Cardioprotective Effects of Stimulation of Peripheral μ-Opiate Receptors and the Role of Opiatergic Mechanisms in the Pathogenesis of Stress-Induced Heart Damage

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Immobilization induces stress damage to the heart. DAGO, an agonist of μ-opiate receptors potentiates, while an agonist of peripheral μ-opiate receptors prevents this damage. Naltrexone reduces, while methylnaltrexone, an inhibitor of peripheral μ-opiate receptors, potentiates the stress-induced damage to the heart. Other opiate ligands have no effect on heart damage. It is suggested that the stress-induced damage to the heart is promoted by activation of central μ-opiate receptors and prevented by stimulation of peripheral μ-opiate receptors.

Key Words: *opiate receptors; stress-induced damage to the heart*

Stress-induced damage to the heart (SIDH) is the less studied pathology of the cardiovascular system. H. Selye originally regarded SIDH as an independent phenomenon [10], which was then termed as stress-induced cardiomyopathy [5,6]. In 1977, D. G. Miller proposed a simple and reliable test for evaluating experimental SIDH by measuring the accumulation of ^{99m}Tc-pyrophosphate (Tc-PPh). Some agents (propranolol, ionol, and γ-hydroxybutyric acid) prevent SIDH [3]. However, none of them completely abolishes this phenomenon; therefore, we agree with H. Selye on the pluricausal nature of the stress-induced cardiomyopathy [10]. Our preliminary data suggest that dalargin, a nonselective ligand of peripheral μ- and δ-opiate receptors (OR) prevents heart damage caused by a 6-h pain-emotional stress [1,2].

The aim of the present study is to evaluate the role of μ-, δ-, σ-, and κ-OR ligands in the pathogenesis of SIDH and possible protective properties of these agents.

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MATERIALS AND METHODS

Experiments were carried out on Wistar rats weighing 150-200 g. Each experimental group comprised no less than 12 animals. Stress was modeled by a 24-h immobilization in the supine position. SIDH was evaluated by Tc-PPh accumulation in rat myocardium as described elsewhere [9].

OR ligands were injected intraperitoneally 30 min before and 12 h after the beginning of immobilization.

DAGO ([D-Ala^2,N-Me-Phe^4,Gly^5-ol]-enkephalin), an agonist of μ-OR, DALDA ([D-Arg^2,Lys^4]dermorphin-(1-4)-amide), an agonist of peripheral μ-OR, and DSLET (D-Ser^2,Leu^5,Thr^6-enkephalin), an agonist of δ-OR were injected in a dose of 0.1 mg/kg. The dose was chosen on the basis of our previous data on the cardioprotective activity of the μ- and δ-OR agonist dalargin [1,2]. The selective agonist of κ-OR U50488H (trans-(±)-3,4-Dichloro-N-methyl-

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N-(2-[1-pyrrolidinyl]cyclohexyl)benzeneacetamide) was used in a dose of 8 mg/kg. The agonist of σ-OR N-allylnormetazocine ((+)SKF 10,047) was injected in a dose of 5 mg/kg.

Central and peripheral μ-OR were completely blocked with 0.5 mg/kg naltrexone. The selective inhibitor of d-OR ICI 174,864 (N,N-diallylTyr-Aib-Aib-Phe-Leu-OH, where Aib-α-aminoisobutyric acid) was injected in a dose of 2.5 mg/kg. The blocker of κ-OR MR2266 [(-)-5,9 α-diethyl-2-(3-furylmethyl)-2'-hydroxy-6,7-benzomorphan] was administered in a dose of 5 mg/kg. The antagonist of peripheral OR naltrexone methylbromide (NxMB) was injected in a dose of 5 mg/kg.

DALDA was synthesized by Prof. P. W. Schiller (Clinical Research Institute of Montreal, Canada), DAGO and DSLET were synthesized at the BioPro (Novosibirsk), naltrexone, (+)SKF, and U50488H were kindly provided by Dr. G. N. Smagin (Pennington BRC, USA), Dr. W. K. Schmidt (Du Pont Merck Pharmaceutical Co., USA), and Dr. P. F. VonVoigtlander (Upjohn Company, USA). MR2266 was produced by Boehringer Ingelheim KG. ICI 174,864 was from Chiron Mimotopes Peptide Systems.

Statistical processing of experimental results was performed using the Student's *t* test.

RESULTS

Immobilization stress enhanced 1.5-fold the ^{99m}Tc-PPh accumulation in rat myocardium, indicating a stress-induced damage to the heart (Table 1).

TABLE 1. Effect of OR Ligands on Stress-Induced Damage to the Heart in Rats Subjected to Immobilization Stress (IS) Measured by Accumulation of ^{99m}Tc-PPh in the Myocardium (*M±m*)

Group	Incorporation of ^{99m}Tc-PPh in the myocardium, % of total dose/g tissue
Intact rats	1.85±0.26
IS, 24 h	2.86±0.31*
IS+DAGO, 0.1 mg/kg	4.75±0.49*+
IS+DALDA, 0.1 mg/kg	1.59±0.22+
IS+naltrexone, 0.5 mg/kg	1.26±0.13*+
IS+NxMB, 5 mg/kg	3.42±0.21+
IS+U50488H, 8 mg/kg	3.09±0.17
IS+MR2266, 5 mg/kg	2.65±0.12
IS+DSLET, 0.1 mg/kg	2.74±0.15
IS+ICI 174,864, 2.5 mg/kg	3.13±0.35
IS+(+)SKF 10,047, 5 mg/kg	2.91±0.19

Note. *$p<0.05$ compared with intact rats, +$p<0.05$ *+$p<0.01$ compared with stress-control.

Administration of selective agonists of κ-OR (U50488H), δ-OR (DSLET), and σ-OR (N-allylnormetazocine) and antagonists of these receptors MR2266 (κ-OR) and ICI-174,864 (δ-OR) did not change the ^{99m}Tc-PPh accumulation during immobilization stress. Hence, there are strong grounds to suppose that these receptors are not involved into the development of SIDH.

The selective μ-OR agonist DAGO potentiated SIDH, which manifested itself as a significantly enhanced ^{99m}Tc-PPh uptake by cardiomyocytes in comparison with the stress-control (Table 1). By contrast, another μ-OR agonist (DALDA) reduced ^{99m}Tc-PPh uptake by 45%.

A clue for understanding this discrepancy is probably the fact that despite similar receptor specificity these agents differ in their ability to cross the blood-brain barrier: DALDA does not cross [10], while DAGO readily crosses [4] the blood-brain barrier. We have assumed that stimulation of peripheral μ-OR improves heart resistance to the stress-induced damage, whereas the activation of central μ-OR potentiates SIDH.

This hypothesis was confirmed by our further experiments. Immobilization stress induced no cardiac damage in rats pretreated with naltrexone, a blocker of central and the peripheral μ-OR (Table 1), whereas the peripheral μ-OR blocker NxMB aggravated SIDH.

What is the mechanism of the observed effects of opioid peptides? Stress-induced cardiomyopathy is known to arise from inadequate hyperfunction of the sympathoadrenal system under extreme conditions [3,6,7,10]. On the other hand, it has been found that stimulation of central OR increases the tone of the sympathetic component of the autonomous nervous system [11], whereas activation of peripheral presynaptic OR reduces the release of norepinephrine from nerve endings in the heart and blood vessels [5].

Considering these data, we have hypothesized that activation of central μ-OR potentiates adrenergic influences on the myocardium, thus enhancing stress-induced damage to the heart, while stimulation of peripheral μ-OR prevents SIDH by reducing the release of norepinephrine from nerve endings. We have previously demonstrated that the μ- and δ-OR agonist dalargin restricts isadrine-induced damage and inhibits isoproterenol-induced cAMP synthesis in the myocardium [2].

Thus, there are strong grounds to believe that the cardioprotective effect of opioid peptides is related to activation of peripheral μ-OR, whereas their cardiotoxic effect is mediated through stimulation of central μ-OR. Other types of receptors (σ, δ, κ) probably play no essential role in the mechanism of stress-

induced damage to the heart. These data suggest that the agents stimulating peripheral m-OR and, unlike morphine, do not cross the blood-brain barrier can be used as effective opiatergic cardioprotectors.

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