ROS induced mitochondrial hormesis partially protects from SGAs mitochondrial toxicity and cardiovascular disease

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The chronic intake of some antipsychotic drugs (SGAs) has been shown to increase CVD risk. Possible interference with mitochondrial bioenergetics, led us to investigate how they impacted mitochondria and its role on CV risk. We tested the effects of Olanzapine (Ola), that induces weight gain, and Aripiprazole (Ari), that does not. We found that at 6 months of treatment, mice developed cardiac and macrovascular fibrosis, with reduced NO levels, with larger alterations in response to Ari than to Ola. Importantly, these were more evident in PGC-1 ✔ KO mice, suggesting there were related to mitochondrial toxicity. Furthermore, treated mice showed reduced respiratory capacity, with Ari showing an earlier and stronger effect. Both drugs accumulated in mitochondria and inhibited mitochondrial respiration. However, Ola, not Ari, increased mtROS at low doses, and induced antioxidant and mitochondrial genes. As a result, Ola treated cells fully recovered their respiration capacity and $\Delta\Psi$, while Ari treated cells did not. To determine if this effect was ROS dependent, and/or mediated by PGC-1 ✔ activation of mitochondrial and antioxidant genes, we monitored the metabolic and redox status at 5 days and 1 month of treatment in the heart of WT and KO mice. At 5 days Ola induced a higher level of HNE protein modification than Ari along with increased levels of PGC-1 ✔, antioxidant and mitochondrial genes, and these compensatory effects were drastically reduced in KO mice. At 1 month, this compensatory response was essentially ablated in WT mice. Consistently, at 6 months the heart of KO mice treated with Ola showed a better preservation of mitochondrial content that those of mice treated with Ari, although cristae density was significantly reduced also in this case. These results support the relevance of mitochondrial toxicity on SGAs induced CVD and the role played by mtROS as mediator of compensatory hormetic responses.