Topic Category: Cardiovascular Physiology

Triiodothyronine improves post-ischemic myocardium recovery: A response associated with enhanced AMP-activated protein kinase activation

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Introduction: Low triiodothyronine (T3) syndrome is the most frequent alteration of thyroid hormone metabolism in acute myocardial infarction, which occurs immediately after the onset of symptoms. Although low T3 state has been interpreted as a merely adaptive mechanism, the experimental and clinical data have rebutted this hypothesis, suggesting that T3 might play an effective role in the cardioprotection against ischemia-reperfusion injury. Recent studies have provided evidence that T3 could enhance the recovery of ischemic myocardium through the preservation of mitochondrial function and the improvement of energy substrate metabolism. To this respect, it has been suggested that T3 could activate AMP-activated protein kinase (AMPK), the cellular "fuel gauge" enzyme, which in previous studies carried out in our laboratory exerted protective effects for the recovery of ischemic-reperfused myocardium.

Objective: The aim of the present study was to investigate the effects produced by the acute treatment with T3 and the pharmacological inhibition of AMPK by Compound C (CC), on isolated rat left atria subjected to 75 min simulated ischemia- 75 min reperfusion (Is-Rs).

Material and Methods: Atria were incubated in Krebs–Ringer containing 10 mM glucose, 95% O_2–5% CO_2, pH 7,4. For Is, the incubation medium contained 10 mM 2-deoxy-D-glucose, 95% N_2–5% CO_2, pH 6.8. T3 (60 nM) and CC (10 mM) were added to the bathing medium at the onset of Is and maintained throughout the experiment. ANOVA, followed by Tukey's test, was used, n=8/group.

Results: T3 increased AMPK activation during Is, which was prevented by CC (End stabilization period (ESP): 1.33 ± 0.02, Is-Rs: 2.20 ± 0.11*, Is-Rs+T3: 2.79 ± 0.10*$^{\#}$, Is-

Rs+CC: 1.08 ± 0.19, Is-Rs+T3+CC: 1.17 ± 0.10 AU; *p<0.05 vs ESP, Is-Rs+CC, Is-Rs+T3+CC; #p<0,05 vs Is-Rs). During Rs T3 increased contractile function recovery, which was prevented by CC (Peak force (%) Is-Rs: 36.1 ± 3.3, Is-Rs+T3: 51.2 ± 1.6*, Is-Rs+CC: 37.8 ± 2.1, Is-Rs+T3+CC: 39.5 ± 4.0; *p<0.05 vs all groups). Mitochondrial ATP production rate and tissue ATP content was enhanced by T3 at the end of Rs, effect that was reverted by CC (Is-Rs: 24.2 ± 1.1, Is-Rs+T3: 58.9 ± 5.7*, Is-Rs+CC: 28.3 ± 3.8, Is-Rs+T3+CC: 39.7 ± 2.4 nmol/min/mg mitochondrial protein; Is-Rs: 420 ± 52, Is-Rs+T3: 608 ± 94*, Is-Rs+CC: 285 ± 86, Is-Rs+T3+CC: 266 ± 46 pmol/mg protein; *p<0.05 vs all groups). Cellular viability was enhanced by T3, effect prevented by CC (Is-Rs: 66 ± 4, Is-Rs+T3: 79 ± 3*, Is-Rs+CC: 57 ± 2, Is-Rs+T3+CC: 54 ± 3; *p<0.05 vs all groups).

Conclusions: The results support that acute treatment with T3 improves the recovery of ischemic-reperfused myocardium. The present study provided evidence that T3 enhances intrinsic activation of AMPK during Is, remaining its activation increased during Rs. The results showed that AMPK is involved, at least in part, in the protective effects exerted by T3, contributing to mitochondrial function preservation and thus to tissue ATP content recovery, improvement of post-ischemic contractile recovery and conservation cellular viability.

Keywords: Triiodothyronine, post-ischemic myocardium recovery, AMP, protein kinase, enzyme activation