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PRODUCTION OF FREE RADICALS BY MITOCHONDRIA: A BIOCHEMISTRY APPROACH

USMAN GARBA KURMI; HADIZA ABUBAKAR BALKORE; ABBAS MUSA; & ABUBAKAR ABDULLAHI

University of Maiduguri, Faculty of Science, Department of Biochemistry, Maiduguri, Nigeria.

ABSTRACT

The development of super Oxide by mitochondria is highly dependent on the mitochondrial respiratory chain, and cytochrome C acetylation by mitochondrial cytochrome oxidase and NASH-or succinate-dependent cytochrome c reductase direct reduction are thought to prevent the reoxidation. Ubiquinone is thought to be

INTRODUCTION

BACKGROUND

Although the first manifestations by mitochondria[1,2] of hydrogen peroxide formation were taken with caution, these results were supported by the following studies[3,4]. The hydrogen peroxide may be considered as a consequence of the dismutation of the superoxide. Also supporting this proposition, Loschen et al.,[5] and Boveris and Cadenas[6] showed that mitochondrial hydrogen peroxide is a stochiometric precursor. Mitochondrial superoxide production is highly dependent upon the respiratory mitochondrial chain. A range of conveyors in the interior mitochondrial membrane according to the redox potential of 320 mV to –380 mV are considered to consist of (pyroidin nucleotides, flavoprotein, sulphur proteins, Ubiquinon, and cytochromes). Typically, cytochrome oxidase converts up to 97% of the dioxygen absorbed by mitochondria to

water and only 1-3% leaks into superoxide de velopment.

DISCUSSION

Detection of active oxygen species in mitochondria

The literary observations of radical oxygen detection in mitochondria have been controversial. Due to experimental problems, several authors had to deal with submitochondrial particles instead of all mitochondria. However, oxygen generating radical oxygen may be artificially increased by submitochondrial particles due to oxygen exposure. On the other hand, such analytical techniques, such as the reduction of cytochrome c, cannot be utilized because mitochondrial components directly reduce cytochrome. In previous trials [5,6] identification of superoxide in mitochondria was equated with formation of hydrogen peroxide. However, while superoxide can be the stochiometrical precursor to mitochondrial hydrogen peroxide, the hydrogen peroxide amount may be reduced because of the reactions with different mitochondrial oxidants. In addition, due to the reaction of mitochondrial MnSOD, superoxide level could be underestimated. Several authors [7,8] took as read that cyanide resistant breathing, which alleges a univalent reduction in dioxygen production, could be estimated at mitochondrial superoxide

one of the main superoxide producers as the depletion of endogenous ubiquinone led to decreased hydrogen peroxide formation. free radicals have been involved in apoptosis as essential modulators, while experiments conducted under hypoxic conditions indicated that there may be apoptosis in their absence. Different stimuli are caused by various apoptotic pathways and in different ways, reactive oxygen species can influence them. The transcriptional activation of redoxrelated genes and reactive oxygen species and degradation of withochondrial oxidative ingredients leading to cell death, was proposed as characteristic of gene-induced apoptosis.

Keywords: *mitochondrial, free radicals, cytochrome*

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production. This approach was used for the in vitro normoxic and hyperoxic measurement of the production of superoxide, While it was found[7], the oxidation of different substrates also results from cyanide resistant breathing (lipids, amino acids, and nucleotides). It had been proposed previously that the superoxide of mitochundria can be determined by the adrenochrome-inhibiting SOD oxidation and the reduction of cytochrome c[8–10] acetylated. This is intended to avoid cytochrome c acetylation from being reoxidized by mitochondrial chrome oxidase and direct NADH or chromium sucinates. 1,2-dihydroxybenzenene-3,5-sulfonate, which has developed a very interesting technique for the measurement of superoxide in mitochondria in reaction to Tiron ESR spectroscopy[11].

Rates and mechanism of superoxide production in mitochondria

Despite comprehensive investigations into superoxides producing mitochondria, the problem is still important. Has mitochonderia also been a characteristic feature of some pathophysiological disorders that lead to normal mitochondrial function damaging superoxide or superoxide release under physiological conditions? There are questions in this area with numerous results on the use of respiratory inhibitors and different research methods. Submitochondrial particle incubation of rotenone first of all with respiratory inhibitors and antifungal, is typically reported for development of mitochondrial superoxide. Superoxide output could reach approximately 1 nmoll1 Min1 per mg of protein under these conditions[14]. Temporary development of superoxides depends on the oxygen stress of the tissue as well as on the redox condition of airline carriers. For instance, hyperoxia increases the development of superoxides in rats lung mitochondria [7] and lung submitochondria [8]. In the case of State IV, which is characterized by a slow respiratory rate and a high degree of reduction in electron carrier levels. In the case of States 3, the development of mitochondria by hydrogen peroxides has been shown to rely on the mitochondrium-based metabolic state [15]. Since superoxides are the precursor of peroxide hydrogen, hydrogen peroxide can also be formed at the same rate. LY et al.[13] showed that mitochondria isolated from macrophages or monocytes produced

substantial lucigenin-amplified CL in the presence of substrates, without respiratory inhibitors. The most compelling evidence of mitochondral superoxide development under physiological conditions. The efficiency of the detection of superoxide is dependent on the ability of superoxide scavengers to enter the sites of development in mitochondria. Superoxide release has been shown [16,17] in the mitochondrial matrix or in the space between the membranes. Lucigenine can therefore quantitatively record superoxide and enter the mitochondrial matrix. However, it should be noted once more that mitochondrial MnSOD could underestimate the superoxide concentration in physiological conditions [18].

Now the mechanism of radical oxygen development by mitochondria can be considered in detail. There are particular thermodynamic conditions, which control the transmission from the mitochondrial respiratory chain electron carriers to the dioxygen: These components must be more negative than the potential for dioxygen in one electron. Moreover, there are likely to be at least two mitochondrial sites: NADH ubiquinone reductase (Complex I) and Ubiquinol-cytochrome C reductase (C) (Complex III). Ubiquinone is thought to be one of the largest superoxide manufacturer because of the decline in hydrogen peroxide due to the depletion of endogenous ubiquinone[21]. Moreover, the most powerful sources of superoxide and hydrogen peroxide are compounds I and III which contain ubicinone as the primary component[20]. With components of the respiratory chain potential reduction from 0.320 V to 0.380 V it is apparent that different mitochondrial output sources can be identified. As stated, the two major sources of superoxide with their dominant position in both complexes I and III of the respiratory chain are present. While the radical (Reaction (1)) radical anion can form superoxide [1,23] or even radical neutro-semiquinone [3], its effect on the formation of superoxids is debatable.

Free radical-mediated damage to mitochondria

There are two causes of freely radical damage to mitochondria, which are the active oxygen released by mitochondria and free radicals that externally target mitochondria (superoxides, peroxides, and secondary

radicals). Earliest studies have shown the ability of mitochondria in active oxygen xanthin oxidases to absorb and retain calcium[29], the state 3 breath decreased[30] and the mitochondrial respiratory pyruvate reduced[31]. The xenebiotics and medications that could be reduced by mitochondria are other exogenous sources of free-radicalised damage. Davies and Doroshow[33,34] have demonstrated that the development of superoxide and potentially hydroxylic radicals through doxorubicin and daunorubicin anthracycline antibiotics reduced to semiquinones by cardiac mitochondria complex I. Menadione was also responsible for producing superoxide and releasing calcium from rats liver mitochondria [35]. Kohda and Gemba[36] suggested the production of superoxides in kidney cortical mitochondria as a function for cerebrospinal nephrotoxicity in rats.

Ethinyl estradiol, an effective promoter of hepatocarcinogenesis, also stimulates the development of superoxide from mitochondria. Ethinyl estradiol has been shown to increase superoxide production under in vivo and in vitro conditions by rat liver mitochondria. The mitochondrial super-oxide development in renal epithelial cells increased significantly with the formation of most renal stones is caused by calcium oxalate monohydrate[42]. Human interleukin recombinance IL-b induced the development by 4'-hydroxy3'-methoxyacetophenone and by the mitochondrial inhalers of diphenylene iodone[43] of radical oxygen in alveolary epithelial cells. Espositio et al. [44] found that adenine nucleotide translocator expression Ant1 was dependent on the radical production of mitochondrial oxygen. Skeletal muscle, heart and brain mitochondria from Ant1-deficient mice have therefore dramatically increased hydrogen peroxide production.

Mechanisms of mitochondria protection from free radical-mediated damage

In mitochondria, Free radical production can be regulated and abolished in various ways. Skulachov [54,55] has suggested the removal of overproduction of free radical in mitochondria from molecular processes such as low dioxygen maintenance, heavy decoupled, and mitochondrium suicide protein releasing Skulachevease and cytochromium c. The free radical mediated damage is prevention of

endogenous antioxide (Ubihydroquinone, Glutathione, and Vitamin E) and antioxidant enzymes (MnSOD first of all). Lass & Sohal, for example, [56] showed that a-tocopherol management in oral terms was suppressing superoxide production with microbial particles; the same findings were obtained in vitro conditions. In comparison, ubiquinone Q10 was administered without any effect on the development of mitochondrial superoxide. In addition, the relative activities of antioxidant enzymes depend on the defenses mechanisms of mitochondria against free radical damage. Mitochondrial glutathione peroxidase does not appear to play a significant role in the degradation of hydrogen peroxide[56] without the use of catalase in mitochonds in most animal cells. NADPH is important in regenerating lower glutathione and maintaining the function of the mitochondrial system glutathione reducctase and peroxidase. Jo et al. [58] have proven to be the main mitochondrial producer of NADPH, which is a key factor in combatting radical free damage, as NADP based isocitrate dehydrogenase (ICDH). ICDH expression reductions have increased significantly free radical development, fragmentation of DNA and mitochondrial oxidation. Nitric oxide was reported to inactivate ICDH by S-nitrosylation of its cysteine residues. It was found[59]. Currently, the study of apoptosis, cell-physiology, is probably the fastest growing aspect of free radical science biology studies. The two-stage mechanism of apoptosis playing a significant role in mitochondria[82]. The first stage is characterized by an invasion on mitochondrias, which increases the mitochondrial membrane permeability by different physiological and pathophysiological stimuli. Mitochondrial permission helps create the dynamic multiprotein complex between the mitochondrial membranes within and outside the site. This is prevented with the development of apoptosis (including the mitochondrial expression of the oncoprotein Bcl-2). The second step is mitochondrial dysfunction, followed by the removal of the respiratory chain and the surplus development of free radicals.

Reactive Oxygen Species as Mediators of Apoptosis

In several studies, free radicals have been involved in apoptosis as essential modulators, while experiments conducted under hypoxic conditions indicated that there may be apoptosis in their absence. Different stimuli are caused by various apoptotic pathways and in different ways, reactive oxygen species can influence them. The

transcriptional activation of redoxrelated genes and reactive oxygen species and degradation of withochondrial oxidative ingredients leading to cell death[60], was proposed as characteristic of gene-induced apoptosis. Johnson et al.[84] demonstrated in VSMC reactive oxygen levels, developed in conjunction with apoptosis production and onset and administered by species of reactive oxygen. Oxygen-radical production and apopdosis have been supposed to be a functional factor for oxygen species to develop stimulated apoptosis, with the inhibitory effect of antioxidant (pyrrolic dithiocarbamate (PDTC), N-acetylezsteine and catalase). Cai and Jones[85] also noted, in staurosporin-treated HL60 cells, that oxygen radicals have been overproduced and the cytochroma c release is a key apoptosis growth event, The mitochondrial respiration was inhibited and the development of superoxides stimulated. They noted, however, that the activation of "death protease" caspase 3 was another major factor in apoptosis, independent of the radical formation of oxygen.

However, several other experiments using various apoptotic triggers have revealed the activation of apoptosis by reactive oxygen species. For example, oxygen species were suggested to mediate fetal hepatocytes mediated apoptosis of transforming growth factor beta (TGF-b) [86,87]. In this case, free radical scavengers removed TGF-b-induced apoptosis (ascorbate and PDTC). A reduction in the production of superoxide prevented apoptosis of the T cell [88]. In Hsieh et al., the VSMC, which is regulated by reactant oxygen species, was shown to be oxidized LDL-induced apoptosis. Mitochondrial and lipoxygenase pathways are included in oxygen production, as rotenone and northern hydroguaiaretic acid have inhibited them. Blatt et al. have investigated the results of 1,4-benzodiazepine proapoptotic Bz-423 in transformed Ramon B cells[90]. Bz-423 was described as an induce of superoxide formation as an upstream signal for release of cytochrome, mitochondrial depols and activation of the caspase. Proapoptotic Bax protein expression has shown that Priault et al. oxidize mitochondrial lipids [91].

It was concluded that Bax-induced peroxidation of lipids is not important to Bax-stimulated apoptosis, nor does superoxide or hydrogen peroxide

formation. The Ras protooncogene is a well-known apoptosis modulator. In the rastreformed NIH/3T3 cells of protein kinase C, for example,[92] apoptosis was shown to occur (PKC). In low oxygen conditions cells obtained N-acetylcysteine were treated and cultivated to suppress apoptotic response. Oxygen species were apparently mediated by ras-induced apoptosis, but not only because continuous progression of cells is necessary to induce apoptosis in these circumstances. A water-soluble Vibrio vulnificus cytolysin (VVC), marine-insulated polypeptide[95] causing infections of wound and septicemia is also an important apoptotic stimulus [93]. In human vascular endothelial cells, VVC-stimulated apoptosis was suggested to be utriggered by superoxide raising, accompanied by cytochromium c release, caspase 3 activation, polymerase cleavage and DNA fragmentation. The synthesis of oxygen species and the Fa / Fas induction in mammoth cancer cells was apparently the mediator of zinc-induced apoptosis[94].

Mechanisms of the Activation of Apoptosis by Reactive Oxygen Species

Following consideration of the involvement in the production of apoptosis of the mitochondrial reactive oxygen species, we may now consider mechanisms to enable apoptosis by oxygen species[77]. Although major events and key oxygen-mediated radical apoptotic trajectory participants are well-known, their positions and the succession of events are not entirely accepted. As superoxide participates well-testedly in apoptosis, its function is strongly linked to cytochrome c release. A change from usual four-electron dioxygen decrease to one-electron decrease of dioxygen in the superoxide via the mitochonde respiratory chain was suggested as an initial event in the production of apoptosis [96]. Other apoptotic forms with or without cytochrome c release stimulation can be triggered by the superoxide. Apoptosis can be caused in different ways by superoxides and hydrogen peroxide[11]. It's interesting. So von Harsdorf et al.[57] shows that superoxide apoptosis induced by cardiomyocyte has no cytochrome c release, and is connected to a growth in apoptotic protein. Hirpara and others[89] have shown that these drugs, together with cytochromes c release, stimulated the production of superoxide through drug-induced tumor

cell apoptosis. They showed that apoptosis depended upon the acidification of hydrogen peroxide and cytochrome c release, both of which are signs of the activation of the cascade.

Protection Against Apoptosis Activated by Reactive Oxygen Species

Findings that show the same oxygen radicals which can inhibit apptosis, in some conditions, constitute the biggest difficulty in understanding the role of reactive oxygen species in apoptosis. As such, anti-oxidants are also able to trigger apoptosis under certain conditions that would predictably inhibit oxygen-based dramatically induced apoptosis. Superoxides, for instance, can also suppress fasmediated apoptosis as an efficient promoter of apoptosis[84]. Reactive oxygen species were indicated to be able to inhibit caspases[15], with antiapoptotic effects rather than proapoptotic. In addition, the generation of superoxides will activate the NF-kB transcription factor, which eliminates apoptosis triggered by TNF[96]. Skulachev [17] indicated that the cytochrome c released oxidizes superoxide, thus exhibiting antioxidant role. This suggestion was support for recent experimental results from Atlantis et al.[88], which proposed a feedback-like mechanism of oxidation of superoxide to release cytochrome c from mitochondria from mitochondria. Multifunctional protein Bcl-2, localized on the mitochondrial external membran, is the most effective physiological inhibitor of apoptosis.

Mitochondrial nitrogen oxide production and apoptosis

Nitric oxide, peroxygnitrite and other species of mitochondria-producing nitrogen oxide can stimulate or Inhibits a reactive oxygen-species similar apoptosis. The first proapoptotic effects of nitric oxide were likely to occur with Albina et al. [98] who showed no macrophage apoptosis. There have since been many primary cell types with NO-stimulated apoptosis, including macrophages, pancreatic cells, thymocytes or neurons[20]. The activation of the soluble guanylyl cyclase in vascular smooth muscle cells[97] appears part of NO stimulated apoptosis. Apoptosis by nitric oxide has been suggested as a result of damage to DNA, which results in the aggregation of the protein suppressing the

proapoptotic tumours[91]. Cheng et al.[142] find apoptosis induced by a nitric oxide in cells of neural progenitor through the activation of the polymerase (ADP-ribose) MAP kinase and caspase 3. Defense from NOinduced apoptosis and inhibition of MAP kinase activities by the Bcl-2 progenitor cells of Antiapoptotic Protein. Nitric oxide regulation of the K(Ca) and K plasma membrane channels have contributed to apoptosis in human and rat pulmonary arteries.

Conclusion

In conclusion it has been suggested to induce phosphorylation in the Channel KATP, by activating protein kinases (e.g. Protein kinase C or tyrosine kinase), which trigger channel opening. It was concluded, however, that the opening of the KATP channel increases the output of species of oxygen that cause the access to a PC state. Differences in preparations and analytical methods can be correlated with the effects of the hypoxia on oxygen provided by different authors.

Authors contribution

All authors contributed extensively to the work presented in this paper.

Conflict interest

The authors declares no conflict of interest

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