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Mitochondrial Uptake of Ca^{2+} and Other Bivalent Cations

Saris N-El*

Department of Food and Environmental Sciences, Bio centre 1, Viikki POB 56, 00014 University of Helsinki, Finland

Abstract

This is a review of the mitochondrial calcium uniporter (MCU), beginning with the early studies where I was involved. I found it at the end of a visit in the academic year 1958-59 to Professor Britton Chance in Philadelphia, and continued the studies back home in Helsinki, and had my dissertation on it in 1963. The uptake of calcium cations was associated with a drop in pH of the medium. The mechanism of that was not clear, could have been due to an exchange. However, after Peter Mitchell discovered the chemiosmotic hypothesis, it became evident that Ca^{2+} uptake was driven by the membrane potential formed by electron transport in the respiratory chain. Normally the protons would be taken back to the matrix by that membrane potential, but since that was consumed by the Ca^{2+} uptake, the H^+ cycling was prevented. After an uptake of Ca^{2+} over a certain level, a permeability transition pore is opened in the inner membrane and the mitochondria underwent a swelling. The composition of the MCU is still not fully established; it has several components, and binds many other polypeptides and substances.

Many inhibitors of MCU are known most used are ruthenium compounds, ruthenium red and Ru360, and lanthanides, those most close in size to Ca^{2+} being most potent. Many other bivalent cations are also transported by the MCU, such as Sr^{2+}, Ba^{2+}, Mn^{2+}, Cd^{2+}, Zn^{2+} and even Pb^{2+}.

Ca^{2+} also was active at low concentrations (0.5-1 μM) to activate ATP synthesis and hydrolysis, and respiration rates, while 5 μM could be inhibitory, Also matrix dehydrogenases could be activated by Ca^{2+}. High [Ca^{2+}] also is important in cell death, apoptosis.

Abbreviations: ΔΨ: Mitochondrial Transmembrane Potential; MCU: Mitochondrial Calcium Uniporter; RLM: Rat Liver Mitochondria; ROS: Reactive Oxygen Species

Early Studies

At the end of my visit to the Johnson Foundation at the University of Pennsylvania as an assistant to Professor Britton Chance in 1959, I discovered the uptake of Ca^{2+} by energized rat liver mitochondria (RLM), associated with drop of the medium pH. It was my task to use a sensitive pH meter to measure the synthesis of ATP in mitochondria and the ATPase activity. The pH drop in Ca^{2+} activated mitochondrial ATPase was larger than due to the ATP hydrolyzed! When a threshold of uptake was reached, mitochondria underwent swelling, the Ca^{2+} was released and medium pH was raised back. Sr^{2+} was taken up in the same way but was not released except by addition of an uncoupler. This was reported at a meeting of Finska Kemistsamfundet (Chemical Society of Finland) on my return in September 1959 [1], and was the subject of my doctoral dissertation a few years later, in 1963 [2]. This active uptake of Ca^{2+} was also reported at a Nordic Biochemical Meeting in 1962 [3], and by Chance in 1963 [4]. In the thesis was also shown that in energized RLM Mn^{2+} also caused similar though slower pH changes indicating its uptake. Before 1963 the Ca^{2+} uptake in RLM was described by DeLuca and Engström [5] and in kidney mitochondria by Vasington and Murphy [6]. A more complete history of early mitochondrial Ca^{2+} uptake studies can be found in [7]. In this publication is also mentioned the stimulation of swelling by Ca^{2+} uptake [8] and the formation of free fatty acids [9]. Sr^{2+} uptake had also been detected by Mraz [10]. Historically it is of interest that binding of Ca^{2+} by mitochondria (heart) was first observed by Slater and Cleland in 1953 [11], but it was not clear that it was an energized one. That question was studied later when it was first reported that mitochondria [12,13] bound Ca^{2+} in a metabolism-independent way to both high and low affinity sites. It was however shown [14] that the apparent high-affinity sites were due to not completely eliminated, energy dependent uptake of Ca^{2+}. One binding site was cytochrome oxidase in the respiratory chain, causing a conformational change and having other effects [15]. Low-affinity binding sites at the outer surface of the mitochondrial inner membrane [16] correspond to 20 nmol/mg protein [17]. They are mainly phospholipids [18,19], that may take part in the Ca^{2+} transport, as has been shown for cardiolipin that may act as a Ca^{2+} carrier [20]. Models of active transport and binding of cations in mitochondria has been treated in detail in [21,22]. Reviews of mitochondrial calcium handling have been published by Mela 1977 [23], and with methodological aspects more recently [24].

Mechanisms of Ca2+ uptake

The association between mitochondrial Ca^{2+} uptake and medium drop in pH could be due to a Ca^{2+}/H^+ antiport in the inner membrane. Indeed, we found an apparent $Ca^{2+}/2H^+$ stoichiometry during Ca^{2+} uptake, while in the efflux of Ca^{2+} the stoichiometry was Ca^{2+}/H^+, though charge stoichiometry was 1:1 when efflux was driven by valinomycin mediated influx of K+ [24]. However, about this time Mitchell presented the chemiosmotic hypothesis according to which electron transport in the respiratory chain is associated with efflux of protons from the matrix [26], causing formation of a membrane potential (ΔΨ), negative on the matrix side. That was driving protons back into matrix. A more detailed description is given in a book by Mitchell [27]. This ΔΨ drives uptake of Ca^{2+} and other divalent cations, which thereby consume the ΔΨ, causing medium pH to stay lower, since H^+ was not driven back into matrix. Ca^{2+} uptake thus is not by an antiport but by an uniport

***Corresponding author:** Saris N-El, Department of Food and Environmental Sciences, Bio centre 1, Viikki POB 56, 00014 University of Helsinki, Finland, E-mail: nils.saris@helsinki.fi

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mechanism, which is why the transporter is called the mitochondrial calcium uniporter (MCU used as an abbreviation by many). Early it was also found, that in the presence of ADP, ATP and Pi, large amounts of Ca^{2+} were accumulated in RLM together with ATP and Pi, also Sr^{2+} but not Mn^{2+}. The uptake of Ca^{2+} under these extreme conditions could have been as a complex with ATP [28]. Ca^{2+} formed precipitate with Pi, stabilized with ATP and ADP. An increased Ca^{2+} uptake may also result from inhibition of Ca^{2+} efflux. Thus Sr^{2+} was found to inhibit Ca^{2+} efflux by the Ca^{2+}-Na^{+} exchange in heart mitochondria and also the Ca^{2+} efflux pathway in RLM, thereby keeping the set point at a lower external level [29]. Sr^{2+} does not readily undergo efflux after being taken up by MCU [30].

Ca^{2+} uptake by the Mitochondrial Uniporter Inhibitors

Lanthanides inhibit the MCU [30] by binding with high affinity to its Ca2+-binding site, those being most effective whose ionic radii were closest to that of Ca^{2+} [31,32]. Ruthenium red, a hexavalent polysaccharide stain is binding noncompetitive with a Ki near 30 nM [33-35]. Another related inhibitor is Ru360 [36]. Mitochondrial Ca^{2+} transport in sucrose medium shows hyperbolic kinetics (rate/[Ca^{2+}]) in sucrose medium, but in the presence of the competitive inhibitors of Ca^{2+} binding, Mg^{2+} and K^{+}, the kinetics become sigmoidal [37,38]. That means that at low [Ca^{2+}] a few μM, the uptake rate is low, and increases then, being half-maximal at 55-70 μM [38]. This is the case in RLM, in tissues like muscles, neurons and glands, where Ca^{2+} activates the cells, and may be stored in sarcoplasmic or enteroplastic reticulum, the [Ca^{2+}] may be much higher, when it is released to the cytoplasm. Ca^{2+} retention is enhanced and its release prevented by agents that stabilize the mitochondrial inner membrane, like Mg^{2+} [2] and oligoamines like spermine [39-41].

The interest in mitochondrial Ca^{2+} uptake declined but was revived in the nineties, when cell death through apoptosis, in which Ca^{2+} handling by mitochondria was found to play a role. Cell death in inflammation-associated necrosis was common, but regulation of cell numbers in tissues was little known, factors affecting cell proliferation were rather well known, but not the regulation of cell death. An early review discussing this is [42], and a recent one [43]. The former mentions mitochondrial Ca^{2+} handling as one of the important factors, the other describes the important apoptosis-inducing factor (AIF). An important factor in cell death is the Ca^{2+} induced increased formation of reactive oxygen species (ROS) in mitochondria, leading to opening of the permeability transition pore, cytochrome *c* release and apoptosis [44-47].

Uptake of other Cations by MCU

Already in [2] it was found that also Sr^{2+}, Ba^{2+} and Mn^{2+} were transported by MCU. This has been verified in [48,49,22]. Thus, a competitive inhibition of Ca^{2+} uptake could be expected. This was found for Sr^{2+} [50,51]. The effect of Sr^{2+} when added before Ca^{2+} was opposite, the release of was stimulated [51]. Heavy metal cations also may be accumulated via MCU. Thus Cd^{2+} was found to be accumulated by renal [52,53] and liver mitochondria [53]. Its uptake was sensitive to ruthenium red [52]. *In vitro* Cd^{2+} inhibited Ca^{2+} uptake, but not *in vivo*, probably it was then bound to SH-groups and did not interfere with Ca^{2+} handling [52]. Interaction between Cd^{2+} and cells is reviewed in [54]. When Pb^{2+} is administrated *in vivo*, mitochondria seem to be a target [55]. Pb^{2+} and Zn^{2+} also inhibit Ca^{2+} uptake [56]. The transport of Zn^{2+} by MCU was confirmed, it being inhibited by ruthenium red, but stimulated by Ca^{2+} [57], just like Ca^{2+} uptake [58,59].

More Recent Studies

The increasing number of publication is due to found influences of cellular and mitochondrial Ca^{2+} on a number of functions. One is the activity ATP synthase/mitochondrial ATPase. Thus it was found that addition of 0.5 μM Ca^{2+} resulted in maximal rates of synthesis and hydrolysis of ATP in RLM inner membrane, while decrease of [Ca^{2+}] to 0.1 μM or its increase to 5 μM inhibited these [60]. This correlated with the phosphorylation level of a 3.5 kD peptide in the inner membrane, which was found to be subunit c of F_0F_1ATPase [61,62]. In brain and heart mitochondria, but not in RLM, an example of effects of [Ca^{2+}] on dehydrogenase activities and thereby on ATP synthase activities via effects on mitochondrial α-ketoglutarate concentration [63].

Another variation of [Ca^{2+}] could be stimulation or inhibition of influx/efflux rates. Thus RLM respiring on succinate were found to be able to temporarily lower the steady state of external [Ca^{2+}] after addition of an external pulse of Ca^{2+} [64]. The rate of efflux was not changed by inhibition of the MCU by ruthenium red, or by following the efflux rate after preloading the mitochondrial Ca^{2+} with ^{45}Ca. Nor was it changed by cyclosporine A or diltiazem to inhibit Ca^{2+} efflux through the permeability transition pore or Ca^{2+} exchange on the Ca^{2+}/nNa^{+} antiporter by which accumulated Ca^{2+} may be returned to the cytosol [65]. The efflux rate was found to be inhibited by certain organic molecules, thus the free radical scavenger butylhydroxytoluene and a related substance without such activity did both inhibit the opening of that pore [66]. The pore has both an internal and external Me^{2+} binding site, when the internal site is occupied by Ca^{2+}, the opening is promoted, while it is decreased when Ca^{2+} is bound to the external site [67]. Binding of Sr^{2+}, Mn^{2+} to the inner site have an inhibitory effect on the opening, while binding of Ca^{2+} to it is decreased also by phospholipase A_2 inhibitors nupercaine and trifluorperazine that are competitive to Ca^{2+} binding to the inner binding site [67]. However, in certain cells under special conditions with accumulation of large amounts of Ca^{2+} in mitochondria, and inhibition of its release by the Ca^{2+}/nNa+ antiporter, Ca^{2+} may be released through the MCU [68]. Of interest is also the kinetics of the MCU described in a mathematical model in [69]. It is thermodynamically balanced and is an improvement of earlier models.

In mitochondrial DNA polymorphism there are certain combinations that increase the vulnerability to certain diseases such as Alzheimer's and Parkinson's [70], other combinations may promote longevity [71]. Inhibition of MCU by Ru360 may have a protective effect against irreversible injury in postischemic rat heart [72]. Human genes for MCU was found and called MICU1 [73]. Genomics has been characterized both for DNA and RNA, and a point mutation found that confers resistance of MCU against Ru360 [74].

Purification of the MCU

The group of Galina Mironova at the Institute of Biological Physics, Academy of Sciences, Pushchino, Moscow Region, has been active in isolation and characterization of the MCU, and I have for many years cooperated with the group. A glycoprotein of 40 kDa glycoprotein and a 2 kDa component were isolated from beef heart homogenate and mitochondria and found to increase substantially the Ca^{2+} conductance, which was inhibited by ruthenium red, indicating that it was MCU [75]. I made an antibody against the glycoprotein and found it to inhibit the MCU [76], I also found in an Ouchterlony test (diffusion in agarose gel of antigen and antibody applied in different places) formation of one single line of precipitate) that there was only one specific protein antigen. The purified component was reconstituted into planar lipid

bilayers, where it showed ruthenium red-sensitive Ca^{2+} channel activity [77] which was inhibited by antibodies against the 40-kDa glycoprotein [78]. The component may be bond to black-lipid membranes in the presence of Ca^{2+}, decreased by 50-100 mM Na^{+}, but not by K^{+} [79]. The component was shown to form conduction channels in bilayer lipid membranes in the presence of 10 mM $CaCl_2$, but not in the presence of potassium ions only. Ruthenium red closes these channels. The channel-forming preparation consists of lipid, amino acids and sugars with a Mr of 1-2 kDa.

Yeast MCU

Yeast species also have mitochondria that also seem to have a MCU driven by the $\Delta\Psi$ [80], but it differs from the animal system in not being inhibited by ruthenium red, but stimulated [81].

Palmitate/Ca^{2+} Channels

The fatty acids palmitic and stearic acids were found to form channels in black-lipid membranes in the presence of Ca^{2+} [82,83].

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