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THE MULTIFACETED THERAPEUTIC APPLICATIONS OF SUCCINIC ACID IN MEDICINE.

Xolboyeva Gulnoz Baxadirovna
Emergency Clinical Hospital. Anesthesiologist, resuscitator, 99-802-94-53.
Xolboevy@mail.ru

Abstract: Succinic acid, a naturally occurring dicarboxylic acid, plays a pivotal role in cellular metabolism as an intermediate in the citric acid (Krebs) cycle. Beyond its metabolic functions, succinic acid has garnered significant attention for its wide array of therapeutic applications in modern medicine. This article delves into the pharmacological activities of succinic acid, emphasizing its anti-inflammatory, antioxidant, neuroprotective, and metabolic regulatory effects. Additionally, the article explores its emerging roles in cancer therapy, antimicrobial treatment, and its potential in combating metabolic syndrome and cardiovascular diseases.
Keywords: Succinic acid, citric acid cycle, anti-inflammatory, antioxidant, neuroprotection, metabolic syndrome, cardiovascular health, cancer therapy, antimicrobial activity.

Introduction: Succinic acid ($C_4H_6O_4$), also referred to as butanedioic acid, is a critical component of the citric acid cycle, essential for energy production in aerobic organisms. Found in various natural sources, including amber, from which it derives its name, succinic acid has been utilized in various industries, such as food, agriculture, and manufacturing. In recent years, its potential medicinal properties have been the focus of extensive research, unveiling its broad-spectrum therapeutic potential. Succinate serves as an essential circulating metabolite within the tricarboxylic acid (TCA) cycle and functions as a substrate for succinate dehydrogenase (SDH), thereby contributing to energy production in fundamental mitochondrial metabolic pathways. Aberrant changes in succinate concentrations have been associated with pathological states, including chronic inflammation, ischemia/reperfusion (IR) injury, and cancer, resulting from the exaggerated response of specific immune cells, thereby rendering it a central area of investigation. Recent studies have elucidated the pivotal involvement of succinate and SDH in immunity beyond metabolic processes, particularly in the context of cancer. Current scientific endeavors are concentrated on comprehending the functional repercussions of metabolic modifications, specifically pertaining to succinate and SDH, in immune cells operating within a hypoxic milieu. The efficacy of targeting succinate and SDH alterations to manipulate immune cell functions in hypoxia-related diseases have been demonstrated.

Methods

1. Literature Review: A thorough review of scientific literature was conducted, focusing on studies published in the last 30 years. Databases including PubMed, Scopus, and Google Scholar were utilized to gather data on the biological and medicinal properties of succinic acid.
2. In Vitro and In Vivo Studies: A detailed examination of laboratory studies involving animal models and cell cultures was performed to elucidate the molecular mechanisms of succinic acid's effects.
3. Clinical Trials and Meta-Analyses: The study also reviewed clinical trials and meta-analyses to assess the efficacy and safety of succinic acid in various therapeutic contexts.

This metabolic shift towards glycolysis in activated immune cells is thought to have a significant impact in low oxygen conditions, such as hypoxic inflammatory sites. The accumulation of succinate has the potential to enhance inflammatory signaling and greatly influence the immuno-inflammatory response. Various potential sources may contribute to the accumulation of succinate. Firstly, these studies have provided confirmation that succinate accumulation resulting from SDH mutations has the ability to stabilize HIF-1α in activated macrophages, particularly when the activity of the prolyl hydroxylase domain (PHD) enzyme is inhibited. Recent studies have provided evidence indicating the involvement of SUCNR1 in multiple succinate-dependent inflammatory processes *in vivo*. Firstly, it was observed that SUCNR1-deficient mice exhibited heightened migration of DCs in comparison to their wild-type counterparts. Secondly, the absence of SUCNR1 in DCs resulted in the absence of cytokine elevation, thereby supporting the notion that succinate functions as a conventional signal to enhance the antigen-presenting function of APCs. Lastly, solid organ transplantation from SUCNR1-deficient mice exhibited prolonged graft survival when compared to that from wild-type mice.

Results

1. Anti-Inflammatory Effects: Succinic acid exhibits significant anti-inflammatory properties by modulating the immune response. It inhibits the production of pro-inflammatory cytokines like TNF-α and IL-6, which are key mediators in chronic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease,

and asthma. These effects are believed to be mediated through its action on the NF-κB signaling pathway.

2. Antioxidant Properties: As an effective antioxidant, succinic acid reduces oxidative stress by neutralizing free radicals and upregulating endogenous antioxidant defenses like glutathione peroxidase and superoxide dismutase. Its antioxidant capacity is particularly beneficial in preventing cellular damage associated with chronic diseases like diabetes, cancer, and neurodegenerative disorders.

3. Neuroprotective Role: Succinic acid's neuroprotective effects are attributed to its ability to enhance mitochondrial function, thereby improving cellular energy production and reducing neurotoxicity. Studies have shown its potential in protecting neurons from damage in models of Alzheimer's disease, Parkinson's disease, and stroke. The compound's role in reducing amyloid-beta accumulation and tau phosphorylation in Alzheimer's disease has been a focal point of recent research.

4. Metabolic Disorders: Succinic acid's role in metabolic health is underscored by its ability to improve insulin sensitivity and glucose metabolism. It enhances the function of the insulin receptor and glucose transporter 4 (GLUT4), which are critical in maintaining glucose homeostasis. Furthermore, succinic acid supplementation has been shown to reduce lipid accumulation in adipocytes, indicating its potential in treating obesity and related metabolic disorders.

5. Cardiovascular Health: Emerging evidence suggests that succinic acid may play a protective role in cardiovascular health. By improving mitochondrial energy metabolism in cardiac cells, succinic acid helps to reduce myocardial ischemia and reperfusion injury. Additionally, it has been shown to lower blood pressure in hypertensive models by modulating the renin-angiotensin system and improving endothelial function.

6. Cancer Therapy: Recent studies have explored succinic acid's potential as an adjuvant in cancer therapy. It has been found to inhibit the growth of cancer cells by inducing apoptosis and disrupting mitochondrial function. In particular, succinic acid shows promise in enhancing the efficacy of chemotherapy drugs by sensitizing cancer cells to treatment.

7. Antimicrobial Activity: Succinic acid exhibits antimicrobial properties against a range of pathogens, including bacteria, fungi, and viruses. It disrupts microbial cell membranes and inhibits biofilm formation, making it a potential candidate for treating infections and preventing the spread of antibiotic-resistant strains.

Discussion

Succinic acid's diverse biological activities make it a promising candidate for therapeutic applications in various fields of medicine. Its natural occurrence and biocompatibility enhance its appeal as a therapeutic agent with minimal side effects. While the current body of research highlights its potential, further studies are necessary to fully elucidate its mechanisms of action, optimize its therapeutic use, and explore its long-term safety in clinical settings. Consequently, there is ongoing research aimed at elucidating these fundamental mechanisms in order to facilitate the development of innovative therapeutic interventions and associated pharmaceuticals. Numerous investigations have demonstrated that succinylation can occur in organisms through both enzymatic and non-enzymatic means.

Conclusion: The therapeutic potential of succinic acid is vast, spanning anti-inflammatory, antioxidant, neuroprotective, and antimicrobial effects. Its role in metabolic and cardiovascular health, as well as its emerging applications in cancer therapy, make it a compound of significant interest for future medical research and clinical use. Continued exploration and development could position succinic acid as a key player in the treatment of a wide range of diseases. Historically, succinate and SDH have been recognized as pivotal contributors to ATP generation in the context of mitochondrial energy metabolism. Nevertheless, it has become evident that comprehending their extensive involvement in IR injury, immuno-inflammatory responses, and tumorigenesis could offer innovative and potent insights into disease control.

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