Effects of succinates on the inflammatory response: a review

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Abstract

INTRODUCTION: Endogenous succinate functions as a pro-inflammatory factor, while exogenous succinate — as an anti-inflammatory factor. The mechanisms of effect of succinates on the inflammatory response are not fully understood. **OBJECTIVE:** Generalization of the current scientific knowledge on the use of exogenous succinate in inhibition of the inflammatory response. **MATERIALS AND METHODS:** The PubMed, Web of Science, Google Scholar, Scopus, and eLibrary international databases were used to search for relevant articles. The search keywords were: "succinic acid", "amber acid", "inflammation", "meglumine sodium/solution". The search was limited to articles published between 2012 and December 2022. The inclusion criteria were: 1) research focused on the cellular energy supply in inflammation; 2) effects of succinate on the inflammatory response intensity due to changes in the cellular energy supply; 3) correlation of the cellular energy supply with clinical and laboratory inflammatory indicators when succinate-containing drugs are used; 4) original studies. **RESULTS:** The initial identification analysis included over 200 published studies. After the screening, 84 full-text articles meeting the selection criteria were included in the final review: 31 literature reviews, 24 of which are dedicated to the pro-inflammatory effects of endogenous succinate, and 7 — to the anti-inflammatory effect of exogenous succinate in succinate-containing agents; and 53 original scientific articles: 27 articles are dedicated to the research of molecular mechanisms of endogenous succinate, and 26 articles are dedicated to the study of the clinical use of succinate-containing drugs. **CONCLUSIONS:** Endogenous succinate is defined as the most important pro-inflammatory factor. Exogenous succinate has a pronounced anti-inflammatory effect mediated by normalization of the immune cell energy supply in hypoxia. No studies have been found on the differences in the mechanism of action of endogenous and exogenous succinate.

Влияние сукцинатов на воспалительную реакцию: обзор литературы

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Реферат

АКТУАЛЬНОСТЬ: Эндогенный сукцинат выступает как провоспалительный фактор, экзогенный сукцинат — как противовоспалительный. Механизмы влияния сукцинатов на воспалительную реакцию до конца не изучены. **ЦЕЛЬ ИССЛЕДОВАНИЯ:** Обобщение современной научной базы по применению экзогенного сукцината для подавления воспалительной реакции. **МАТЕРИАЛЫ И МЕТОДЫ:** Для поиска статей использованы международные базы данных PubMed, Web Of Science, Google Scholar, Scopus, eLibrary. Использованы запросы: «succinic acid», «amber acid», «inflammation», «meglumine sodium/solution». Поиск ограничен статьями, опубликованными в период с 2012 г. по декабрь 2022 г. Критерии включения: 1) исследования, посвященные изучению энергетического обеспечения клеток в условиях воспаления; 2) влияния сукцината на интенсивность воспалительного ответа за счет изменения энергетического обеспечения клетки; 3) корреляции энергетического обеспечения клетки с клинико-лабораторными показателями воспаления при применении сукцинатсодержащих препаратов; 4) оригинальные исследования. **РЕЗУЛЬТАТЫ:** Первоначальный идентификационный анализ включал более 200 опубликованных исследований. В результате проведенного скрининга в конечный обзор литературы были включены 84 полнотекстовые статьи, соответствующие критериям отбора: 31 обзор литературы, 24 из которых посвящены провоспалительным эффектам эндогенного сукцината, 7 — противовоспалительному эффекту экзогенного сукцината в составе сукцинатсодержащих препаратов, а также 53 оригинальные научные статьи: 27 статей посвящены изучению молекулярных механизмов эндогенного сукцината, 26 статей — изучению клинического применения сукцинатсодержащих препаратов. **ВЫВОДЫ:** Роль эндогенного сукцината определена как важнейшего провоспалительного фактора. Экзогенный

сукцинат оказывает выраженное противовоспалительное действие, опосредованное нормализацией энергетического обеспечения иммунных клеток в условиях гипоксии. Не найдено исследований, посвященных различиям механизма действия эндогенного и экзогенного сукцината.

KEYWORDS: succinic acid, meglumine sodium succinate, succinate-containing drugs, reamberin, inflammation, anti-inflammatory

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КЛЮЧЕВЫЕ СЛОВА: сукцинат, натрия меглюмина сукцинат, сукцинатсодержащие препараты, воспаление, противовоспалительный эффект

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Introduction

The main source of biochemical reactions energy in the human body are phosphate bonds accumulated as adenosine triphosphate (ATP). The source of the 2 ATP molecules is glucose which is converted into pyruvate as part of glycolysis, then to acetyl-coenzyme A, and afterwards, it is converted into nicotinamide adenine dinucleotide and flavine adenine dinucleotide in the tricarboxylic acid (TCA) cycle or citric acid (Krebs) cycle taking place in the mitochondrial matrix. As electron donors, these two molecules transfer electrons in the mitochondrial chain during oxidative phosphorylation (OP) which results in formation of 34 additional ATP molecules [1]. The above pathway functions under perfect conditions of sufficient oxygen level.

The way cells compensate for reduced energy efficiency despite their high capacity of adaptation to hypoxia still requires detailed investigation. In hypoxia, glycolysis is ended by formation of lactate instead of acetyl-coenzyme A.The hypoxic stress interferes with the functioning of the high-capacity OP pathway and limits ATP production by glycolysis. There are four mitochondrial enzyme complexes: I — nicotinamide adenine dinucleotide dehydrogenase, II — succinate dehydrogenase, III — cytochrome C reductase, and IV — cytochrome C oxidase. In hypoxia, the electron transport chain functioning is disrupted, with stepwise impairment of enzyme complexes I, III and IV. The activation of succinate oxidase oxidation pathway (complex II) plays the main role. The activity of this pathway is time-limited and declines significantly with prolonged oxygen deficiency. The respiratory chain disorder results in ATP deficiency which leads to glycolysis activation, lactate accumulation, and acidosis development followed by glycolysis autoinhibition. The energy deficiency and single electron transfer in the respiratory chain triggers the formation of free radicals, reactive oxygen species [2]. In normoxia, the ten key glycolytic enzymes are diffused throughout cell cytoplasm. In hypoxia, glycolytic enzymes are separated into cytoplasmic structures. Biophysical studies have shown that cytoplasmic structures have the properties of phase-separated biomolecular condensates similar to the properties of stress granules. Combining several glycolytic enzymes by phase separation may promote enhancement of activity of the entire pathway and an increase in the response rate critical for the energy generation by forming a metabolon, a supramolecular complex of enzymes catalyzing consecutive steps of the metabolic pathway

and cell structural elements, during hypoxic stress. Hypoxia is associated with development of almost all critical conditions. Its significance in intensive care is extremely high [3].

Succinate is formed in the Krebs cycle through hydrolytic release of coenzyme A catalyzed by succinyl coenzyme A synthetase. Bypassing TCA, succinate is formed via the gamma aminobutyric acid shunt which uses glutamine for the synthesis of glutamate, gamma aminobutyric acid, succinic semialdehyde, and, ultimately, succinate [2, 4]. The succinyl coenzyme A synthetase complex consists of two α and β subunits promoting its catalytic activity. Succinyl coenzyme A synthetase cleaves off succinyl coenzyme A, H_3PO_4 becomes the donor of H^+, the residual phosphorus group H_2PO_4 joins guanidine diphosphate or adenosine diphosphate followed by formation of guanosine triphosphate or ATP. The energy value of 1 guanosine triphosphate molecule is equal to 1 ATP molecule. The formation of guanosine triphosphate and ATP in the Krebs cycle is a substrate-linked phosphorylation reaction as is the synthesis of ATP during glycolysis. In the sixth step of the citric acid cycle, succinate is oxidized to fumarate by oxidoreductase. Succinate is accumulated in the mitochondrial matrix where it is oxidized by succinate dehydrogenase to serve as an electron donor for the respiratory chain. The principal recipient of released electrons is nicotinamide adenine dinucleotide [5]. Evidently, normalization of cellular energetic supply in hypoxia will ensure an adequate immune response through the synthesis and functioning of a sufficient number of immune cells and mediators. Therefore, the search for medications allowing to provide the cell with sufficient energy in hypoxia is of great importance. One of the trends is the delivery of substances allowing to trigger the TCA or OP process to the cell. Succinate-containing drugs can reduce or completely eliminate the energy deficiency in hypoxia. In contrast to nicotinamide adenine dinucleotide-dependent substrates, exogenous succinate enters the cell without any obstacles and is able to oxidize and reproduce ATP in hypoxia in OP reactions. The energy capacity of succinate salt solutions in hypoxia is greater than that of exogenous glucose [6, 7].

Objective. Generalization of the current scientific knowledge on the use of exogenous succinate in succinate-containing drugs for inhibition of systemic inflammatory response.

Materials and methods

Study endpoints

The primary endpoint of the study is to answer the question of how normalization of the cellular energy supply by succinate-containing drugs in hypoxia contributes to inhibition of systemic inflammatory response. The secondary endpoint of the study is to answer the question whether there are any differences in the effects and functioning mechanisms of exogenous and endogenous succinates.

Search for studies

The PubMed, Web of Science, Google Scholar, Scopus, and eLibrary international databases were used to search for relevant articles. Search queries were generated on 30.12.2022. The following queries were used for the search: “succinic acid”, “amber acid”, “inflammation”, “meglumine sodium/solution”. The search was limited to the articles published between 2012 and December 2022. The citation searching method was also used to search for articles.

Effect of cellular energy supply in critical conditions on the cell functioning and immune response

Activated macrophages differentially use metabolic pathways of energy generation to support the maximum activation of effector functions [8]. OP occurs in M1 macrophages activated by lipopolysaccharide (LPSMs) or LPS + interferon gamma and M2 macrophages activated by interleukin (IL-4). LPS or interferon gamma promote the activation of pro-inflammatory macrophages that produce pro-inflammatory cytokines and nitric oxide [9]; they play the main role in initiation of inflammation [10]. M1 macrophages play an important role in fighting microbial infections and regulation of inflammation. M2 macrophages participate in the regulation of inflammation and tissue repair. Stimulation of dendritic cells and M1 reduces the intensity of OP processes with a concomitant increase in glycolysis and activity of pentose phosphate pathway [11]. Mitochondrial collapse (a sharp decrease in ATP production) occurs in dendritic cells and LPSMs as a consequence of nitric oxide production from arginine [12]. Nitric oxide inhibits mitochondrial respiration by nitrosylation of iron-sulfur proteins including mitochondrial complexes I, II, IV of the electron transport chain, thereby inhibiting the electron transport and subsequent ATP production [13]. One of the results of the reduced ATP production in LPSMs via OP is repurposing of mitochondria for generation of reactive oxygen species and signaling molecules required for generation of the respective immune response. Activated macrophages exhibit the immunologic cancer-like Warburg effect with the formation of large amounts of lactate [14]. After removal of the pathogen from the body, anti-inflammatory macrophages should suppress the inflammatory response in order to prevent excessive self-damage of the host tissues, and switch to OP provides a sustained support of the cellular bioenergetics necessary for tissue homeostasis and wound healing in this situation [15].

Unlike dendritic cells and inflammatory macrophages, adaptive immune cells do not avoid OP. The metabolism

of T-cells varies depending on their effector function and maturity. Juvenile T-cells metabolize glucose, amino acids, and lipids to initiate TCA and OP. Inactive juvenile T-cells are activated by T-cell receptor ligation combined with costimulation of clusters of differentiation 3 and 28 resulting in rapid proliferation and differentiation. The energy supply of these processes is characterized by enhanced glycolysis [16].

Enhanced glycolysis is also characteristic of proliferating cells or cells with high biosynthetic capacity (T-cells activated for cytokine production). Mitochondrial metabolism is increased and sufficient for support of T-cell activation even in the absence of glucose [17]. Bypassing glycolysis by means of T-cell costimulation by pyruvate for direct induction of TCA increases the expression of T-cell activation markers (CD25 and CD69). Mitochondria undergo radical changes after the T-cell activation; their quantity, mass, membrane area and the amount of template deoxyribonucleic acid increase [18].

The foregoing indicates that an increase in the "energy supply capacity" of the cell in glucose deficiency and hypoxia can improve the anti-inflammatory response.

Signaling role of cytokines and endogenous ligands in hypoxia and energy deficiency

Cytokines of T-helpers 2, IL-4 and IL-13, contribute to proliferation of anti-inflammatory macrophages which express anti-inflammatory cytokines: IL-10, transforming growth factor beta, arginase 1 [19].

Endogenous succinate is accumulated in inflammation and metabolic stress areas [20, 21]. Endogenous succinate is known to play a key role in macrophage activation [22]. Succinate is a metabolite with high level of accumulation in macrophages in response to LPS stimulation. Endogenous succinate contributes to increased pro-inflammatory activity in macrophages by stimulating the expression of IL-1β, a key pro-inflammatory cytokine [23–25]. Endogenous succinate acts as an endogenous alarmin to support production of IL-1β by promoting binding of hypoxia-inducible factor (HIF-1α) with the hypoxia response element [26]. HIF-1α inhibits OP by inducing types 1 and 3 pyruvate dehydrogenases that ensure further stabilization of HIF-1α [28]. Recent studies have shown that inhibition of succinate dehydrogenase induces stabilization of HIF-1α through suppression of reactive oxygen species (ROS). Oxidation of succinate in LPSMs indirectly inhibits the activity of pyruvate dehydrogenase via mitochondrial ROS leading to stabilization of HIF-1α and production of IL-1β [27]. This metabolic mechanism is important for survival and normal functioning of immune cells in anaerobic inflammatory lesions. Hypoxia-inducible factor (HIF-1α) plays the key role in this process allowing the cells to adapt to an environment with low oxygen content as a key oxygen acceptor [29]. Succinate is synthetized in mitochondrial matrix and is a ligand for electron transport chain complex II supplying ATP synthase with electrons. When the Toll-like receptor 4 is activated, a standard TCA is shortened causing a decrease in activity of succinate dehydrogenase at site II resulting in limited succinate oxidation followed by its accumulation. As a consequence, reactive oxygen species production by mitochondria is increased and HIF-1α is stabilized [30, 31].

In dendritic cells, endogenous succinate triggers intracellular calcium mobilization, induces migratory reactions, and acts in synergy with Toll-like receptors to induce pro-inflammatory cytokine production [32]. A number of studies have found that the expression of IL-1β is enhanced in bone marrow dendritic cells of mice concomitantly exposed to succinate and LPS [33]. Endogenous succinate is known to act in synergy with Toll-like receptors 3 to increase the production of tumor necrosis factor alpha (TNFα). Endogenous succinate also increases the ability of dendritic cells to present antigens to T-cells and induce adaptive immune reactions, which enhances their pro-inflammatory properties [34]. When dendritic cells are primed simultaneously by endogenous succinate and antigen, the production of TNFα and interferon-γ by these cells is increased [35]. The study by Wobben R. et al. (2013) showed that HIF-1α-deficient dendritic cells demonstrated impaired ability to activate T-cells supporting the assumptions that this transcription factor is important for T-cell polarization and activation [36].

In vitro studies showed that succinate could induce activation of hematopoietic stem cells and regulate their proliferation, migration and apoptosis along with an increase in secretion of pro-inflammatory cytokines, IL-6 and TNFα [37, 38]. Succinate accumulates in hypoxia associated with ischemia reperfusion injury [39, 40]. Endogenous succinate is manifested similarly in inflammatory diseases [41]. Increased amounts of circulating endogenous succinate are observed both at physiological conditions such as strenuous exercise [42], and at certain diseases where its accumulation rate depends on severity of hypoxia: inflammatory bowel diseases [43–45], sepsis [4, 46], ischemic heart disease [47], type II diabetes [48], obesity [49]. Numerous studies support the effects of endogenous succinate as a pro-inflammatory mediator, the accumulation of which should be considered as a marker of severity of hypoxia [50]. During inflammation, IL-37 restores cellular metabolism by reducing endogenous succinate [51].

Effect of exogenous succinate on cellular energy supply in hypoxia and energy deficiency

In normoxia, endogenous succinate concentrations reach 20 μmol/L [52]. Accumulation of endogenous succinate in plasma and extracellular matrix is the result of its accumulation in cells, which is observed in hypoxia [53], hyperglycemia, and strenuous exercise [54].

It has been found that most human and mammalian tissues have receptors towards which endogenous succinate acts as a ligand. Initially, these receptors were considered

orphan and were included into the (G-protein coupled receptor) group 91. Further research showed their exceptional sensitivity to succinate, and the receptors were given a new name: succinate receptors. The activation of receptors coupled with receptor 91 G-protein is observed when the concentrations of exogenous succinate exceed the normal endogenous succinate plasma levels twice or more (> 55 μmol/L). This receptor type has a high expression level in human platelets. It is known that their aggregation rate increases when endogenous succinate concentrations increase up to 300–500 μmol/L. Succinate receptor 1 expression was also found in human bone morrow cells: stem cell pool, megakaryocytes, erythroid lineage [55–57].

The effect of endogenous succinate on inflammatory process is mediated by its impact on stability and activity of HIF-1α. It triggers the expression of peptides: erythropoietin, endothelial growth factor, glucose transporters 1 and 3, and glycolysis enzymes. In hypoxia, endogenous succinate is accumulated in immune cells, which also leads to stabilization of HIF-1α. The increased expression of HIF-1α-dependent genes results in rapid production of ATP and pentose phosphate pathway activation, thereby contributing to the enhanced biosynthetic capacity of the activated cell. Endogenous succinate increases glycolysis by proteolysis of the HIF-1α alpha subunit by prolyl hydroxylase that leads to accumulation of HIF-1α and increased glycolysis. The elevated levels of HIF-1α increase the expression of genes containing HIF-1α response elements including the gene of interleukin IL-1β (1b). Recent studies indicate that all body cells have HIF-1α receptors and are able to respond with activation manifested as expression of genes including those coding IL-1β. In normoxia, HIF-1α is inactive in the cell. It is activated when the partial pressure of oxygen decreases and/or endogenous succinate concentrations increase suggesting that the HIF-1α/succinate relationship can be considered as a receptor/signaling molecule. The role of the succinate molecule in stabilization of HIF-1α has been previously demonstrated in cancer. Mutations of the succinate dehydrogenase enzyme in tumors, such as paraganglioma, led to accumulation of endogenous succinate molecules, prolyl hydroxylase inhibition, and HIF-1α activation. This metabolic mechanism is important for survival and normal functioning of immune cells in anaerobic inflammatory lesions allowing them to adapt to an environment with low oxygen content [58].

Relation of energy supply in critical conditions with laboratory inflammatory parameters and clinical outcomes

The analysis of scientific literature for the previous decade (2012–2022) showed a great interest of the medical research community to succinate-containing drugs (SCDs). Their widespread use in clinical practice provided extensive insight into the role of exogenous succinate in inhibiting the inflammatory response in various diseases. Anti-inflammatory effects of SCDs have been well demonstrated in a number of clinical studies.

Endogenous intoxication is an integral component of the systemic inflammatory response syndrome. In acute intestinal infections, it is caused by:

- accumulation of medium molecular weight peptides in high concentrations;
- accumulation of natural metabolic products;
- activation of aggressive complement components, circulating immune complexes;
- activation of inflammatory mediators;
- activation of lipid peroxidation, with accumulation of reactive oxygen species and depletion of antioxidant defense system, which in turn leads to cell membrane destruction;
- impaired cytokine balance (IL-1b, IL-6, IL-10, and TNFα).

Inclusion of SCDs into the acute intestinal infection treatment regimen is justified as pathogenetic and aimed at correction of lipid peroxidation processes. The study by V.F. Pavelkina et al. (2018) in 70 salmonellosis patients which included SCDs into the treatment regimen showed normalization of lipid peroxidation due to the decrease in lipid peroxidation products, i. e. diene conjugates, diene ketones, malondialdehydes in plasma and red blood cells, and the increased activity of antioxidant factors, i. e. plasma and red blood cell catalase and superoxide dismutase [59]. The additional molecules by which researchers assess the efficacy of SCD administration are medium-weight molecules at 254 and 280 nm wavelengths, and the synergy of albumin detoxification properties by total and effective concentrations of albumin [60]. The study by V.F. Pavelkina et al. (2012) in 66 patients with acute intestinal salmonella infection showed that the use of SCDs led to the decrease in medium-weight molecules$_{254}$ from 0.270 ± 0.010 to 0.220 ± 0.010 relative units, and in medium-weight molecules$_{280}$ to 0.256 ± 0.010 relative units. The use of SCDs contributed to the increase in total albumin concentration in 80 %, and in effective albumin concentration in 90 % of patients. The decreased leukocytic intoxication index was also observed in 73.3 % of cases [61]. The study by V.M. Frolov et al. (2013) in 66 patients with acute intestinal opportunistic infections showed that the use of SCDs led to a more rapid decrease in medium-weight molecules (by 3 times or faster), and circulating immune complexes by 1.5 times [62]. Similar results were published in the extensive retrospective study conducted by V.A. Zaplutanov et al. (2012). The authors analyzed 215 case records and found that the inclusion of SCDs into the treatment regimen led to a 2.8-fold faster decrease in medium-weight molecules, a 1.8-fold faster decrease in the Kalf—Kalif leukocytic intoxication index, a 1.3-fold faster decrease in the Ostrovsky leukocytic intoxication index, and a 0.86-fold faster decrease in the nuclear intoxication index [63].

Acute intestinal infection in subjects with severe comorbidities is associated with potentiation of tissue hypox-

ia. The study by E.O. Tikhonova (2013) included 4 groups of 18 to 22 patients with comorbidities (chronic alcoholism and ischemic heart disease). Addition of SCDs to the complex infusion therapy contributed to rapid improvement of clinical intoxication symptoms. The recovery dynamics was comparable to that of acute intestinal infection patients with no comorbidities; abstinence syndrome was observed 5.5 times less frequently [64]. Similar results were obtained by E.O. Tikhonova et al. (2017) in 197 patients with comorbidities, such as ischemic heart disease, diabetes mellitus, mental and behavioral disorders associated with alcohol consumption [65].

Alcohol intoxication leads to impaired synthetic function of the liver due to activation of free radical oxidation and triggering of apoptosis in hepatocytes, as well as due to impaired cellular immune response caused by disruption of routine energy metabolism of immune cells (T-helpers). An active inflammatory response is associated with increased secretion of pro-inflammatory markers and decreased secretion of anti-inflammatory markers. A recent study conducted by Ch.Lhagvadorzh and Yu.Sodnom in 2020 in 140 patients showed that the inclusion of SCDs into infusion therapy regimens for patients with alcohol intoxication contributes to normalization of hepatic enzyme levels, decrease in blood total bilirubin, alkaline phosphatase, and gamma glutamyl transferase suggesting a decrease in intensity of free radical oxidation in hepatic cells. A significant increase in blood anti-inflammatory cytokines was observed: IL-4 by 2.2 times, and IL-10 by 1.2 times, compared to baseline values ($p < 0.05$), in the SCD group [66].

Endogenous intoxication in purulent inflammatory abdominal diseases occurs as a result of a vigorous inflammatory response with development of excessive activation of motor control sympathetic component, release of cytokines, hormones and metabolites. The inflammatory response of abdominal organs is associated with paralytic ileus, intestinal wall ischemia with impairment of resorptive and barrier functions of the intestine [69].

The inclusion of SCDs into the abdominal sepsis treatment regimen showed positive effects related, primarily, to the resolution of tissue hypoxia. The study by A.B. Tolkach, V.T. Dolgikh (2012) in 64 abdominal sepsis patients showed that the inclusion of SCDs into the treatment regimen promoted increase in macrophage phagocytic activity on Days 3 and 7 [68]. Similar research by Yu.P. Orlov et al. (2013) in 23 patients with advanced abdominal sepsis showed that the inclusion of SCDs into the treatment regimen decreased the intensity of free radical oxidation and lipid peroxidation by 60 %: a 2-fold decrease in malondialdehyde levels, and a 3.8-fold decrease in lactate concentrations were observed [69]. In the research by K.M. Kurbonov et al. (2016), an SCD was used for whole bowel irrigation. The analysis included 140 patients with diffuse purulent peritonitis. The results showed that the inclusion of an SCD into the complex enteral correction led to a significant decrease in lipid peroxidation and endogenous intoxication activities by Days 3–4 of the post-operative period [70]. The study by V.A. Zavyalkin et al. (2019) included 327 children with diffuse purulent peritonitis of various etiologies. An SCD was administered to suppress the systemic inflammatory response syndrome. The examination of white blood cell levels, erythrocyte sedimentation rate, Kalf—Kalif leukocytic intoxication index, C-reactive protein over time indicated a statistically significant decrease in these values on Days 3 and 5 in the SCD group. The analysis of total albumin concentration values over time indicated statistically significant improvement on Days 3 and 5 in children of the SCD group [71]. Similar results were obtained in the study by Sh.A. Yusupov et al. (2019) in 402 children with diffuse appendicular peritonitis. The antecedent patient screening showed an increased number of total white blood cells (by 1.7–2.3 times), a left shift, an increase in the leukocytic intoxication index over 2.0 units (by 4.1 times), a two-fold decrease in superoxide dismutase and catalase concentrations, a more than two-fold increase in malondialdehyde and medium molecular weight peptides [72].

Coronavirus infection studies made a significant contribution to evaluation of anti-inflammatory properties of SCDs.

The study by I.S. Simutis et al. (2021) conducted in 12 coronavirus pneumonia patients confirmed the anti-inflammatory effects due to inclusion of SCDs into the treatment regimen based on the statistically significant changes in white blood cell, ferritin, C-reactive protein, fibrinogen, and platelet levels over time. The investigators believe that these effects of SCDs may be explained by several mechanisms of action [73]:

1. The endogenous succinate molecules accumulated in macrophages when their metabolic activity is increased maintain their pro-inflammatory program via stabilization of HIF-a transcription factor [74].
2. Exogenous succinate, most likely, acts via special succinate receptors and is able to exert a regulatory influence between inflammation and metabolic stress [75].

The experimental research by N. Keiran et al. (2019) showed that the disruption of succinate receptor 1-mediated signal in myeloid cells inhibits the induction of pro-inflammatory program in macrophages while activation of succinate receptors 1 in macrophages promotes anti-inflammatory phenotype development and increases the synthesis of anti-inflammatory cytokines, including IL-4, by these cells. The investigators believe that the role of extracellular succinate is to counterbalance inflammatory signals in order to restore metabolic homeostasis [76].

COVID-associated coagulopathy also considered to be related to the systemic inflammatory response syndrome accompanied by excessive release of cytokines and chemokines demonstrate increased production of IL-6, IL-7, TNFα, and inflammatory chemokines, such as: CC chemokines 1

and 2, and soluble IL-2 receptor; hyperactivation of monocytes and macrophages [76, 77].

The study by E.V. Mikhailova et al. (2015) indicated a decrease in C-reactive protein levels and hematologic intoxication parameters following the inclusion of SCDs into the infusion therapy program in 130 children aged 5 months to 12 years with severe influenza [78].

Some studies evaluate antioxidant/anti-inflammatory properties of SCDs based on dynamics of nitrogen oxide. Its excess causes an increase in vascular permeability as a result of peroxynitrite accumulation and increased production of pro-inflammatory cytokines which leads to disorders of body organs and tissues. The study by L.I. Ratnikova et al. (2016) conducted in 70 patients aged between 18 and 57 with various degrees of intoxication in influenza indicated normalization of nitrogen oxide blood levels following the inclusion of SCDs into the treatment regimen by Day 4.8 ± 0.25 while in the comparator group, the normalization occurred only by Treatment Day 6.18 ± 0.26 [79].

In the study by T.V. Stoieva et al. (2018), the use of SCDs was effective in correction of the secondary acetonemic syndrome associated with respiratory viral infection in children. The authors found that acetonemic syndrome accompanied inflammatory diseases of upper and lower respiratory tracts: acute rhinopharyngitis, 53.125%; acute non-obstructive bronchitis, 21.875%; acute obstructive laryngotracheitis, 12.5%; community-acquired pneumonia, 9.375%, acute tracheitis, 6.25%; acute obstructive bronchitis, 6.25%. The administration of SCDs improved the energy metabolism indicators with significant concomitant improvement of acetonemic syndrome laboratory parameters [80].

Conclusion

Energy metabolism plays an important role in the regulation of inflammation, and the role of succinate in it is ambiguous. If the mitochondrial matrix does not function properly, and the electron transport chain, TCA, is broken, endogenous succinate is accumulated and acts as a ligand and signaling molecule triggering the immune cell activation cascade, HIF-1α stabilization, exerting a pronounced pro-inflammatory effect. Endogenous succinate plays the key role in macrophage activation, is a metabolic switch ensuring adaptation of immune cells to energy substrate and oxygen deficiency. The use of exogenous succinate in an SCD, in its turn, leads to effective inflammatory response inhibition by normalization of immune cell energy supply, electron transport chain function restoration, glycolysis suppression, restoration of HIF-1α stability regulation. Exogenous succinate showed dose-dependent inhibition of inflammatory mediators, such as IL-6, TNFα, and nitrogen oxide, suggesting that extracellular succinate plays a role in inflammatory response inhibition. Further detailed research of the succinate's role in SCDs in inflammatory response regulation, its potential use in diseases associated with excessive inflammatory response, and identification of differences in the mechanisms of action of endogenous succinate and exogenous succinate are required.

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