

## **Myocardial ischemia-reperfusion induces STAR translocation and cholesterol accumulation via TSPO in cardiac mitochondria.**

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**Introduction :** Myocardial ischemia-reperfusion (IR) increases cholesterol and oxysterols, in cardiac mitochondria. This mitochondrial accumulation of sterols is deleterious and leads to the emergence of reperfusion injury. In steroidogenic organs, cholesterol transfers via TSPO (translocator protein) and STAR (steroidogenic acute regulatory protein). However little is known regarding their effects in the heart.

**Objective :** This study aims to investigate the mechanisms involved in cholesterol transfer via TSPO and STAR in cardiac mitochondria after IR in order to develop cardioprotective strategies.

**Methods:** Wild type rats (TSPO+/+) and TSPO-/- rats (depleted for TSPO by deleting 89 base pairs between exon 3 and intron 3 of TSPO gene) underwent 30 min of coronary occlusion followed by 15 min of reperfusion. Chlorodiazepam (CDZ, 10mg/kg, IV), an inhibitor of TSPO, was administered 10 min before ischemia. After 15 min of reperfusion, cardiac cytosols and mitochondria were isolated from the ischemic area. TSPO and STAR protein expression were quantified by western blot and mitochondrial function were studied. Sterols were assessed by isotope dilution-mass spectrometry. Some rats underwent sham procedure.

**Results:** In TSPO+/+, IR altered mitochondrial function which was restored by CDZ. Mitochondrial TSPO expression remained unchanged after IR but we observed an increase in mitochondrial STAR and a decrease in cytosolic STAR. This was concomitant with sterol accumulation. CDZ inhibited mitochondrial STAR translocation and sterol increase without effect on cytosolic STAR. . Experiments are undergoing to investigate these phenomenon in TSPO-/-.

**Conclusion:** IR increases STAR translocation into cardiac mitochondria, responsible of sterol accumulation and mitochondrial dysfunction. This process is modulated by TSPO. So, targeting TSPO-STAR seems to be a potential cardioprotective strategy.