A LONG TERM TREATMENT WITH TAURINE COUNTERACTS THE LATE CARDIAC DYSFUNCTION IN DYSTROPHIC MDX MICE: AN ULTRASONOGRAPHY STUDY

1)Mele A. 2)Rana F. 3)Sanarica F. 4)Mantuano P. 5)Capogrosso RF. 6)Morgese MG. 7)Trabace L. 8)De luca A.

University of Bari

Taurine is a sulfur-containing aminoacid very abundant in mammalian tissues. The high intracellular concentration of taurine is guaranteed by the presence of a sodium and chloride – dependent transporter (TauT) ubiquitously expressed. Taurine is known to act as osmolyte, since changes in the intracellular concentration of taurine contributes to the maintenance of cell volume that is in turn determinant for cell survival. Taurine concentration is particularly high in skeletal muscle and heart. In these tissues taurine is involved in different processes and functions. Several studies have demonstrated that taurine has antioxidant properties both directly scavenging the reactive oxygen species (ROS) and regulation the ROS production (Shaffer et al., 2010). Moreover, taurine plays an important role in membrane stabilization as well as in the regulation of different physiological functions through the alteration of the phosphorylated state of some proteins, among which ion channels. Taurine is also involved in normal contractile function of the heart and skeletal muscle by regulating the calcium homeostasis, the calcium sensitivity of the contractile proteins and the ATP cell content (De Luca et al., 2015; Shaffer et al., 2010). Thus taurine exerts benefical effect on cardiac failure and arrhythmias as well as on skeletal muscle performance, excitation-contraction coupling and resistance to fatigue. Preclinical studies in mdx mice disclosed promising effects of taurine as a countermeasure for the early alterations of skeletal muscle in Duchenne muscular dystrophy (DMD) in which the alteration of calcium homeostasis and oxidative stress are important hallmark (De Luca et al., 2003). DMD is an inherited muscular dystrophy in which mutations on the dystrophin gene result in the absence of this protein with structural and functional alterations of the sarcolemma that in turn induce fibrotic replacement of skeletal and cardiac muscle. We presently focused on the potential effectiveness of supplementation on later cardiac muscle dysfunction in DMD, since this has never been investigated up to now. Taurine was orally administered (1g/kg/daily) in male wild type (WT) and mdx mice at an initial age of 6 months. The treatment duration was 6 months.

Taurine effects were tested on WT and mdx mice by measuring body mass, in vivo force and resistance to treadmill exercise. In parallel, by using an UBM system (Vevo 2100; VisualSonics, Canada), ultrasound evaluation of the left ventricular function and hindlimb volume (V) and percentage of vascularization (%V) were also performed. Our results showed a significant reduction of stroke volume (SV; -30%), ejection fraction (EF; -18.4%) and fractional shortening (FS; -23%) in 12 months old untreated mdx mice with respect to the age-matched untreated WT. Interestingly, taurine treatment significantly and selectively counteracted the alterations of SV, EF and SF in mdx mice as the values were similar to those of untreated WT mice. No significant effects were observed on the V and %V of hindlimb skeletal muscle as well as on the other functional parameters in response to taurine. Interestingly, HPLC determination showed that the taurine concentration was markedly reduced in both heart and quadriceps muscle of mdx mice with respect to wild-type ones. The taurine treatment lead to a partial and no significant increase

in taurine content in both tissues. The mechanisms underling the lack of restoration of taurine content are currently under investigation; however the data support the need of a pharmacological action by taurine supplementation for maintaining cardiac function in dystrophic animals. This study provides the new evidence that long term taurine supplementation could be an effective specific countermeasure for DMD cardiomyopathy (DPP-NL and PRIN-MIUR).