



Research Article

A SCITECHNOL JOURNAL

Mitochondrial Inhibitors and Alteration in Bioenergetics-the Dose makes the Poison

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Abstract

Mitochondrial inhibitors such as hydrogen sulfide and cyanide have traditionally been associated as a poison due to its ability to interfere with mitochondrial respiration resulting in decreased mitochondrial bioenergetics leading to cellular failure. While on one side of the spectrum these mitochondrial inhibitors are poisonous there is also a potential protective aspect of these inhibitors currently being explored, particular to prevent ischemic-reperfusion injuries related to reactive oxygen species and the ability to decrease metabolic demand similar to what is described as "hibernation" or "suspended animation."

Keywords

Mitochondrial inhibitors; Bioenergetics

Introduction

"All things are poisons, for there is nothing without poisonous qualities. It is only the dose which makes a thing poison." – Paracelsus

The following quote from the father of toxicology illustrates the interaction of pharmaceuticals, environmental hazards and chemicals with the human body. Mitochondrial inhibitors such as hydrogen sulfide and cyanide demonstrate these complex interactions. On one side of the spectrum, these mitochondrial inhibitors are poisonous with their ability to interfere with mitochondrial respiration resulting in alterations of mitochondrial bioenergetics. On the other side of the spectrum, some mitochondrial inhibitors such as hydrogen sulfide may potentially prevent ischemic-reperfusion injuries by minimizing injuries from reactive oxygen species and by reducing metabolic demands.

Methods

The authors conducted a scientific review of all available literature published over the last 20 years. Our primary objective was to evaluate both the protective and poisonous aspects of known mitochondrial inhibitors such as hydrogen sulfide and cyanide. We initiated a PubMed database search using the MESH terms "mitochondria inhibitors," "metabolic hibernation," "cyanide," "carbon monoxide," "mitochondrial bioenergetics," and "ROS." Articles were selected and agreed upon by the authors based on relevance and impact. Effort was made to include both positive and negative studies where

appropriate. Emphasis was placed on well-conducted experimental data, case studies, and controlled trials when possible. Studies were only excluded due to redundancy. After analysis of the available data, this paper concludes with recommendations based on the existing scientific evidence.

Overview of the mitochondria

The mitochondrion (plural mitochondria) is a unique organelle found in most eukaryotic cells that performs many important tasks. One of the most critical functions of the mitochondria involves the production of energy, typically over 90% of the energy production in the cell. Due to the important role the mitochondria play in cellular function, inherited mitochondrial disorders result in a wide range of disease that include cancer, autism, blindness, and other degenerative diseases [1]. Acquired mitochondrial dysfunction from an inhibitor such as hydrogen sulfide, can result in serious toxicity and death. However, a very low-dose exposure to hydrogen sulfide may attenuate various states of cellular hypoxia, illustrating the complex interaction of mitochondrial inhibition [2,3]. Knowledge of the structure and function of the mitochondria will allow better understanding of the effects of mitochondrial inhibition. The mitochondrial genome, which is distinct from the nuclear genome, is composed of approximately 16 kilobases that code for 13 proteins, 22 transfer RNAs, and 2 mitochondrial ribosome-coding RNAs [4].

Structure and function of the mitochondria

The size of the mitochondria ranges from 8-10 micrometers in length with a diameter of 0.5 to 1 micrometers. The mitochondria are composed of a double-membrane organization critical to the energy production of the cell. There are five distinct elements to the mitochondria described from the outer portion to the inner portion: 1. Outer membrane: The outer membrane contains a large number of integral proteins (porins) and completely encloses the entire mitochondria. Smaller molecules (less than 5000 Daltons) can cross the membrane through the porins whereas larger molecules can actively move through the membrane through large proteins. Disruption of the outer membrane may lead to efflux of proteins into the cytosol resulting in cell death. 2. Intermembrane space: It is the space between the outer and inner membrane. 3. Inner membrane: The inner mitochondrial membrane contains various proteins critical for function such as transport of protein into and out of the matrix, redox reactions of oxidative phosphorylation, and ATP generation through ATP synthase. 4. Cristae space: The inner mitochondrial membrane is compartmentalized into numerous structures called cristae. Cristae significantly increase the surface area of the inner mitochondrial membrane that enhances the ability to produce ATP. 5. Matrix: The matrix is the space found within the inner membrane that contains two-thirds of the total protein of the organelle. The matrix is important in the production of ATP and the function of ATP synthase (Complex V).

The primary function of the mitochondria is the production of ATP through a series of redox reactions but perform many other crucial functions. Other metabolic tasks involved with the mitochondria include heme synthesis reactions, calcium signaling, apoptosis, regulation of membrane potential, and signaling through

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Received: June 15, 2016 Accepted: July 27, 2016 Published: August 05, 2016

reactive oxygen species (ROS). Another function of the mitochondria is heat production, a process known as mitochondrial uncoupling. Protons can re-enter the mitochondrial matrix without being involved in ATP production. The electrochemical gradient created from the unharnessed movement of protons results in the generation of heat [5].

Reactive oxygen species (ROS)

Another critical function of the mitochondria is the generation of ROS. A wide range of diseases such as diabetes, neurologic disorders, and cardiac disease have implicated the role ROS in oxidative damage. ROS also participate in redox signaling from the mitochondria to the rest of the cell. Pioneering work by Chance in 1966 revealed the production of ROS from the respiratory chain by demonstrating the production of hydrogen peroxide (H_2O_2) from isolated mitochondria [6]. Later studies demonstrate that mitochondria contain superoxide dismutase (SOD), which is responsible for the production of H_2O_2 from superoxide (O_2^-) [7]. Current research focuses on sources of ROS production and consequences of ROS related to oxidative damage and ischemic-reperfusion injury [8,9]. Figure 1 illustrates the complex interactions of the production and role of ROS in the mitochondria.

The production of ROS occurs in complex I and III. Complex I serves as the entry point for electrons from NADH in the electron transport system, and it is the primary site of ROS generation [10]. A cofactor accepts electrons from NADH and passes them through a series of iron-sulfur centers to the CoQ reduction site. One of the mechanisms where complex I produces large amounts of superoxide is through a highly reduced CoQ (coenzyme Q) pool. In conjunction with a maximal proton motive force, the absence of ATP synthesis leads to reverse electron transport through complex I, resulting in the production of superoxide [11]. Complex III is another site of ROS production that channels electrons from the CoQ pool to cytochrome *c*. It is thought that its contribution to superoxide production is much less significant than complex I. There are other sites within the mitochondria that produce ROS either from the CoQ or NADH pool [12].

Electron transport system and common inhibitors

The mitochondrial electron transport system (ETS) transfers electrons through a series of redox reactions from the $NAD^+/NADH$ pair to the O_2/H_2O pair. Complexes I, III, and IV act as proton pumps, which generate the proton motive force necessary for the production of ATP at complex V through a series of oxidation-reduction reactions. With the exception of complex IV, the reactions of the respiratory chain are reversible. There are approximately 20 discrete electron carriers in the ETS where the only mobile components are cytochrome *c* and ubiquinone (UQ). UQ acts as a mobile redox center linking complexes I and II with complex III. NADH reduces complex I, succinate reduces complex II, and N,N,N',N' -tetramethyl-p-phenylenediamine (TMPD) reduces complex IV through cytochrome *c* [13]. Figure 2 contain examples of common inhibitors of the mitochondrial respiratory chain.

Complex I (NADH-UQ Oxidoreductase) is responsible for coupling the passage of two electrons from NADH to ubiquinone to the translocation of four protons [14]; it is also a major site of ROS production. Rotenone and piericidin are known inhibitors of complex I. Also a pesticide, rotenone is used to study the interactions of electron flow and ROS generation with complex I inhibition. It is

also commonly used to study mitochondrial bioenergetics in various disease state as a reliable complex I inhibitor. Complex II (succinate dehydrogenase) is made up of four polypeptide subunits. Complex II utilizes succinate as a substrate to contribute electrons to the UQ pool. While complex II will contribute electrons, it is not a proton pump [15].

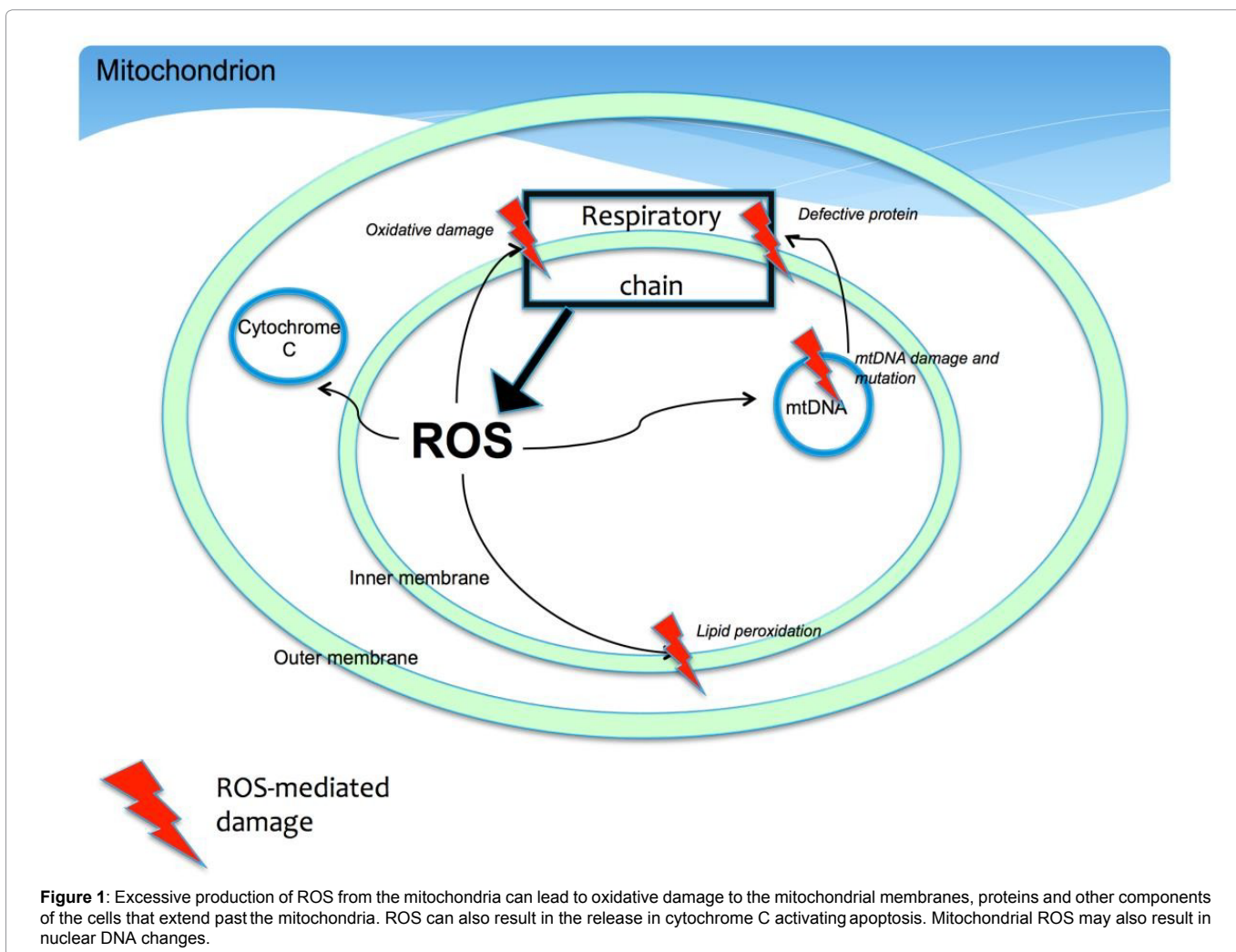
Complex III (cytochrome bc_1 complex) is known as ubiquinol-cytochrome *c* oxidoreductase, and it catalyzes the transfer of electrons from the UQ pool to cytochrome *c*. Complex III also contributes to the proton motive force. The pathway of electron flow involving complex III is often termed the Q-cycle. The Q-cycle is a series of reactions with a sequential oxidation and reduction of Coenzyme Q10 (CoQ10) between the ubiquinol and ubiquinone forms and results in the net pumping of protons across a lipid bilayer [16]. Inhibitors of complex III include antimycin, myxothiazol, and stigmatellin, which are commonly used to study mitochondrial physiology. Cytochrome *c* is not a proton pump but plays an important role in the mitochondrial ETS by interacting with complex III and IV. It is a 12-kDa water-soluble protein located on the inner membrane that accepts an electron from complex III and donates it to complex IV. Cytochrome *c* is also an intermediate in apoptosis that may be mediated by ROS generated in the ETS [17].

Complex IV (cytochrome *c* oxidase) or *aa3* oxidase serves as the final step in the ETS where four electrons from the reduced cytochrome *c* pool contribute to the proton motive force and generate H_2O . Clinically relevant complex IV inhibitors include cyanide, carbon monoxide, and hydrogen sulfide. Complex V (ATP synthase) is responsible for the synthesis of ATP. ATP synthase (F-type) consists of 2 regions: the F_0 portion, which is located within the membrane, and the F_1 portion, which is located above the membrane inside the matrix of the mitochondria. Under normal circumstances, complex V will generate ATP with a proton motive force [18]. However, in the absence of a proton motive force, the reaction of complex V is reversible and generates a proton motive force with large quantities of ATP.

Toxic effect of mitochondrial inhibition

The list of mitochondrial inhibitors as listed above are vast and beyond the scope of this review to describe each one as only a small proportion are of clinical relevance with the majority used for mitochondrial physiology research. The following is a concise overview of two mitochondrial inhibitors: Hydrogen sulfide and cyanide. The former illustrates the dual nature of mitochondrial inhibition with both toxic and protective effect.

Hydrogen sulfide: Hydrogen sulfide (H_2S), a well-known mitochondrial inhibitor, is a colorless gas with a rotten egg odor. Bacterial breakdown of proteins produces H_2S , and therefore, it is found in many natural and industrial settings. Animal waste products are a common source of H_2S , particularly as they decompose, and exposures can occur in sewers or near tanks used to store livestock manure [19]. H_2S is found in communities through volcano and geothermal field emissions. H_2S also poses a substantial risk to a large number of occupational workers in many industries such as paper, leather, rayon, gas, and oil. In 2007, there was an epidemic of suicides in Japan involving H_2S made from common household chemicals. Directions for mixing these chemicals were easily found on the internet, and this sparked a similar suicide fad in the United States [20]. Despite the long history of hazards associated with H_2S , there is growing body of evidence that small concentrations of H_2S may have a protective effect in the setting of ischemia-reperfusion injury [21].



The mechanism of action of H_2S is complex and multifactorial. The primary mechanism of toxicity is disruption of mitochondrial oxidative phosphorylation by binding to the ferric (Fe^{3+}) component on complex IV in a similar manner to cyanide although with more affinity [22]. H_2S can also directly produce toxic effects on the central nervous system (CNS) by altering neurotransmitters. Free radical formation of reactive oxygen and reactive sulfur species also causes direct toxicity [23].

Manifestations of cellular hypoxia *via* cytochrome inhibition are multi-organ dysfunction. Organ systems that have a high reliance on energy production from the mitochondria, such as the CNS and the cardiovascular system are the most susceptible to this poison. H_2S is known as a “knock-down” agent, meaning significant exposure results in cardiovascular collapse and neurologic sequelae such as seizures and coma. H_2S has a dose-dependent effect. Exposure at 100 ppm results in olfactory fatigue resulting in inability to smell its characteristic rotten egg odor. Exposure at 500 ppm result in severe toxicity, and death occurs at concentrations of 1000 ppm [24]. Other consequential clinical effects include acute lung injury and possible caustic injury H_2S when in contact with moist dermal and mucosal surfaces.

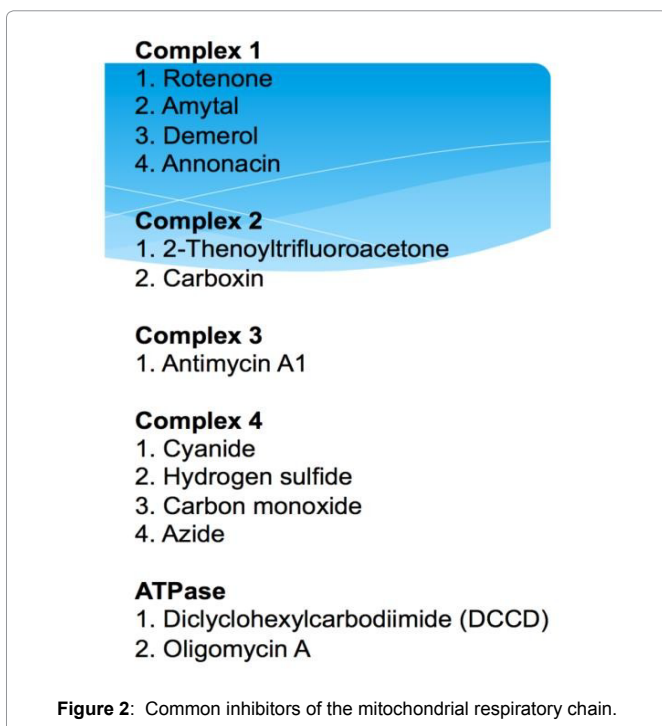
Since the primary route of exposure is inhalation, multiple patients

may be involved, even those in different rooms because the gas does permeate through building structures. Management of consequential H_2S exposure rests on removal from the exposure site (ensuring adequate protection for the healthcare provider) and aggressive supportive care. As with many mitochondrial inhibitors such as cyanide and carbon monoxide, antidotal therapy is limited with possible role of hyperbaric oxygen and methemoglobin-inducers (nitrites) [25,26].

Cyanide

Cyanide is encountered as hydrogen cyanide (HCN), inorganic cyanide salts, and cyanogen. Clinically significant toxicity can occur after exposure to any form. HCN is commonly exists as a gas or liquid, and can be formed upon combustion of carbon and nitrogen containing products [27]. Cyanide salts are crystalline solids that release HCN when exposed to aqueous or acidic solutions, or upon contact with water vapor. Cyanogens require transformation in the body to form cyanide and subsequently present with delayed toxicity [28-30]. Specific occupations and scenarios associated with cyanide exposure include metal reclamation, jewelry making, laboratory work, and pesticide manufacturing [31].

Cyanide’s toxicity results from its high affinity for the copper-iron center of complex IV in the mitochondrial inner membrane. Bound to cytochrome oxidase, cyanide prevents the transfer of electrons onto



oxygen in the final step of the electron transport chain, thus inhibiting oxidative phosphorylation and the formation of ATP. Decreased ATP production leads to a net increase in hydrogen ions resulting in the classic metabolic acidosis associated with cyanide toxicity [32,33]. In addition mitochondrial toxicity, cyanide inhibits over 40 enzymes, including glutamate decarboxylase which may contribute to seizure activity through GABA depletion [31].

Similar to H_2S , exposure to high levels of cyanide results in near immediate onset of symptoms due to interference with mitochondrial bioenergetics. Neurologic and cardiovascular toxicity, accompanied by metabolic acidosis, are predominant findings in cyanide toxicity due to high reliance of these organ systems on mitochondrial energy production. In survivors, delayed neurologic sequelae including Parkinsonian-like symptoms may be seen. Injury to the basal ganglia is evident on neuroimaging in these patients, a finding common to mitochondrial toxins and not specific to cyanide poisoning [34-36].

In the United States treatments for cyanide toxicity include sodium nitrite with thiosulfate, and hydroxocobalamin. Sodium nitrite induces methemoglobinemia which functions therapeutically as a cyanide scavenger due to cyanide's high affinity for the oxidized ferric form of iron in methemoglobin. Cyanide is thus displaced from cytochrome oxidase with subsequent restoration of function to the electron transport chain. Peak methemoglobin levels following nitrite treatment, however, may lag behind clinical improvement [14]. Such findings prompted consideration of an alternative mechanism to explain efficacy of sodium nitrite, including nitric oxide formation [15]. Thiosulfate acts as an exogenous sulfur donor and promotes rhodanese-mediated sulfation of free cyanide to thiocyanate which is renally cleared [32]. Though harnessed for therapeutic purposes, nitrite-induced methemoglobinemia can result in clinical toxicity, limiting its use. Such risks are particularly relevant in anemic patients and in victims of smoke inhalation with coexistent carbon monoxide poisoning, both of which may reduce an individual's ability to tolerate moderate methemoglobin levels [37,38].

Hydroxocobalamin utilizes cyanide's affinity for cobalt, forming cyanocobalamin that is less toxic and can be renally excreted. Hydroxocobalamin has known adverse effects such as bright red discoloration of skin and body fluids [20] which can interfere with colorimetric laboratory testing including cooximetry panels, creatinine, AST, bilirubin, iron, and magnesium [39-42]. Another known side effect is hypertension, likely secondary to nitric oxide scavenging [43,44].

Active research for alternative antidotes is ongoing. A porcine model shows cobinamide, a cobalt-based water-soluble antidote, to be as effective as hydroxocobalamin in acute cyanide poisoning with the potential advantage of intramuscular administration [45,46].

Protective effect of mitochondrial inhibition

It is clear that bioenergetic dysfunction from inhibition of mitochondrial respiration results in significant toxicity from compounds such as cyanide, carbon monoxide and hydrogen sulfide. However, a few select mitochondrial inhibitors (CO and H_2S) have also been shown to have a protective effect in various states of shock such as traumatic shock and cardiac arrest. In very low doses, H_2S have been shown to lower metabolic outputs when animals are challenged with an insult that may result in increased in metabolic demands that surpass their ability to meet these demands [47].

In many disease states such as sepsis and cardiac arrest, such conditions often result in an increase in metabolic demand. This increase in metabolic demand is often multifactorial which may be due to over stimulation of the immune system as in the case of sepsis. Strategies have focused on increasing or enhancing utilization of substrates to meet these increased demands. Findings with this strategy have met with variable success [48-50].

Another metabolic strategy is to induce a hypo metabolic state. Instead of increasing oxygen delivery or providing mitochondrial substrate in an attempt to meet increased metabolic demands, an alternative approach is to reduce the energetic demands. Many researchers in this area have described this induction of a hypo metabolic state as "hibernation" or "suspended animation." In general many organisms respond to changes in environmental conditions by hibernation with a reduction in core body temperature and metabolic rate. Many have hypothesized that the induction of a decreased metabolic state may have a variety of benefits for conditions such as cardiac arrest and bypass. This concept is already being applied with the use of hypothermia to induce a decreased metabolic state. While many benefits have been demonstrated with induced hypothermia, there are also complications associated with this mode of hypo metabolic induction such as increased susceptibility to infection and alterations in coagulation [51].

Researchers have used select mitochondrial inhibitors such as H_2S to induce "hibernation" or "suspended animation" to decrease metabolic demands. It is known that H_2S is endogenously produced from L-cysteine within the vasculature. By competing with oxygen in binding to cytochrome c oxidase, H_2S can inhibit mitochondrial respiration and reduce oxygen consumption. One study demonstrated a reduction in metabolic rate, oxygen consumption and core body temperature in mice exposed to H_2S with no permanent injury. Mice exposed to varying concentrations in H_2S (0-80 ppm) demonstrated a linear relationship between the concentration of H_2S and core body temperature. Mice were also exposed to 80 ppm of H_2S for 6 hours with no changes in functional or behavioral differences when compared to

control mice [52]. Another study was able to demonstrate increased survival in a hypoxic environment in animals that received H₂S compared to controls [53].

H₂S have also been studied as protective in other disease states such as traumatic injuries [54-56]. One study subjected rats to controlled hemorrhage (60% reduction in total blood) over 40 minutes. One group received H₂S gas at 300 ppm in room air 20 minutes after initiation of blood loss for 20-minutes. Another group received a single IV dose (1 mg/kg) of sulfide solution (100-150 mL) 20 minutes after the initiation of blood loss. There was a significant increase in survival in both treatment groups compared to control rats. Long-term tests for function and behavior in survivors showed no observable defects. The demonstrates that H₂S lowers metabolic output in rats and also improves survival in a rat model of life-threatening hemorrhage.

Carbon monoxide is another mitochondrial inhibitor that physiologically may play a signaling role within the body at very low doses. While carbon monoxide has many mechanisms of action that involve lipid peroxidation and oxygen displacement from hemoglobin, CO also inhibits complex IV. Inhibition of cytochrome c oxidase by carbon monoxide can protect nematodes against hypoxia by inducing a hypo metabolic state [57]. This study and others have led to the conclusion that decreasing oxygen demand may protect the generation of reactive oxygen species and subsequent cell damage [58].

While experimental data in the use of mitochondrial inhibitors as a protective agent is promising there are many practical hurdles that prevent clinical use at this time. It is unclear what the buffer or is between the protective and toxic effect of these agents. There are also many logistical issues that prevent their clinical use as well such as the possibility of exposing personnel to these gaseous agents, highly flammable nature of H₂S, and the need for higher animal models to better support their use.

Conclusion

Mitochondrial inhibition is a complicated process with important interactions in energy bioenergetics and ROS generation that involve not only the RTC but also both the nuclear and mitochondrial genome among other pathways. There is clearly a dual role that mitochondrial inhibitors play in these processes displaying both a toxic and protective effect depending on the dose. There is a fine balance between oxygen demand and utilization in the mitochondria. Mitochondrial inhibitors provide a novel approach to critically ill patients for their potential protective effects but one must also be mindful of the toxicity these agents are associated with. As this time their use in the clinical setting is not recommended.

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