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Physiological levels of glutamine prevent morphine-induced preconditioning in the isolated rat heart

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ABSTRACT

Morphine induces cardioprotection against ischaemia–reperfusion injury. While aiming to investigate the underlying signal transduction cascade of morphine preconditioning in isolated Langendorff-perfused rat hearts, the expected cardioprotection was not detectable. Thus, we investigated the influence of different preconditioning protocols and substrate conditions on cardioprotection in this experimental model. Isolated rat hearts underwent 35 min global ischaemia followed by 60 min reperfusion. Morphine PC was initiated by 3 cycles of 5 min 1 μM morphine with either 5 min washout [3PC5 (5)] or 15 min washout [3PC5 (15)] before ischaemia; by 15 min morphine with 15 min washout before ischaemia [PC15 (15)]; or by 15 min 10 μM morphine with 15 min washout [PC15 (15)-10 μM]. Ischaemic preconditioning was initiated by 3 cycles of 3 min ischaemia; in another group, hearts received 1 μM morphine continuously for 10 min before ischaemia until the end of reperfusion [continued morphine]. To investigate the effects of glutamine, two groups received a glutamine-free perfusate: a control group, and a morphine preconditioning group [3PC5 (15)]. Ischaemic preconditioning reduced infarct size by 75%, and continued morphine by 46% compared to control group. With the glutamine containing perfusate, none of the morphine PC pretreatments had an effect on infarct size. In glutamine-free perfusate, 3 cycles of 5 min 1 μM morphine with 15 min washout reduced infarct size from 45%±8% (control) to 20%±5% (3PC5 (15). Cardioprotection by morphine-induced preconditioning is model dependent: in the isolated rat heart, morphine preconditioning is prevented by a glutamine containing perfusate.

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1. Introduction

Stimulation of opioid receptors both by endogenous and exogenous opioids increases the resistance of the myocardium against ischaemia and reperfusion injury (Cohen et al., 2001; Schultz et al., 1995, 1996; Zhang et al., 2004).

The mechanisms by which opioids protect the myocardium share common pathways with ischaemic preconditioning. It is shown that opening of mitochondrial ATP-sensitive potassium (mK_{ATP}) channels, which are involved in regulation of mitochondrial functions, is a key step to mediate both morphine and ischaemic preconditioning induced cardioprotection, possibly due to inhibition of mitochondrial permeability transition pore (mPTP) opening (Cohen et al., 2001; Murphy and Steenbergen, 2007). In 2002, Hausenloy et al. (2002) demonstrated that prevention of mPTP opening is involved in ischaemic preconditioning.

In this context, we initially aimed to investigate, whether morphine also induces preconditioning by prevention of mPTP opening in the isolated rat heart. However, the expected protective effect of morphine was surprisingly not detectable in our experimental model of the isolated Langendorff-perfused rat heart.

Based on these unexpected results, we hypothesized in the present study that morphine-induced cardioprotection might be strongly dependent on the experimental conditions and the protocol by which morphine is administered. Most studies investigating the protective potency of morphine in intact hearts are conducted using non-classical preconditioning protocols (i.e. without washout of morphine before ischaemia), or in *in vivo* models where, dependent on the half-time of morphine, it can be assumed that morphine is still present during ischaemia. In addition, differences in experimental conditions related to the substrates present in the perfusate may also affect cardioprotective interventions. Recent work suggests e.g. that glutamine may have cardioprotective potential (Liu et al., 2007).

Thus, we investigated whether the cardioprotective effect of morphine-induced preconditioning in the isolated rat heart depends

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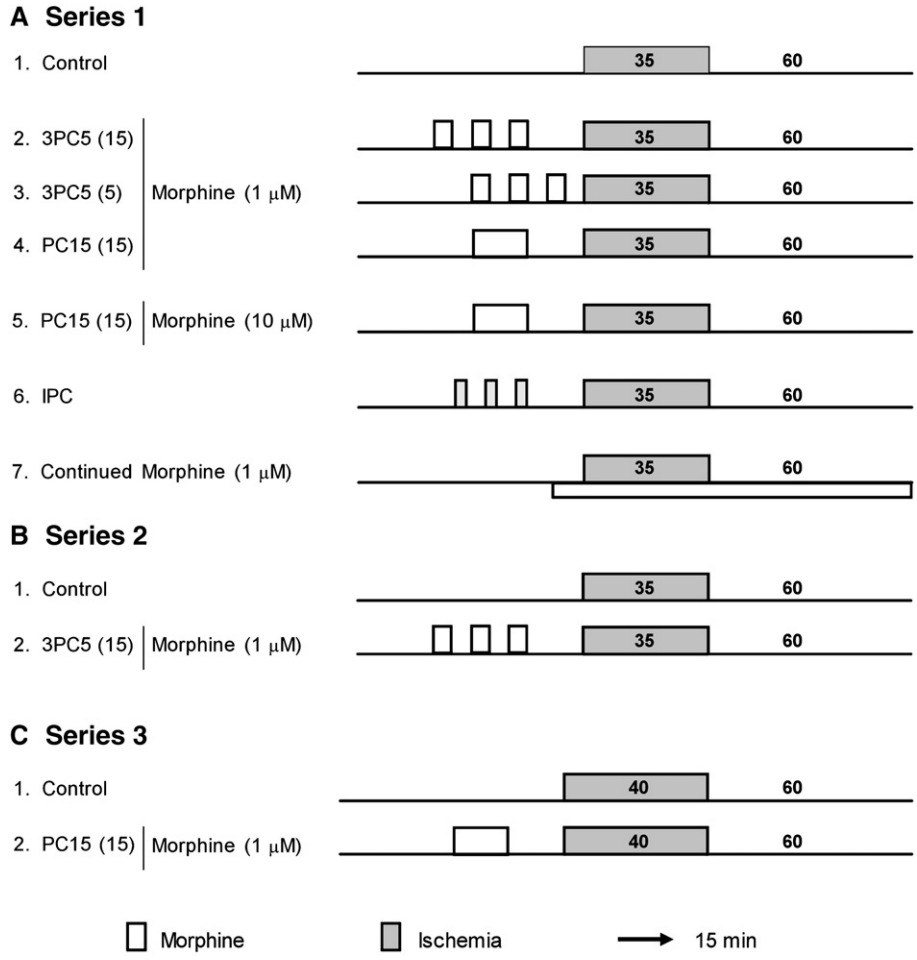

Fig. 1. Experimental protocol. *Panel A:* Experimental series 1. The perfusate contains 11 mM glucose and physiological concentrations of lactate (1 mM), pyruvate (0.1 mM) and glutamine (0.5 mM) as substrates. *Panel B:* Experimental series 2. The perfusate contains 11 mM glucose and physiological concentrations of lactate (1 mM) and pyruvate (0.1 mM) as substrates. *Panel C:* Experimental series 3. The perfusate contains 11 mM glucose and physiological concentrations of lactate (1 mM), pyruvate (0.1 mM) and glutamine (0.5 mM) as substrates.

on the preconditioning protocol and experimental substrate conditions.

2. Materials and methods

All experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996), and approved by the Animal Ethical Committee of the University of Amsterdam.

2.1. Chemicals and reagents

Morphine-HCl was purchased from Centrafarm (Etten-Leur, The Netherlands). All other chemicals were purchased from Sigma-Aldrich (Zwijndrecht, The Netherlands).

Table 1
Weights and ischaemic contracture

	Body weight (g)	Heart weight wet (g)	Heart weight dry (mg)	Time of max. ischaemic contracture (min)	Level of max. ischaemic contracture (mm Hg)
Series A) with glutamine — 35 min ischaemia					
Control	325±17	1.5±0.2	176±18	17±1	81±14
3PC5 (15)	332±27	1.5±0.2	183±16	17±1	86±6
3PC5 (5)	340±37	1.6±0.2	177±7	17±2	92±2
PC15 (15)	338±22	1.5±0.1	185±12	17±0	94±8
PC15 (15)-10 μM	322±18	1.5±0.2	185±7	17±2	77±13
IPC	330±35	1.5±0.1	182±17	17±2	74±8
Continued morphine	334±27	1.5±0.1	185±13	17±2	87±16
Series B) without glutamine — 35 min ischaemia					
Control	320±23	1.4±0.1	172±6	17±1	82±11
3PC5 (15)	316±13	1.5±0.2	180±13	17±2	68±8[a]
Series C) with glutamine — 40 min ischaemia					
Control	288±11	1.3±0.1	180±6	17±1	70±17
3PC5 (15)	289±14	1.2±0.1	173±9	18±2	72±10

Data are mean±S.D.; [a]$P<0.05$ vs. control. PC = preconditioning; IPC = ischaemic preconditioning.

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