FURTHER EVIDENCE THAT MC_3 RECEPTORS MEDIATE THE PROTECTIVE EFFECT OF MELANOCORTINS AGAINST THE MYOCARDIAL ISCHEMIA/REPERFUSION DAMAGE

Mioni C., 3° anno di corso del Dottorato in Metodologie Precliniche e Cliniche di Valutazione dei Farmaci, I ciclo nuova serie. Durata del dottorato in anni: 4. Sede di servizio: Dipartimento di Scienze Biomediche, Sez. di Farmacologia, Università di Modena e Reggio Emilia, via Campi 287, 41100 Modena.

We previously reported that in an experimental condition of myocardial ischemia/reperfusion in rats, causing a high incidence of severe ventricular tachycardia (VT), ventricular fibrillation (VF) and lethality within 5 min, melanocortin (ACTH/MSH) peptides, including γ_1-MSH (γ_1-melanocyte-stimulating hormone), are able to prevent the development of such severe arrhythmias and the death, through the activation of central nervous system (CNS) MC_3 receptors. It has been hypothesized that a non-melanocortin receptor belonging to a group of receptors for Phe-Met-Arg-Phe-NH_2 (FMRFamide) and/or neuropeptide FF (Phe-Leu-Phe-Gln-Pro-Gln-Arg-Phe- NH_2) – localized in CNS – may be involved in some of cardiovascular effects of γ-MSHs. These effects seem to be linked to the presence of the C-terminal Arg-Phe sequence. Therefore, we studied the possible effect of the Arg-Phe containing peptides γ_2-MSH, γ_2-MSH (6-12) and [D-Trp^8]-γ_2-MSH on the consequences of short-term myocardial ischemia followed by reperfusion. Ischemia was produced in anesthetized rats by ligature of the left anterior descending coronary artery for 5 min, and VT, VF and lethality within the 5 min following reperfusion were evaluated. Saline and peptides (at equimolar doses, 162 nmol/kg) were i.v. injected during the ischemic period. Groups of 10-15 rats were used. In saline-treated rats, postischemic reperfusion induced VT in all rats, and VF and death in 80%. The MC_3 agonist γ_2-MSH significantly reduced the incidence of VT, VF and lethality (40%, 30% and 30%, respectively; $P<0.05$ versus saline; Fisher's test). Also the more selective MC_3 agonist [D-Trp^8]-γ_2-MSH reduced, in a significant manner, VT, VF and death (incidence of 50%, 40% and 30%, respectively; $P<0.05$ versus saline). On the other hand, γ_2-MSH (6-12), which has no affinity and cannot activate any of the brain MC receptors, failed to significantly reduce the incidence of VT, VF and lethality (80%, 65% and 65%, respectively; $P>0.05$ versus saline). The present results confirm the ability of melanocortin peptides to exert a protective effect in a condition of myocardial ischemia/reperfusion in rats. Furthermore, these results confirm that CNS MC_3 receptors are involved, because the MC_3 selective agonists γ_2-MSH and [D-Trp^8]-γ_2-MSH, but not γ_2-MSH (6-12), significantly reduce VT, VF and death. So, in conclusion, the C-terminal Arg-Phe sequence, which is essential for bioactivity of FMRFa and neuropeptide FF, is not important for the protective effect of ACTH/MSH peptides in myocardial ischemia/reperfusion, and this gives further support for the notion that MC_3 receptors are involved.

References

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