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SCIENTIFIC ARTICLE

Pretreatment with remifentanil protects against the reduced-intestinal contractility related to the ischemia and reperfusion injury in rat

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KEYWORDS
Intestinal contractility;
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Remifentanil

Abstract
Background and objectives: Serious functional and structural alterations of gastrointestinal tract are observed in failure of blood supply, leading to gastrointestinal dismotility. Activation of opioid receptors provides cardioprotective effect against ischemia–reperfusion (I/R) injury. The aim of the present study was to determine whether or not remifentanil could reduce I/R injury of small intestine.
Methods: Male Wistar Albino rats were subjected to mesenteric ischemia (30 min) followed by reperfusion (3 h). Four groups were designed: sham control; remifentanil alone; I/R control; and remifentanil + I/R. Animals in remifentanil + I/R group were subjected to infusion of remifentanil ($2\,ug\,kg^{-1}\,min^{-1}$) for 60 min, half of which started before inducing ischemia. Collecting the ileum tissues, evaluation of damage was based on contractile responses to carbachol, levels of lipid peroxidation and neutrophil infiltration, and observation of histopathological features in intestinal tissue.
Results: Following reperfusion, a significant decrease in carbachol-induced contractile response, a remarkable increase in both lipid peroxidation and neutrophil infiltration, and a significant injury in mucosa were observed. An average contractile response of remifentanil + I/R group was significantly different from that of the I/R group. Lipid peroxidation and neutrophil infiltration were also significantly suppressed by the treatment. The tissue samples of the I/R group were grade 4 in histopathological evaluation. In remifentanil + I/R group, on the other hand, the mucosal damage was moderate, staging as grade 1.
Conclusions: The pretreatment with remifentanil can attenuate the intestinal I/R injury at a remarkable degree possibly by lowering lipid peroxidation and leukocyte infiltration.

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PALAVRAS-CHAVE
Contratilidade intestinal;
Lesão intestinal de isquemia/reperfusão;
Rato;
Remifentanil

Pré-tratamento com remifentanil protege contra a redução da contratilidade intestinal relacionada à lesão de isquemia e reperfusão em ratos

Resumo
Justificativa e objetivos: Alterações funcionais e estruturais sérias do trato gastrointestinal são observadas na insuficiência de irrigação sanguínea, levando a alterações da motilidade gastrointestinal. A ativação dos receptores opioides proporciona um efeito cardioprotetor contra a lesão de isquemia/reperfusão (I/R). O objetivo do presente estudo foi determinar se remifentanil pode ou não reduzir a lesão de I/R do intestino delgado.
Métodos: Ratos machos albinos, da linhagem Wistar, foram submetidos à isquemia mesentérica (30 minutos) seguida de reperfusão (3 horas). Quatro grupos foram designados: *sham* controle; remifentanil isolado; controle I/R; remifentanil + I/R. Os animais do grupo remifentanil + I/R foram submetidos à infusão de remifentanil ($2\,\mu g\,kg^{-1}\,min^{-1}$) por 60 min, metade dos quais iniciou antes da indução da isquemia. Coletando os tecidos do íleo, a avaliação dos danos foi baseada nas respostas contráteis ao carbacol, nos níveis de peroxidação lipídica e infiltração de neutrófilos e na observação das características histopatológicas no tecido intestinal.
Resultados: Após a reperfusão, uma diminuição significativa da resposta contrátil induzida por carbacol, um notável aumento tanto da peroxidação lipídica quanto da infiltração de neutrófilos e uma lesão significativa da mucosa foram observados. A média da resposta contrátil no grupo remifentanil + I/R foi significativamente diferente daquela do grupo I/R. A peroxidação lipídica e a infiltração de neutrófilos também foram significativamente suprimidas pelo tratamento. As amostras de tecido do grupo I/R apresentaram grau 4 na avaliação histopatológica. No grupo remifentanil + I/R, por outro lado, a lesão da mucosa foi moderada, apresentando estadiamento de grau 1.
Conclusões: O pré-tratamento com remifentanil pode atenuar a lesão intestinal de I/R em um grau notável, possivelmente pela redução da peroxidação lipídica e da infiltração leucocitária.

Introduction

Activated opioid receptors (ORs) protects against ischemia/reperfusion (I/R) injury in heart and neurons.[1–3] Opioid peptides and ORs are present in gut.[4,5] An ultra-short-acting phenylpiperidine opioid analgesic, remifentanil is cardioprotective against the I/R injury via mediating ORs,[1,6] activating protein kinase C (PKC), and driving mitochondrial ATP-sensitive potassium (KATP) channels[7] which mimic ischemic preconditioning (PC).[1,8]

Sepsis, hemorrhage, intestinal transplantation, severe burns, and mesenteric thrombosis cause mesenteric ischemia,[9,10] making a dramatic impact on the intestine. Intestinal I/R have a major role in the development of primary graft dysfunction.[11,12] The intestinal tissue is very sensitive to the I/R. In fact, even though the gastrointestinal tract represents about 5% of the body weight, its oxygen consumption constitutes roughly 20% of the total oxygen usage.[13] Interruption of the oxygen supply decreases the intracellular ATP content, disturbing the cellular homeostasis through the increased reactive oxygen species (ROS). Reperfusion induces structural and functional damage of mucosa and interstitial edema (reperfusion injury),[14] which is primarily due to the generation of ROS from various sources including the electron transport chains of mitochondria, xanthine oxidase metabolism, prostaglandins, endothelial cells, and activated neutrophils.[14–17] I/R damages the mucosal barrier function, causing the mucosal and vascular permeabilities and bacterial translocation, ending up with systemic inflammation and multiple-organ failure.[18] It also changes the contractile response of the intestinal smooth muscle,[19–22] which is associated with the local inflammatory response augmented by the infiltrating neutrophils[10] and ROS.[23]

Some pharmacological agents including anesthetics produce PC.[24–28] Specifically, ORs are involved in the PC of rat heart.[7,8] Moreover, pharmacologic postconditioning induced by remifentanil also protects against the I/R-induced cardiac injury.[3] On the other hand, whether or not the possible beneficial effect occurs in the intestinal I/R injury is extremely limited. Only one study by Cho et al.[29] reports that remifentanil protects the intestine against I/R injury. They clearly demonstrate that remifentanil significantly reduces oxidative stress, inflammatory response, and tissue injury. However, they did not study directly the effect on physiological functions of the tissue (e.g. contractility). Therefore, our aim was to determine whether remifentanil has beneficial effect on the I/R-disturbed intestinal contractility. We evaluated the contractile response, histopathological changes and measured the tissue levels of malondialdehyde (MDA), lipid peroxidation marker, and myeloperoxidase, neutrophil infiltration marker, (MPO).

Materials and methods

Animals

A total of 32 Wistar adult male rats weighing 220 ± 20 g were used in the study. The animals were obtained from the