Basic Science - Cardiac Diseases

SERCA2a stimulation by istaroxime improves intracellular Ca2+ handling and diastolic dysfunction in a model of diabetic cardiomyopathy

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Diabetic cardiomyopathy is a multifactorial disease characterized by an early onset of diastolic dysfunction (DD) that precedes the development of systolic impairment. Mechanisms that can restore cardiac relaxation improving intracellular Ca2+ dynamics represent a promising therapeutic approach for cardiovascular diseases associated to DD. Istaroxime has the double property to accelerate Ca2+ uptake into sarcoplasmic reticulum (SR) through the SR Ca2+ pump (SERCA2a) stimulation and to inhibit Na+/K+ ATPase (NKA). The project aims to characterize istaroxime effects at a concentration (100 nM) marginally affecting NKA, in order to highlight its effects dependent on the stimulation of SERCA2a in a model of mild diabetes.

Streptozotocin (STZ) treated diabetic rats were studied at 9 weeks after STZ injection in comparison to controls (CTR). Istaroxime effects were evaluated in vivo and in left ventricular (LV) preparations. STZ animals showed 1) marked DD not associated to cardiac fibrosis, 2) LV mass reduction associated to reduced LV cell dimension and T-tubules loss, 3) reduced LV SERCA2 protein level and activity and 4) slower SR Ca2+ uptake rate, 5) LV action potential (AP) prolongation and increased short-term variability (STV) of AP duration, 6) increased diastolic Ca2+, 7) unaltered SR Ca2+ content and stability in intact cells. Acute istaroxime infusion (0.11 mg/kg/min for 15 min) reduced DD in STZ rats. Accordingly, in STZ myocytes istaroxime (100 nM) stimulated SERCA2a activity and blunted STZ-induced abnormalities in LV Ca2+ dynamics. In CTR myocytes, istaroxime increased diastolic Ca2+ level due to NKA blockade albeit minimal, while its effects on SERCA2a were almost absent.

SERCA2a stimulation by istaroxime improved STZ-induced DD and intracellular Ca2+ handling anomalies. Thus, SERCA2a stimulation can be considered a promising therapeutic approach for DD treatment.

Abstract Figure.