New insights in how nitrite can be involved in cardioprotection

Nitrite, an inorganic ion which abundantly occurs in green leaves and other vegetables, is known to help to prevent and counteract cardiovascular diseases, but the mechanisms involved are still partially unclear. In the attempt to cast light on these mechanisms, since such diseases are often associated with defective energy production, we directly focused on mitochondria, the subcellular organelles known as powerhouse of the cell, and particularly on the master enzyme which makes ATP, the universal energy currency. From a close insight, mitochondria are separated from the cellular environment by two membranes. The inner mitochondrial membrane is particularly interesting, since it contains the key bioenergetic characters, namely the respiratory chain complexes and the ATP synthase. One after the other, the respiratory complexes drive electrons from nutrients to oxygen, thus performing the so-called mitochondrial respiration. This step-by step electron cascade releases energy: the point is to convert the chemical energy contained in nutrient molecules into a form of available energy to be exploited by the cell whenever necessary, namely the molecule of ATP. So, the F_1F_O-ATP synthase is the master player, since it can perform this task. As a whole the enzyme has a mushroom shape, with a sort of root named F_O embedded in the inner mitochondrial membrane and the head, the so-called F_1, protruding in the core of the mitochondrion. The mechanism of ATP synthesis is quite complicated and involves the coupled rotation of the two F_1 and F_O portions. Due to its function of making ATP, the F_1F_O-ATPsynthase is universally known as the enzyme of life. Conversely, the same enzyme can also work in reverse and split ATP into ADP and inorganic phosphate, leading to ATP waste. This happens during myocardial hyschemia. The energy released by ATP hydrolysis can be also partially employed to restore the membrane conditions which make it work properly and allow ATP synthesis. Apart from its vital role, recently the same enzyme complex has been also implicated in the death of cells, because under certain conditions it can also favour or even cause an increase in permeability of the mitochondrial membrane, an event which destroys the mitochondrion and ultimately leads the cell to death.

In mitochondria from pig heart, a tissue rich of mitochondria, when the ATP synthase is activated by calcium ion, rather than by its natural activator magnesium ion, it becomes especially susceptive to nitrite. As a matter of fact the same low millimolar concentrations of nitrite which inhibit the calcium-activated ATPase leave unaffected the magnesium-activated ATPase, even if the two working modes most likely refer to the same F_1F_O complex. Different mechanisms were explored and finally we concluded that probably nitrite, by binding to the enzyme protein activated by calcium, somehow alters some crucial aminoacids, namely nearby tyrosines, which connect to each other. The dityrosine formation would modify the protein structure and prevent the enzyme from working properly. So, these findings may cast light on some peculiar nitrite properties which can be helpful to clarify one of the intimate mechanisms of its beneficial effects. Accordingly, since an increase in calcium in mitochondria is associated to molecular signals leading to cell death, the preferential inhibition by nitrite of the ATPase when activated by calcium, may quench the negative

events linked to the calcium-dependent mode of the F_1F_O complex which occur under pathological conditions. In other words, when calcium rises, ATP breakdown may be prevented by nitrite while the magnesium-activated enzyme fully maintains its functionality of life enzyme. In this intriguing perspective, nitrite by modulating the key enzyme in bioenergetics could make the cell switch from death to life.

Publication

Preferential nitrite inhibition of the mitochondrial F1FO-ATPase activities when activated by Ca2+ in replacement of the natural cofactor Mg2+.
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