SERCA2a stimulation by Istaroxime improves Ca\(^{2+}\) handling in a model of diabetic diastolic dysfunction

Torre E.\(^1\)*, Arici M.\(^1\), Lodrini A.M.\(^1\), Ferrandi M.\(^2\), Barassi P.\(^2\), Boz E.\(^3\), Altomare C.\(^4\), Mostacciolo G.\(^1\), Bussadori C.\(^3\), Ferrari P.\(^2\), Bianchi G.\(^2\), Rocchetti M.\(^1\)

*eleonora.torre@unimib.it

\(^1\)Department of Biotechnology and Biosciences, Università degli Studi di Milano-Bicocca, Milan, Italy.
\(^2\)Windtree Therapeutics Inc., Warrington, Pennsylvania.
\(^3\)Clinica Veterinaria Gran Sasso, Milano, Italy.
\(^4\)Fondazione Cardiocentro Ticino, Lugano, Switzerland.

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Diabetic cardiomyopathy (DCM) is a multifactorial disease characterized by an early onset of diastolic dysfunction (DD), which precedes the development of systolic impairment. Mechanisms that can restore cardiac relaxation (lusitropic effect) improving intracellular Ca\(^{2+}\) dynamics, represent a promising therapeutic approach for cardiovascular diseases associated to DD. Istaroxime is a NaK ATPase (NKA) inhibitor with the property of accelerating Ca\(^{2+}\) re-uptake into sarcoplasmic reticulum (SR) through the SR Ca\(^{2+}\) pump (SERCA2a) stimulation. The project aims to characterize Istaroxime effects at a concentration mostly unaffecting NKA to isolate its effects dependent on SERCA2a only in a model of mild diabetes (type 1).

Streptozotocin (STZ) treated rats were evaluated at 9 weeks after STZ injection in comparison to control (CTR) ones. SERCA2a-dependent Istaroxime effects were evaluated in cell-free system and in isolated left ventricular (LV) myocytes. STZ animals showed reduced SERCA2a protein level and activity and increased monomeric PLN/SERCA2a ratio, implying that SERCA2a was not only reduced but also much more inhibited in comparison to CTR animals. Intracellular Ca\(^{2+}\) handling and electrical activity were evaluated in isolated ventricular myocytes. In STZ myocytes, SERCA downregulation caused 1) increased diastolic Ca\(^{2+}\), 2) reduction in SR Ca\(^{2+}\) content and Ca\(^{2+}\) transient amplitude following control of membrane potential, 3) slower SR reloading process under Na/Ca exchanger (NCX) inhibition, 4) unchanged SR stability and Ca\(^{2+}\) sparks rate. Action potentials (APs) were significantly prolonged, resulting in an increased short-term variability (STV) of APD. Istaroxime (100 nM) significantly stimulated SERCA2a activity and reverted STZ-induced effects by 1) reducing diastolic Ca\(^{2+}\), 2) increasing Ca\(^{2+}\) transient amplitude and SR Ca\(^{2+}\) content, and 3) accelerating SR Ca\(^{2+}\) reuptake in STZ group. Moreover, Istaroxime, by stimulating SERCA2a, partially restored Ca\(^{2+}\) sparks characteristics and significantly accelerated Ca\(^{2+}\) sparks decay.

SERCA2a stimulation by Istaroxime restores STZ-induced intracellular Ca\(^{2+}\) handling anomalies. Thus, SERCA2a stimulation can be considered a promising therapeutic approach for DD treatment.