Endocrinología, Diabetes y Nutrición

CO-035 - ROLE OF ANTIPSYCHOTICS-INDUCED MITOCHONDRIAL DYSFUNCTION IN INCREASED CARDIOVASCULAR RISK

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Resumen

Introduction and objectives: Second generation antipsychotics (SGAs) are preferred during chronic therapy for schizophrenic and psychotic patients due to less extrapyramidal side effects. On the other hand, they are associated with increased risk of cardiovascular diseases (CVDs), which is major cause of mortality among these patients. The SGAs are associated with metabolic side effects, where Olanzapine (Ola) is associated with increased metabolic risks; whereas Ari (Ari), less vigorously studied so far, is regarded as relatively safer. However, clear cause-effect relationships explaining such diverse metabolic profiles are yet to be established. Recently many drugs, including some SGAs, are found to induce mitochondrial dysfunction, which might be linked to metabolic and cardiovascular risks. Hence, we decided to evaluate role of mitochondrial function in development of cardiovascular risk due to SGAs in order to determine whether it can be used as risk predictor.

Materials and methods: In light of this, we investigated mitochondrial distribution of Ola and Ari in mice, as well as their effects on mitochondrial respiration clinically. We studied effects of subacute and chronic treatment with Ari and Ola on metabolic and cardiovascular functions in wild type (WT) and PGC-1?-deficient mice (KO), a model of mitochondrial dysfunction.

Results: We observed that both Ari and Ola enter mitochondria at significant levels. Ari reduced mitochondrial respiration efficiency, mitochondrial content, and cristae density severely and irreversibly; whereas Ola affected mitochondrial respiration and cristae density with compensatory recovery in mitochondrial content and respiration. Ari reduced whole body respiration and energy expenditure *in vivo* which was persistent and evident in both WT and KO mice, whereas Ola reduced respiration and energy expenditure which was dependent on genotype and tends to recover with time. In line with these observations, Ari was found to cause glucose intolerance earlier than Ola with the effect being earlier and severe in KO mice compared to WT mice. Such metabolic changes coincided with profibrotic changes in cardiovascular structure especially in KO mice treated with Ari and Ola for long duration, which ultimately affects macrovascular function, and cardiac recovery after ischemia-reperfusion injury. Such detrimental effects of Ari and Ola on cardiovascular structure and functions were found to be dependent on mitochondrial function.

Conclusions: The results indicate protective role of PGC-1? against drug-induced toxicity in cardiovascular system. These results could encourage potential use of drug screening for their mitochondrial effects during drug development. Also, evaluation of mitochondrial function in patients before and during therapy could be used to predict the risk of developing cardiovascular diseases and to guide selection of therapy as a part of

personalized medicine.