α-linolenic acid prevents β-adrenergic-induced myocardial damage

A.E. Sprio[1], A. Folino[1], F. Carotenuto[2], G. Losano[3], P. Di Nardo[2], G. N. Berta[1], R. Rastaldo[1]

1 Dept. of Clinical and Biological Sciences, 'S. Luigi Gonzaga' Hospital, University of Turin, Orbassano, Italy
2 Dept. of Clinical Sciences and Translational Medicine, University of Rome 'Tor Vergata', Rome, Italy
3 Dept. of Neuroscience, University of Turin, Turin, Italy

Myocardial infarction represents a main cause of death in the Western countries. It leads to the rearrangement of cardiac structure, which includes thinning of the infarct wall, cardiac dilatation, hypertrophy and fibrosis. At molecular level, the up-regulation of TGFβ1 and TNFα stimulates fibroblast and cardiac mast cell proliferation accelerating fibrosis and alterations in the extracellular matrix. An increased adrenergic tone, as it may occur in chronic hyperactivity of the sympathetic nervous system and in heart failure, can trigger myocardial hypertrophy and fibrosis that is not remissible. The possibility to prevent or repair the occurring lesions could greatly enhance both expectancy and quality of patients' life. Recently, poly-unsaturated-fatty-acids, and in particular α-linolenic fatty acid (ALA), have demonstrated protective affects against myocardial apoptosis and fibrosis in an animal model of hereditary cardiomyopathy, thus opening a new scenario to a possible preventive treatment of cardiac fibrosis.
The present study aim to ascertain whether ALA can exert beneficial effects in a well-known experimental model of infarct-like myocardial damage obtained by administering injuring doses of isoproterenol (ISO) in adult Wistar rats. Rats were subdivided into three groups: in CTRL they received 5 daily subcutaneous injections of 0.5 ml of saline solution, while in ISO group saline solution was replaced by 100 mg/kg of ISO. Both these groups were fed with a standard chow diet for 2 months. The animals of the ALA-ISO group were treated as the ISO group, but they were fed before, during and after ISO treatment with an ALA-enriched diet consisting of carrots (15%), apples (50%) and flaxseed (35%).
Our results showed that the ALA-enriched diet is able to preserve both myocardial structural and functional integrity. In fact, ISO treatment induced high mortality in the animal model, likely due to severe arrhythmic occurrences. Moreover, it caused a decrement in contractility, as revealed by a reduction of ejection fraction (EF) in surviving animals. On the other hand, the nutritional supplementation with flaxseed-enriched diet preserved rats' survival and maintained a physiological EF, which remains comparable with that of CTRL group.
As expected, extensive fibrosis and myocardial hypertrophy were observed in ISO-treated rats. While cardiac fibrosis was proved by an increased collagen deposition, hypertrophy was demonstrated by the simultaneous increases in heart to body weight ratio, cardiomyocyte cross sectional area and myosin content. These morphological alterations are consistent with the decreased TIMP expression and the increased MMP activities and TGF-β expression, which were observed in ISO group. On the contrary, ISO treatment was unable to damage myocardium in rats fed with ALA-enriched diet. In fact, in ALA-ISO group fibrosis and hypertrophy were absent and all considered markers were in the range of the healthy controls. These results demonstrated that ALA is able to prevent the heart remodeling induced by ISO treatment. Finally, in order to uncouple the protective activity mediated by ALA from those of other substances present in flaxseeds, the effect of purified ALA was studied in vitro model. It was able per se to suppress the cardiomyocytes apoptosis induced by ISO treatment.
These findings demonstrate that ALA can exert evident cardioprotective effects against the adrenergic-related damage preserving the myocardium from excessive accumulation of fibrotic material and hypertrophy. The preservation of the cellular and tissue structural integrity could mediate anti-arrhythmic effects and explain the suppression of mortality observed in ALA-ISO group. In conclusion, ALA could represent a model to design novel classes of cardioprotective pharmacological agents, characterized by a broad spectrum of action and able to counteract the myocardial structural and functional damage.