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Oxidation of hydrogen sulfide by human liver mitochondria

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ABSTRACT

Hydrogen sulfide (H_2S) is the third gasotransmitter discovered. Sulfide shares with the two others (NO and CO) the same inhibiting properties towards mitochondrial respiration. However, in contrast with NO or CO, sulfide at concentrations lower than the toxic (μM) level is an hydrogen donor and a substrate for mitochondrial respiration. This is due to the activity of a sulfide quinone reductase found in a large majority of mitochondria. An ongoing study of the metabolic state of liver in obese patients allowed us to evaluate the sulfide oxidation capacity with twelve preparations of human liver mitochondria. The results indicate relatively high rates of sulfide oxidation with a large variability between individuals. These observations made with isolated mitochondria appear in agreement with the main characteristics of sulfide oxidation as established before with the help of cellular models.

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1. Introduction

1.1. Hydrogen sulfide a gasotransmitter, a mitochondrial poison, a mitochondrial substrate

Hydrogen sulfide was recognized as the third gasotransmitter in mammals [1]. The two others are NO and CO. The three gases are equally toxic to mitochondrial respiration with an inhibiting power on the mitochondrial complex IV (Scheme 1) similar to that of cyanide [2].

Sulfide brought a further level of complexity because of two opposite/complementary metabolic strategies with regard to sulfide linked to the presence/absence of oxygen. For anaerobic microbes, sulfide is a metabolic waste resulting from the use of an oxidized form of sulfur (such as sulfate) as final electron acceptor. In presence of oxygen, sulfide is used as an electron donor by sulfo-oxidant bacteria. Moreover, a majority of mitochondria in a mammalian organism are able to oxidize sulfide by means of a sulfide quinone reductase (SQR) [3]. Present knowledge shows that this duality exists in a single eukaryotic cell [4] and is sometimes presented as the grounding principle of oxygen sensing [5]. Therefore, and in contrast to the other gasotransmitters, sulfide has two opposite effects on mitochondria: at low concentrations it is a mitochondrial substrate and at high concentrations it is a poison. SQR initiates sulfide oxidation with nanomolar concentrations of sulfide while the transition to toxicity occurs in the micromolar range reviewed in [6].

Another complication with sulfide is that two different sources exist in the organism. The first is the metabolism of eukaryotic cells in which three different enzymes are susceptible to release hydrogen sulfide [7] and are thought to be key elements of the sulfide signaling pathway. The second source is the anaerobic microbiota hosted in the digestive tract where sulfide concentrations could reach values well within the toxic range representing a threat for the surrounding mammalian tissues [8]. Fortunately, the colonic wall has a large capacity to oxidize sulfide based on the SQR activity, restraining diffusion of colonic sulfide in the whole organism [9]. Whether the colonic sulfide is to be considered for signaling is still unclear but at least it contributes to blood levels in sulfide and related molecules [10].

The presence of the SQR in many different cell types/organs of the mammalian organism suggests that the need to oxidize sulfide is not restricted to the gastrointestinal tract and that the spontaneous sulfide release by tissues has to be checked either to avoid toxic accumulation and/or to control sulfide signaling.

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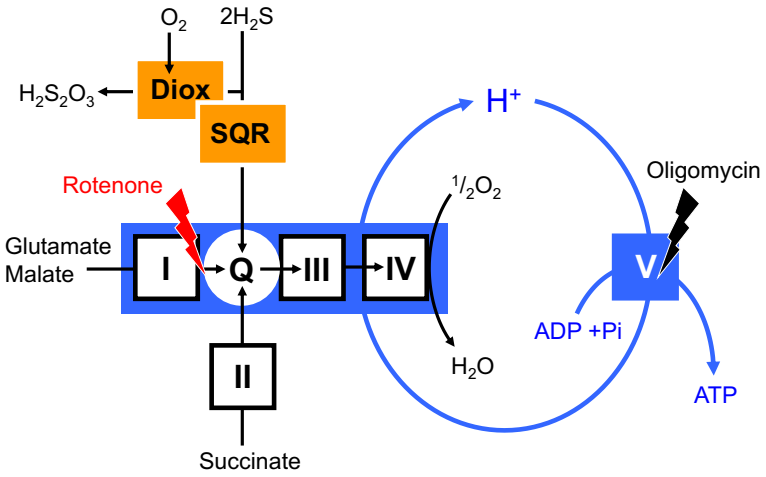

Scheme 1. This scheme presents the different partners controlling mitochondrial sulfide oxidation in our experiments. The different complexes of the mitochondrial respiratory chain are shown as squares with roman numerals with the redox enzymes as black and white boxes. The sulfide oxidation pathway is simplified to two enzymes: the sulfide quinone reductase (SQR) and the dioxygenase (Diox). The quinone (Q) is the redox shuttle between the different hydrogen donors shown (complexes I, II and SQR) and one acceptor (complex III). The reactants (sulfide and dioxygen) as well as final products (thiosulfate and water) are shown. The blue circuit divides these complexes into two functional domains: the first (complexes I, III and IV) associates redox reactions to proton pumping, and the second (complex V) uses the proton gradient to phosphorylate ADP into ATP. Therefore, via the proton circuit the activity of complex V controls the redox activity of the other complexes (coupling). Rotenone inhibits complex I redox activity and thus blocks oxidation of glutamate/malate but not that of sulfide or succinate. Oligomycin blocks the phosphorylating activity of complex V. When phosphorylation indeed controls electron transfer (coupling), oligomycin represses oxygen consumption to a low value explained by a proton leakage across the inner membrane, which is low in coupled mitochondria.

Liver mitochondria are the more commonly used to study mitochondrial metabolism. The liver is in a peculiar situation with regard to sulfide. On one side, liver mitochondria are considered as representative of mitochondria on a general basis. On the other side, the liver might be seen as a second barrier against colonic sulfide diffusion as in case sulfide would escape to the oxidation by the colonic wall it would be driven first to the liver through the portal vein [6]. Within the frame of an ongoing study on the mitochondrial state in the liver of obese people an evaluation of the intensity of the sulfide oxidation process was made in a few samples.

1.2. Quantifying mitochondrial tolerance to sulfide: the relative sulfide exposure

The toxicity of sulfide makes impossible to probe for sulfide oxidation by adding an amount of this substrate sufficient to sustain oxidation for minutes. Therefore, to establish a stable oxidation rate sulfide has to be provided continuously as it is consumed. The consequences of this infusion protocol are (i) the actual concentration of sulfide is unknown. (ii) If a steady state is maintained without net sulfide accumulation then the infusion rate equals oxidation rate. At the opposite, if effect of known concentrations is to be observed conclusions should be deduced from the subsequent transient oxidation/inhibition states.

The sulfide oxidation pathway could be divided into two different blocks: one is SQR itself and associated enzymes (yellow in the Scheme 1). The second block (blue in the Scheme 1) is constituted by the mitochondrial respiratory chain as sulfide oxidation is dependent upon the electron transfer rate in complexes III and IV, which in coupled mitochondria is essentially controlled by the downstream complex V activity. Therefore, unless sulfide would uncouple mitochondria, the electron transfer rate in the mitochondrial respiratory chain is not supposed to change when sulfide is infused and the maximal sulfide oxidation rate results from the interplay between these two blocks. The practical consequence is that the measurement of the respiratory rate (oxygen consumption) in absence of sulfide provides a reference rate directly proportional to the electron transfer rate in complexes III and IV. The ratio between the sulfide infusion rate and this reference rate (JH_2S/JO_2) defines a relative sulfide exposure (RSE) imposed to the respiring preparation [3]. Two molecules of sulfide are engaged in the reduction of quinone while only half a molecule of dioxygen is needed to re-oxidize the quinone (scheme 1), this explains why the RSE value could rise above one [3]. By increasing gradually the sulfide infusion rate, the aim of this study was to determine the maximal value of RSE at which the human liver mitochondria could still oxidize all the incoming sulfide. Theoretically, the respiring mitochondria would be able to support indefinitely any sulfide delivery rate lower or equal to this maximal RSE value as no sulfide accumulation occurs. Practically, it has been demonstrated for example that CHO cells could sustain intense sulfide oxidation for a period of 20 min [6].

2. Materials and methods

2.1. Human patients

This study was included in an ongoing survey of the mitochondrial state in the liver of obese patients undergoing bariatric procedures and enrolled in a prospective cohort at a specialized university hospital. Morbidly obese patients fulfilled the indications of eligibility for bariatric surgery in accordance with French High Authority of Health (HAS) recommendations [11]. Patients showing evidence of autoimmune, inflammatory, or infectious hepatic diseases including viral hepatitis, cancer, hepatotoxic treatment, or known alcohol consumption (>20 g/day) were excluded from this study. The research protocol obtained the agreement of the regional Person Protection Committee (CPP Ile de France X) in February 2010. All patients, after oral information, signed an informed consent. Preoperative routine workup was performed, and all patients underwent at the morning of the operation: (1)vital signs check-up, of which the blood pressure (systolic/diastolic), was used as reference for this study; (2) a blood test including full liver functions, fasting glycemia and insulinemia. Liver biopsies were realized during laparoscopy, at the beginning

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