressure is ≤15 mmHg, and pulmonary vascular resistance is >2 WU. [28] Subsequently, these changes lead to an increase in the load on the right ventricle of the heart, its further hypertrophy and decompensation. According to the latest revision of the classification (recommendations of the European Society of Cardiology 2022), [81] PAH is divided into idiopathic, hereditary, induced by drugs and toxins, PAH with signs of venous/capillary damage, persistent PAH of the newborn, as well as associated with other diseases (connective tissue diseases, HIV-infection, portal hypertension, schistosomiasis), including those with congenital heart disease (CHD). The prevalence of CHD according to the latest data is about 30% of all congenital malformations. The incidence of CHD is from 4 to 50 cases per 1000 live births. The frequency of moderate and severe CHD among US children is about 6 cases per 1000 live births [81, 10].

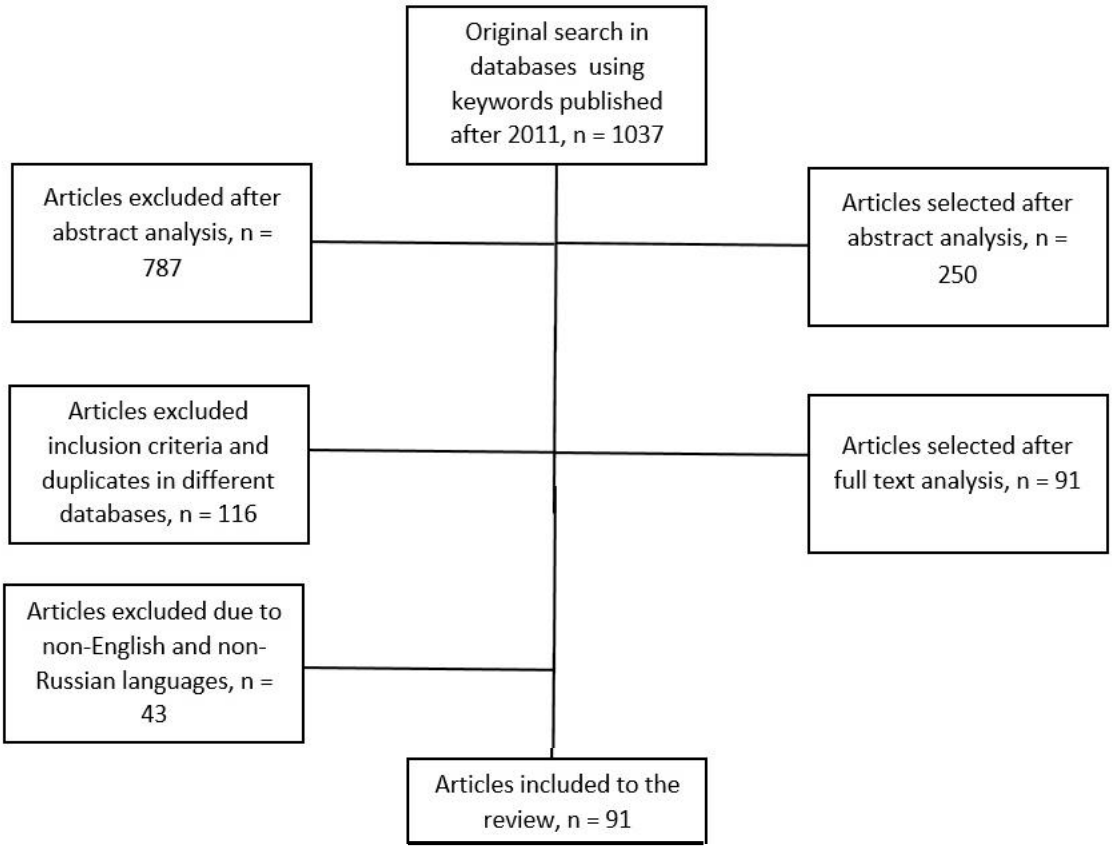
PAH is one of the most common complications of many congenital heart diseases (ventricular septal defect, atrial septal defect, patent ductus arteriosus), which, if not diagnosed and treated in time, is a highly lethal disease. About one third of children with uncorrectable heart disease die from complications in the pulmonary vessels [91, 8]. Therefore, early diagnosis and treatment is critical in order to reduce complications, mortality and improve the quality of life of patients with CHD complicated by PAH. Right heart catheterization is currently the gold standard for diagnosing PAH, but being an invasive interventional technique, this method also has a number of disadvantages, such as high injury risk, risk of thrombosis, rhythm disturbances, development of pseudo aneurysms, etc. [25,53]. Echocardiography is a valuable routine tool and a non-invasive method for diagnosing PAH, which makes it possible to describe the morphology and hemodynamics of the heart, but this method also has limitations [55]. MRI of the heart or CT of the chest may be performed to determine the volume of the ventricles, valvular regurgitation,

obstruction in the circulation [20, 59]. Thus, it is important and promising today to identify biomarkers of PAH, which plays a critical role in the prevention and control of this serious disease, since early diagnosis and intervention can significantly improve the patient's prognosis and increase the effectiveness of treatment. Biomarkers for the development of PAH are measurable and objective indicators that can indicate the presence of an incipient disease process in the body. They may be molecular, genetic, or functional markers that change in response to pathological changes associated with PAH. The development of such biomarkers has several important advantages. First of all, early identification of PAH can help clinicians and patients take steps to prevent disease progression and mitigate its consequences. Early biomarkers can detect changes in the body long before clinical symptoms such as shortness of breath, fatigue and chest pain appear. This makes it possible to start treatment at a very early stage, when it can be most effective. Secondly, the development of biomarkers makes it possible to more accurately determine the prognosis and risk of developing PAH in individual patients. Biomarkers can help identify such features and assess the likelihood of developing PAH in a particular case, which allows more effective efforts to be directed towards prevention and treatment. The development of biomarkers based on the pathogenesis of PAH is of great importance for accurate diagnosis, disease monitoring and development of new therapeutic approaches. Serotonin, one of the best known neurotransmitters in the human body, is the object of increasing interest in the context of its role in the development of pulmonary arterial hypertension in children. Serotonin plays a key role in the regulation of vascular tone and endothelial cell growth. Its effect on the growing pulmonary arteries has long-term consequences, especially during the developmental period of children. Studies show that altered serotonin metabolism can significantly influence the processes of vascular wall remodeling leading to the onset of pulmonary hypertension. Expanding knowledge about serotonin metabolism, as well as its impact on the development of PAH, will provide an opportunity to develop new methods of diagnosis and treatment [12, 16, 44, 48, 50].

Aim. To study and systematize the available scientific evidence on the influence of serotonin metabolism on the pathogenesis of pulmonary hypertension for a more complete and in-depth understanding of the molecular and cellular mechanisms associated with the development of this disease. As a result of this review, to provide a synthesized review of current scientific evidence that can serve as a basis for further research and improvement in clinical practice in the field of pulmonary arterial hypertension.

The research method. A search strategy for conducting a literature review on the involvement of the serotonergic system in the pathogenesis of pulmonary arterial hypertension (PAH) was developed. The review includes data from articles, predominantly original research and literature reviews, found in the Scopus, Web of Science, and Pubmed (Medline) databases using relevant keywords. Sources published within the last decade were utilized due to the limited research conducted on this topic and the relatively recent interest among researchers in this field. Inclusion criteria for the literature review encompassed reports from randomized and cohort studies conducted on large populations, meta-analyses, systematic reviews, and full-length articles. Exclusion criteria involved articles describing isolated cases, conference abstracts, personal communications, and newspaper publications.

Scheme 1. Search Algorithm.



Biomarkers of PAH

Although pulmonary arterial hypertension (PAH) is typically not categorized as an inflammatory condition, emerging evidence suggests that inflammation may play a pivotal role in the pathogenesis of certain PAH subtypes [16, 77]. The relationship between platelets and PAH is intricate, as indicated by several research studies. Pulmonary hypertension can arise from four major categories: passive elevation in pulmonary artery pressure due to increased left atrial pressure and left ventricular dysfunction, veno-occlusive disorders, conditions leading to an excessive demand on the pulmonary arterial circulation beyond its compensatory capacity, and conditions associated with vasospasm or occlusion. Extensive research is underway to understand the alterations occurring in the pulmonary arteries as a consequence of hypertension, with various pro-inflammatory factors identified that could influence these changes. Thrombotic injury to pulmonary vessels, vasoconstriction, and remodeling represent the primary mechanisms of pulmonary vascular pathology in PAH. Platelets are implicated in all these mechanisms through diverse pathways (Table 1). In cases of idiopathic PAH, platelet functional disturbances, endothelial disintegration or dysfunction, and impaired fibrinolysis have been observed. However, it remains uncertain whether these abnormalities are primary contributors to PAH development or secondary manifestations of the disease [49, 56, 89].

Platelets are not only actively involved in thrombosis, but also produce cytokines (TxA2, LIGHT, PDGF), are a depot of biologically active substances (serotonin, vWF and VEGF) and release mediators that can contribute to the onset or exacerbation of PAH. Platelets are associated with all three major PAH mechanisms: vasoconstriction (serotonin and TxA2), thrombotic lesions (aggregation, serotonin, TxA2, CD40L and vWF) and remodeling (serotonin, CD40L, proangiogenic and antiangiogenic factors) [9, 19, 21, 41, 60].

Table 1.

Main substances in the pathophysiology of pulmonary arterial hypertension released by activated platelets [9, 19, 21, 41, 60].

Group	Substance	Effect
Vasoactive substances	5-HT, thromboxane A2	Increased vasoconstriction and impaired endothelial-smooth muscle cell (SMC) interaction
Growth factors	Platelet growth factor	Promotes a higher rate of proliferation of SMCs and fibroblasts.
	Transforming growth factor beta Insulin-like growth factor 1	Excessive proliferation of pulmonary smooth muscle cells leads to vascular remodeling.
Pro-inflammatory cytokines	TNF-α, IL-1α, IL-1β, IL-6	Enhanced inflammatory response in EC contributing to endothelial dysfunction
	P-selectin	Promotes platelet aggregation and migration of leukocytes to the damaged area of the endothelium.

Metabolism of serotonin and its involvement in the development of PAH

A number of biogenic and synthetic amines are capable of causing endothelial damage and platelet stimulation. Thrombosis in situ in PAH is the result of damage to the pulmonary vessels. Procoagulant and antifibrinolytic changes are manifested in the form of an increase in substances that cause platelet aggregation in plasma, such as serotonin [21].

Serotonin acts through serotonin receptors (5-HT1B, 5-HT2A and 5-HT2B) in pulmonary artery smooth muscle cells and fibroblasts to stimulate proliferative processes leading to pulmonary vasoconstriction. The study of the effect of serotonin on the development of PAH has been going on for several decades [39, 58].

In the 1960s, there was a notion of a potential association between the usage of appetite suppressants and the development of pulmonary arterial hypertension (PAH). Subsequently, it was revealed that this relationship was due to an interaction with the serotonin transporter, where serotonin serves as a substrate. Since then, an increasing body of research has been dedicated to investigating serotonin (5-HT) and its metabolic pathways in the context of PAH pathogenesis. Nevertheless, the evidence regarding serotonin's role as a biomarker in the pathophysiology of pulmonary hypertension remains inconclusive. *Herve P.* et al. [50]demonstrated that patients with idiopathic PAH exhibited elevated plasma serotonin levels (alongside reduced platelet 5-HT levels) that persisted even after heart and lung transplantation [50].

Thus, the authors suggested that higher serotonin levels are not secondary to PAH. However, plasma serotonin levels were not always correlated with disease severity. Later, *Zeynaly F.* [50]et al were unable to find significantly different measurements in serum 5-HT concentration between controls and patients with idiopathic PAH, nor could they establish an association between these values and the degree of hypertension [50, 76].

These disparities could potentially stem from the limited sample size, with the most extensive study encompassing only 16 patients and 16 controls, variations in quantification methods, or the inclusion of different PAH subtypes within the research cohort. Through the utilization of a rat model of mitomycin-induced pulmonary veno-occlusive disease, *Mano O.A.* et al. [27] illustrated that serotonin levels exhibited elevation during the advanced phases of pulmonary hypertension, characterized by established vascular remodeling. This finding suggests that serotonin assumes a role in the later stages of pathogenesis and serves as a marker for disease severity in PAH [27, 28, 50, 25, 76].

Serotonin was originally isolated in 1937 from the intestinal mucosa. Initially, it was recognized as a vasoconstrictor released from platelets during blood clotting, and later identified as a monoamine neurotransmitter in the brain. Serotonin is predominantly stored in the gastrointestinal tract, platelets, and the central nervous system. The human body metabolizes serotonin through various pathways, including oxidative deamination (catalyzed by monoamine oxidase, MAO), conjugation with sulfuric and glucuronic acids, N-acetylation, 5-O-methylation, and their combinations. These enzymatic reactions are distributed across different organs and tissues in varying concentrations. Monoamine oxidase (MAO) accounts for the majority of serotonin metabolism. This enzyme, located on the outer mitochondrial membrane, facilitates the oxidative deamination of specific monoamines into corresponding aldehydes, ammonia, and hydrogen peroxide. The oxidation of serotonin's product, 5-hydroxyindoacetaldehyde, leads to the formation of 5-hydroxyindolacetic acid (5-HIAA) or the decomposition to 5-hydroxytryptophol. Aldehyde dehydrogenase, assisted by NAD as a coenzyme, catalyzes the generation of 5-HIAA. Aldehyde dehydrogenase is present in numerous tissues and organs, including the brain and liver. The formation of 5-hydroxytryptophol represents approximately 1% of the total serotonin metabolism in normal conditions, while 99% involves the synthesis of 5-HIAA. Serotonin and 5-HIAA are primarily excreted in the urine in their free forms [22, 34].

Most of the serotonin in the body (95%) is located in enterochromaffin cells of the gastrointestinal tract, from which it can be released into the intestinal cavity and into the blood as a result of exposure to sympathetic or parasympathetic nerve stimuli, increased intra-intestinal pressure and pH changes. Since serotonin is a vasoactive amine that causes vascular and smooth muscle hypertonicity, elevated plasma concentrations can be dangerous. In this connection, in the body there are mechanisms for the rapid clearance of serotonin from the blood plasma or its deactivation, among which are: capture of serotonin by platelets, binding to plasma transport proteins, catabolism of serotonin in the liver and lungs [58, 9].

Serotonin plays a crucial role in the process of heart development. Research findings using immunolabeling antibodies targeting serotonin have revealed that embryonic mouse hearts, grown in the presence of serotonin, actively uptake this mediator. Experiments involving the introduction of thymidine have shown that serotonin, as well as serotonin reuptake inhibitors such as fluoxetine or sertraline, suppress the proliferation of cardiac mesenchyme, endocardium, and myocardium. Studies demonstrate that preparations from ventricles of patients with end-stage heart failure exhibit a significant inotropic effect of 5-HT, particularly in the presence of the phosphodiesterase 3 inhibitor, isobutylmethylxanthine.

There are three main subtypes of serotonin receptors: 5-HT1, 5-HT2, and 5-HT3, which exist in flies, shellfish, worms, rodents, rabbits, cats, dogs, and humans. The classification of the International Union of Pharmacologists divides them into 5-HT 1A, 5-HT 1B, etc. The 5-HT1B receptor commonly mediates pulmonary arterial responses to serotonin in large animals and humans. The 5-HT2B receptor has been shown to have therapeutic effects. The 5-HT1B receptor can mediate proliferation, vasoconstriction, and fibrosis in human pulmonary circulation and animal models [6, 11, 13, 30].

The results of experimental studies demonstrate that the development of hypoxia-induced pulmonary arterial hypertension is completely prevented in mice by using the selective antagonist of 5-HT2B receptors, RS-127445. The increase in the expression of 5-HT2B (and 5-HT1B) receptors in the pulmonary arteries of rodents and humans is associated with the development of pulmonary hypertension [43].

In 2018, *Delaney C.* et al. [22] proposed that heightened serotonin signaling contributes to the pathogenesis of neonatal pulmonary hypertension (PH) complicating bronchopulmonary dysplasia and neonatal lung injury. To investigate this hypothesis, neonatal wild-type mice were subjected to intraperitoneal administration of PBS, ketanserin (1 mg/kg), bleomycin (3 U/kg), or a combination of bleomycin (3 U/kg) with ketanserin (1 mg/kg) three times a week for 3 weeks. Following bleomycin treatment, there was a significant increase in the pulmonary expression of tryptophan hydroxylase-1 (Tph1), the rate-limiting enzyme involved in 5-HT synthesis. However, bleomycin did not affect the expression of the pulmonary 5-HT 2A receptor, but it led to an upregulation of the pulmonary 5-HT 2BR gene and the serotonin transporter (SERT). Subsequently, the administration of ketanserin mitigated bleomycin-induced pulmonary hypertension and pulmonary vascular remodeling. These findings indicate an augmentation of serotonin signaling in a neonatal pulmonary hypertension mouse model, and the pharmacological inhibition of 5-HT 2AR demonstrated protection against the development of pulmonary hypertension in the context of neonatal lung injury [22].

Plasma circulating serotonin is taken up by platelets by active transport via the serotonin transporter (SERT) protein and deposited in platelet granules. In addition to active transport, there is also a passive mechanism for the transport of serotonin to platelets at high plasma concentrations (more than 20 nmol/10^9 platelets). Serotonin transport and signaling may be promising therapeutic targets in PAH [38, 39, 43, 86].

In the examination of children with CHDs complicated by PAH, a meticulous analysis of SERT concentrations was performed. The research findings unveiled a compelling disparity, as the level of SERT in children with PAH exhibited a substantial and statistically significant elevation compared to the SERT level observed in children without PAH. This intriguing observation suggests a potential

association between SERT and the development of PAH in children with congenital heart defects, warranting further investigation into the role of serotonin signaling pathways in the pathogenesis of this condition [61].

The liver exhibits the capacity to clear and metabolize serotonin from the bloodstream, leading to its oxidation to 5-HIAA. Experimental investigations have demonstrated a significant disparity in serotonin levels between the portal vein, responsible for transporting blood from the gastrointestinal tract to the liver, and the hepatic vein, responsible for carrying blood away from the liver. This disparity can reach up to 30% and may even rise to 80%. Additionally, the lungs play a substantial role in serotonin utilization, with approximately 90% of intravenously administered or endogenously secreted serotonin being removed through the lungs via uptake and subsequent oxidation by endothelial cells, leading to the production of 5-HIAA [62].

Studies indicate elevated urinary concentrations of the serotonin metabolite 5-HIAA in patients with secondary PAH due to congenital heart disease (CHD) with predominantly left-right shunt (VSD, ASD, PDA). This picture does not exclude an increased turnover of serotonin and, as a result, accelerated metabolism. *Mustafin A.A.* et al. [5] in their studies of children with congenital heart defects complicated by PH, identified a significant increase in the concentration serotonin in patients with PH. The researchers proposed a hypothesis about the pathogenesis of PH, which is associated with pulmonary vascular injury caused by elevated hydrostatic pressure, leading to platelet aggregation and release of serotonin. This, in turn, results in an elevated concentration of serotonin and its metabolite, 5-HIAA. However, the concentrations of total and free serotonin in most studies did not differ significantly between the main and control groups. After surgical correction of CHD, the total concentration of serotonin changed significantly. Some authors point to a decrease of up to 65% due to a postoperative decrease in the level of platelets [5, 89].

Moreover, in a recent study conducted by a group of Japanese scientists (*Tanaka T.T.*) [84] in 2021, involving 157 patients diagnosed with acute respiratory distress syndrome (ARDS), a condition with pathogenesis akin to PAH, 5-HIAA emerged as a robust and independent predictor of mortality. The study suggested 5-HIAA as a potential early biomarker indicative of the severity of the inflammatory process within the pulmonary system. [84]

Thus, the study of serotonin is promising as an early biomarker for the development of pulmonary hypertension.

Discussion

A comprehensive literature review has been undertaken to investigate the impact of serotonin and its metabolism on the pathology of pulmonary arterial hypertension (PAH). Despite the growing interest in this area, it is evident that there is a scarcity of research on this topic, highlighting the need for further exploration and in-depth studies involving larger and more diverse populations.

The strengths of this review lie in its systematic approach to gathering and analyzing the existing literature related to serotonin and its role in PAH. The researchers utilized reputable databases, such as Scopus, Web of Science, and Pubmed (Medline), to ensure a comprehensive and up-to-date collection of relevant studies. By focusing on original research articles and literature reviews published within the last decade, the review maximizes its relevance to contemporary research trends in the field.

However, the review also faces certain limitations, which should be acknowledged. The scarcity of available studies on this specific topic may have restricted the scope of the review and resulted in a limited number of relevant articles. Additionally, variations in methodologies, quantification methods, and the inclusion of different PAH subtypes across the selected studies may have introduced heterogeneity and challenges in drawing definitive conclusions.

In conclusion, this literature review sheds light on the potential significance of serotonin and its metabolism in the pathology of PAH. However, the limited number of available studies underscores the necessity for more extensive and well-designed research involving larger and diverse populations to fully comprehend the complex interactions and underlying mechanisms of serotonin in the development and progression of PAH. Addressing these research gaps will undoubtedly contribute to advancing our understanding of PAH pathogenesis and pave the way for more targeted therapeutic approaches in the future.

Conclusions

Various studies confirm the bonding between serotonin metabolism and PAH, thus being an important step in understanding the complex dynamics of the serotonin system and its impact on the cardiovascular system. The results confirm that serotonin plays a key role in the development and progression of PAH. However, despite significant progress in our knowledge, much remains unknown about the specific mechanisms of interaction of the serotonin system with the cardiovascular system and pulmonary hypertension. Further research should be directed towards a deeper understanding of this system and its effects in order to unlock its full potential for developing new approaches to the diagnosis, treatment and prevention of PAH by developing its early biomarkers.

Understanding the relationship between serotonin metabolism, the cardiovascular system, and pulmonary hypertension could lead to new medical breakthroughs that will enable us to use more effective treatment of this serious disease.

The prospects for the development of innovative treatments and strategies for the prevention of PAH are enormous and require further study of the serotonin system and its association with the cardiovascular system.

Expanding our knowledge in this area can lead to personalized approaches to the diagnosis, treatment and prevention of this disease, improving the quality of life of patients and reducing its negative consequences.

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Contribution of authors:

Ospanova M.D. - conceptualization, formal analysis, writing (original draft preparation);

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