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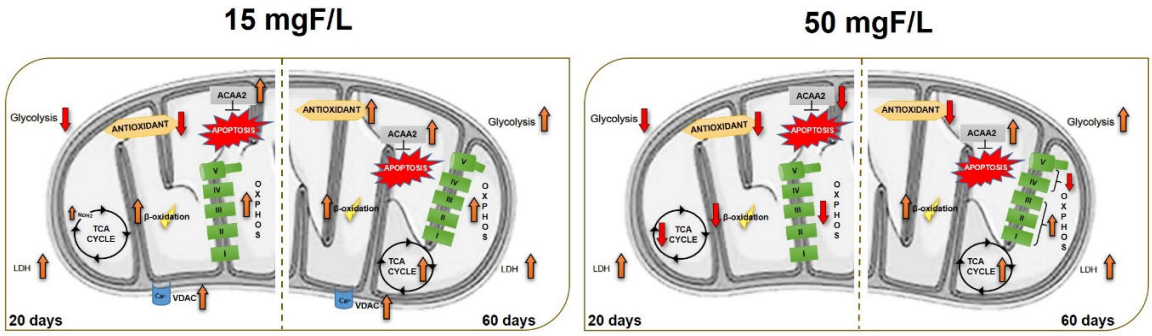
Alterations in mitochondrial metabolism induced by chronic fluoride exposure

Fluoride (F) is widely available in nature and has been successfully used to control dental caries worldwide. In addition, beneficial effects have been shown on the development of teeth and bones. However, high concentrations of F over time can cause side effects such as fluorosis that can affect both teeth and soft tissues due to disturbances in cellular processes and pathways, such as signaling pathways, mitochondrial energy metabolism and redox status. Since F alters energy metabolism, a common effect associated with overexposure to F is oxidative stress, which, if not contained, can lead to cell death. Thus, our study investigated the changes in proteins related to mitochondrial metabolism, after exposure to F in drinking water for 20 or 60 days, according to the groups (control – only water; 15 mgF/L or 50 mgF/L). For this, we performed proteomics analysis of rat liver mitochondria.



Graphical abstract

The main findings in this work indicate that the direction of the energy flow depends on the F dose and the exposure time. The dose of 15 mgF/L when administered for 20 days leads to a reduction in glycolysis, which is counterbalanced by the increase in β-oxidation, the urea cycle and the electron transport chain (ETC). For the same dose in the period of 60 days, there is an increase in all the energy pathways of the mitochondria. It is important to highlight that the excessive release of electrons during ETC is one of the causes of the generation of ROS, since 90% of the O_2 consumed is used in oxidative phosphorylation (OXPHOS) to generate ATP. To compensate for the generation of reactive oxygen species (ROS) due to the vigorous state of energy production, there is a concomitant increase in antioxidant enzymes (SOD, PHB, GPx, PRX and CAT) and anti-apoptotic proteins such as ACAA2. On the other hand, the dose of 50 mgF/L when administered for 20 days reduced the proteins involved in all energy pathways. With less energy production, there is less ROS generation, leading to a reduction in antioxidant enzymes. However, when 50 mgF/L was administered for 60 days, an increase in energy metabolism was observed, though, antioxidant enzymes, in general, did not show changes in expression. Also, our findings related to Ca^{2+} homeostasis and apoptosis that were altered after exposure to F generally showed an attempt to maintain Ca^{2+} homeostasis and prevent mitochondrial apoptosis. The increase in Calmodulin protein

(in treated groups/both periods-except for the highest dose of F for 20 days), contributes to the inactivation of mCU activity, preventing the accumulation of Ca^{2+} in the mitochondria. On the other hand, regardless of the period, the dose of 15 mgF/L showed an increase in VDAC, which is responsible for the release of mitochondrial products, which can lead to apoptosis that was counterbalanced by the increase in ACAA2, responsible for inhibiting pro-apoptotic proteins. As a result, mitochondrial damage could result in an energy imbalance due to reduced mitochondrial respiration, excessive ROS generation and reduced ATP synthesis that can lead to cell death. However, the increase in ACAA2 in high energy flow groups appears to have helped to prevent greater mitochondrial damage.

Additional studies using longer periods with higher doses of F should be performed, so that the relationship between energy production and oxidative balance can be better clarified. Thus, our results, when analyzed together, suggest that the organism seems to adapt to the effects of F over time, activating ways to reduce its toxicity. Ultimately, our findings confirm the safety of using F for caries control.

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