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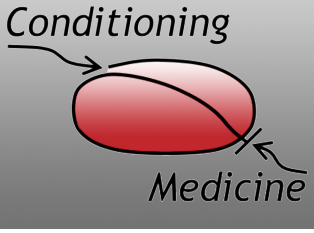

REVIEW ARTICLE | OPEN ACCESS

Hypoxic conditioning and succinate: relevance to COVID-19

E.I. Maevsky[1]

Modeling of natural adaptive signals is an important way to design and examine the mechanism of action of a multitude of biologically active compounds and pharmaceuticals, as well as methods used in sports and internal medicine. It appears that initially, hypoxic pre- and postconditioning gained most prominence in sports and cardiovascular surgery, particularly in cardioplegia. This letter briefly introduces certain aspects of potential application of small doses of succinate, as one of hypoxia's and ischemia's key signaling products, with a track record of being an effective antihypoxic agent. Metabolic and regulatory succinate-dependent antihypoxic mechanisms are considered as a possible justification for its administration to alleviate the course of coronavirus disease 19 (COVID-19) illness. This is due to the fact that it is precisely mixed hypoxia of different genesis that plays a key role in the complex pathophysiology of coronavirus that largely determines the outcome of the illness.

Preconditioning and postconditioning are generally the result of harmful effects that are subthreshold (in effect, non-damaging) in intensity and duration. They serve as warning signals, provide for preemptive mobilization of functions, and allow the body to "anticipate" and prepare not only for a more stressful specific harmful effect, but also for other aggressive environmental and internal stressors. There is an increase in nonspecific resistance and tolerance to physical and psycho-emotional stresses, extreme (stressful) injuries, and intoxication, and innate and acquired immunity is activated (Marongiu and Crisafulli, 2014; Rybnikova and Samoilov, 2015; Verges et al., 2015; Tobin et al., 2020). This phenomenon has been developed and reinforced in the process of evolution. Hypoxic pre- and postconditioning trigger a series of defensive processes, the extent and duration of which are determined by the magnitude and frequency of subthreshold damaging signals. The formation of immediate, rapid, and extended responses to subthreshold signals enables hormesis and adaptation of the body. This is the basis for the adaptive effect of intermittent hypoxic episodes, athletic training design, radiation hormesis, vaccination, prophylaxis, and the prevention of the progression of numerous ischemic and metabolic diseases.

The body's responses to conditioning signals are triggered and controlled by the neuroendocrine immune system. In response to conditioning stimuli, there occurs a reprogramming of ongoing reactions and related epigenetic changes with corresponding alteration in gene expression. Physiological and molecular genetic mechanisms and metabolic changes enabling a cascade of conditioning-triggered processes are receiving considerable attention. An understanding of these mechanisms is fundamental to the development of new drugs, prophylaxis, treatment, eating and social behavior rehabilitation, and ultimately, a polymodal increase in tolerance to damaging effects. The modeling or at least partial reproduction of conditioning mechanisms is widely used in pharmacology for liver diseases and ischemic heart damage, as well as in therapeutic surgical, neurological, and other types of care.

This paper considers the feasibility of modeling the effect of one of hypoxic conditioning's metabolic elements. In the practice of conditioning, commonly used agents include glucose, fructose, lactate, adenosine, inosine, hypoxanthine, ATP, coenzyme Q, and lipoic acid, as well as diets such as the ketogenic diet, the low-carbohydrate diet, and the low-fat diet. A unifying aspect of these methods is the catabolic effect: the correction of substrate deficiency and enzyme system activity and the prevention of intermediate and end metabolite accumulation. The commonality among all types of organisms in hypoxic conditions with carbohydrate deprivation is an increase in succinate production, even accumulation under anaerobiosis and ischemia, similar to lactate accumulation during anaerobic glycolysis (Hochachka et al., 1975; Taegtmeyer, 1978; Peuhkurinen et al., 1983; Pisarenko et al., 1986).

Through the research of B. Chance (Chance and Williams, 1955; Chance and Hollunger, 1961) and M.N. Kondrashova (Kondrashova, 1968; 1970), it has been known for over half a century that succinate is the most energetically powerful substrate of the Krebs cycle in animal and human cells' mitochondria. Mitochondria play a special role in supplying energy to high-intensity processes in the most vulnerable essential organs. At the mitochondrial level, succinate oxidation optimally enables energy-dependent processes under stress (by means of ATP resynthesis, ion accumulation, phosphocreatine synthesis, and glucose phosphorylation) and reduction processes (gluconeogenesis, repletion of energy deficit, ammonia neutralization, and fatty acid, amino acid, and nucleotide synthesis). The mitochondrial catabolism trait produced in the process of evolution manifests with oxygen deficit: instead of the Krebs cycle's regular (circular) pathway, all of the cycle's substrates transform into succinate. Our studies have demonstrated the activation sequence of anaerobic succinate formation pathways common to all types of mitochondria. The first seconds show reductive inversion of the tricarboxylic acid (TCA) cycle from oxaloacetate to succinate associated with oxidative phosphorylation at the level of

[1]Institute of Theoretical and Experimental Biophysics, Russian Academy of Sciences, Pushchino, Moscow Oblast, Russia.

Correspondence should be addressed to E.I. Maevsky (maevsky.eugene@gmail.com).

respiratory complex I. Then, within 2-5 minutes, by oxidizing nicotinamide adenine dinucleotide (NADH), the reductive inversion of the TCA cycle sustains the cycle's oxidative part from isocitric and 2-oxoglutarate to succinate. At the same time, substrate phosphorylation at the level of succinyl-coenzyme A is also activated. Ultimately, under severe de-energization, anaerobic dismutation of 2-oxoglutarate into succinate and glutamate takes place as ammonium is accumulated (Mayesvsky et al., 2000). Therefore, the end products are succinic acid, ammonium succinate, and glutamate. Anaerobic formation of succinate has benefits for mitochondria and cells: it promotes ATP resynthesis and inhibits mitochondrial consumption of glycolytic ATP despite the absence of oxygen. However, as soon as oxygen is present, accumulated succinate is oxidized at a high rate. Its oxidation rate is higher than any other substrate, especially under hypoxia. Succinate can be preferentially oxidized under various injuries to the respiratory chain's most vulnerable component, complex I, including under hypoxic conditions (Galkin et al., 2009; Stepanova et al., 2019).

This characteristic is related not only to the high activity and stability of succinate dehydrogenase (SDH), but also to its direct involvement in the functioning of the segment of the mitochondrial respiratory chain closer to oxygen than dehydrogenases of other substrates. Under conditions of anaerobiosis, ischemia, or deep hypoxia, succinate is an end product of mitochondrial catabolism and can be rapidly utilized with the recovery of oxygen supply (post-ischemic reperfusion). Furthermore, hyperproduction of the active forms of oxygen occurs (Drose, 2013; Andrienko et al., 2017). On the other hand, succinate oxidation clearly interferes with peroxidation of lipid membranes (Grishina et al., 2015). The properties of succinate metabolism formed the basis for the widespread use of succinate-containing agents in various extreme and pathological energy-deficient scenarios. However, effective doses of succinate proved to be incomparably small relative to the requirements and scale of energy production. This discrepancy undermined all metabolic substantiation of the use of exogenous succinate. The deciding factor in the resolution of this discrepancy was the discovery of the signaling regulatory role of low concentrations of extramitochondrial and extracellular succinate, in quantities 2-3 orders of magnitude smaller than those required to sustain mitochondrial function. This led to an understanding of the relationship between catabolism, signaling systems, epigenetic changes, and adaptive gene expression.

Currently, it is well known that unoxidized succinate is released from mitochondria into the cytosolic space of cells, where it stabilizes the oxygen sensor, hypoxia-inducible factor-1 (HIF-1) (Wang et al., 1995; Lukyanova et al., 2018). Under conditions of oxygen deficit and/or succinate release into the cytosol, the HIF dimer is formed and triggers the expression of genes in the cell's nucleus, which are responsible for the formation of antihypoxic adaptation. A multitude of syntheses are activated anew, including synthesis of a glucose transporter and glycolysis enzymes. As a result, the supply as well as oxidation of glucose increases. Oxygen delivery increases significantly due to the stimulation of erythropoietin synthesis and angiogenesis factors that promote new blood vessel sprouting in hypoxic tissue areas. Stabilization and induction of HIF-1 formation are enabled by small concentrations of extramitochondrial succinate, about 50 μM, which inhibit prolyl hydroxylase and, as such, prevent subsequent proteolysis of HIF-1. Hyperproduction of the active forms of oxygen also contributes to an increase in HIF-1 levels (Movafagh et al., 2015). .It is worth noting that the amount of succinate needed to suppress prolyl hydroxylase is less by an order of magnitude than a Km quantity for succinate dehydrogenase (at the 500 μM level); while at least 2-10 mM of succinate intake is necessary for a noticeable stimulation of mitochondria's oxygen use.

Due to the release of endogenous succinate from cells, its concentration in the blood can rise several fold: from several to hundreds of micromoles. As He et al. (2004) established in 2004, extracellular succinate is a highly specific ligand of the orphan G receptor GRP91, currently known as SUCNR1. The affinity of this receptor to succinate is almost as high as that of prolyl hydroxylase. A succinate receptor is found on the external membrane of nearly all cells (Diehl et al., 2016; Fonseca et al., 2016). The result of the ligand's interaction with SUCNR1 is a short-term increase in calcium ion concentration in the cytosol of cells. As a multifunctional intracellular messenger, Ca2+ oscillation promotes a spike in functional cellular activity of numerous tissues: the kidneys, brain, hypothalamus, endocrine system, myocardium, liver, endothelium of vessels and their receptors, dendritic cells, and macrophages (Rubic et al., 2008).

In this way, the brief information signal provided by extramitochondrial and extracellular succinate is transmitted through HIF-1 and SUCNR1. The result is the mobilization of cells, readiness for work, and formation of adaptive changes for more effective functioning and recovery under stress, hypoxia, and infection. One can assume that the existing positive two-way relationship between an increase in the HIF-1 level and another transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), which triggers antioxidant and detoxification defense gene expression, plays out in the presence of a succinate signal the same way as with a short-term hypoxia (Johansson et al., 2017; Ji et al., 2018).

Conversely, a stable catabolic change seen in chronic ischemia, inflammatory reactions, metabolic syndrome, obesity, insulin resistance, permanent hyperglycemia with diabetes mellitus, disruptions in blood flow to the kidneys, and any inhibition of SDH due to a genetic defect, accumulation of oxaloacetate or the production of itaconate, specifically in neoplasms, dendritic cells, macrophages, and so on, triggers and sustains a pathologically high level of succinate in the cytosol and extracellular space. As a result, the information signal becomes a pathological factor contributing to the development of arterial hypertension, excess vessel sprouting (which may be fatal with pulmonary fibrosis and lead to the development of proliferative retinopathy), sustained inflammatory reactions in various organs and tissues, and carcinogenesis. These consequences of a permanently elevated level of succinate have been the target of numerous research inquiries with a clearly negative bias, which raised the question: is succinate friend or foe (Fernanddez-Veledo and Vendell 2019)? Recently, there has been an emergence of studies demonstrating a more balanced approach to the problems of metabolism and the signaling role of succinate (Grimolizzi and Arranz, 2018).

The formulation and application of a succinate-containing compound based on rapidly digestible ammonium succinate (with succinate and ammonium being two important end products of anaerobiosis and ischemia) allowed us to model hypoxic conditioning to some extent. It was discovered that a single dose of ammonium succinate, even in the quantity of 1.2–12 mg per kg of body mass, is not accompanied by a noticeable change in the concentration of succinate or ammonium in the blood. However, the effect becomes apparent within 15–20 min in the form of transient hyperemia in areas with disrupted blood flow, mood improvement and simultaneous calmness, anxiety relief, and enhanced performance. In rare cases, a hypnotic effect is observed after a dose of ammonium succinate. These are all characteristic indications of the effect of a bona fide ammonium-succinate-based agent, which back in 1856 was named "tonico nervina mixture" (Hager, 1897). A course of ammonium succinate and sodium succinate promotes a significant increase in tolerance to any hypoxic states

and decreases metabolic acidosis under functional hypoxia (Maevsky et al., 2001), improves resistance to viral infections, and boosts the activation of innate and acquired immunity. This might be related to the associated stabilization of HIF-1 and Nrf2 (Maevsky et al., 2001). Thus, following a week-long course of a succinate-containing agent during influenza season, patients using the agent averted the influenza infection. The patients maintained this resistance to infection for more than a month. Surprisingly, a beneficial effect of small doses of succinate was also observed on a large scale in the context of severe stress, chronic ischemic heart disease, and type 2 diabetes.

The COVID-19 epidemic made it possible to observe significant alleviation of the disease and rapid recovery when short courses of a succinate-containing agent were combined with known immunomodulatory agents and multivitamins. We attribute it to the antihypoxic effect of succinate, which manifests at both metabolic and signaling regulatory levels. Moreover, with COVID-19, hypoxia is precisely the leading pathogenetic factor and the reason for adverse outcomes (Kashani, 2020), when it is associated with damage to the lungs' alveolar epithelium (Bradley et al., 2020), impairment of erythrocytes and hemoglobin (Cavezzi et al., 2020), generalized inflammatory and thromboembolic damage to vessels' endothelium or blood flow obstruction (Iba et al., 2020), severe and compound myocardial injury (Babapoor-Farrokhran et al., 2020), or the development of atypical so-called "silent hypoxemia," which is baffling to physicians (Tobin et al., 2020).

Our experience with alleviating different types of hypoxic states with small doses of succinate-containing compounds leads us to believe that the same antihypoxic mechanisms could be applied successfully to hypoxia associated with COVID-19. Special attention should be afforded to experimental observations of the potential to inhibit the development of a viral infection in infected pregnant animals and their offspring with a course of succinate injections into the pregnant females. Together with the aforementioned limited clinical material, this provides justification for conducting a separate study aimed at determining the antiviral activity of succinate-containing agents and their potential to improve the state of the immune system.

It is also worth noting that from the time of the succinate receptor's discovery, there have been claims and the continuous expectation of a hypertensive response of arterial pressure (AP) due to the release of renin influenced by SUCNR1 in the juxtaglomerular apparatus of the kidneys (Sadagopan et al., 2007). However, we have not recorded a single occurrence of AP increase in either spontaneously hypertensive rats of the SHR line or patients taking the developed succinate-containing compound.

Theoretical and experimental analysis leads to the conclusion that small, apparently preconditioning doses of succinate provide beneficial effects. Short, small signals increase the body's tolerance not only to physiological stresses, but also to the effects of a number of adverse factors and infections. Since it is precisely a retroviral pandemic that makes the current situation so precarious, it is worth mentioning again that the activation of the antioxidant defense system by means of the stabilization and activation of Nrf2 is a considerable inhibitor of coronavirus's entry into cells and intracellular development (Hassan et al., 2020). Antioxidant defense genes are activated by the Nrf2 transcription factor, which is somehow closely linked to an increase in HIF-1 (Johansson et al., 2017; Ji et al., 2018), which in turn is stabilized by succinate, among others.

We believe that the duration and magnitude of the succinate signal are of great importance. Prolonged stimulation of the succinate receptor and continuous initiation of HIF dimer formation are harmful and dangerous. This is precisely the case in the development of obesity, severe diabetes, metabolic syndrome, persistent oxygen deprivation, chronic inflammation, and carcinogenesis.

A brief spike in the level of succinate, barely detectable after an intake of a small dose and due to a short duration of exogenous succinate's presence in the bloodstream, is merely a physiological alarm signal that promotes the mobilization of cellular and bodily functions, in particular, increased control accuracy of the neuroendocrine system. In this context, we recall that small doses of succinate significantly increase the sensitivity of the hypothalamus to efferent and afferent signals (Dil'man et al., 1976; Chen et al., 2015). This is especially important in view of the leading role of the central nervous system, foremost the hypothalamus, in the regulation of stress responses and the balance of immune system function (Liu et al., 2016; McDonough and Weinstein, 2018; Zhang et al., 2020), which is substantially compromised by viral infection.

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