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SCIENTIFIC ARTICLE

Local analgesic effect of tramadol is not mediated by opioid receptors in early postoperative pain in rats

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KEYWORDS
Tramadol;
Postoperative pain;
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Abstract
Background and objectives: Tramadol is known as a central acting analgesic drug, used for the treatment of moderate to severe pain. Local analgesic effect has been demonstrated, in part due to local anesthetic-like effect, but other mechanisms remain unclear. The role of peripheral opioid receptors in the local analgesic effect is not known. In this study, we examined role of peripheral opioid receptors in the local analgesic effect of tramadol in the plantar incision model.
Methods: Young male Wistar rats were divided into seven groups: control, intraplantar tramadol, intravenous tramadol, intravenous naloxone-intraplantar tramadol, intraplantar naloxone-intraplantar tramadol, intravenous naloxone-intravenous tramadol, and intravenous naloxone. After receiving the assigned drugs (tramadol 5 mg, naloxone 200 μg or 0.9% NaCl), rats were submitted to plantar incision, and withdrawal thresholds after mechanical stimuli with von Frey filaments were assessed at baseline, 10, 15, 30, 45 and 60 min after incision.
Results: Plantar incision led to marked mechanical hyperalgesia during the whole period of observation in the control group, no mechanical hyperalgesia were observed in intraplantar tramadol group, intraplantar naloxone-intraplantar tramadol group and intravenous naloxone-intraplantar tramadol. In the intravenous tramadol group a late increase in withdrawal thresholds (after 45 min) was observed, the intravenous naloxone-intravenous tramadol group and intravenous naloxone remained hyperalgesic during the whole period.
Conclusions: Tramadol presented an early local analgesic effect decreasing mechanical hyperalgesia induced by plantar incision. This analgesic effect was not mediated by peripheral opioid receptors.

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PALAVRAS-CHAVE
Tramado;
Dor no pós-operatório;
Receptores opioides;
Ratos Wistar

O efeito analgésico de tramadol não é mediado por receptores opioides na dor de ratos no pós-operatório imediato

Resumo
Justificativa e objetivos: Tramadol é conhecido como um fármaco analgésico de ação central, usado para o tratamento de dor moderada a grave. O efeito analgésico local foi demonstrado, em parte devido ao efeito semelhante ao anestésico local, mas outros mecanismos permanecem obscuros. O papel dos receptores opioides periféricos no efeito analgésico local não é conhecido. Neste estudo, examinamos o papel dos receptores opioides periféricos no efeito analgésico local de tramadol em modelo de incisão plantar.
Métodos: Ratos Wistar, jovens e machos, foram divididos em sete grupos: controle, tramadol intraplantar, tramadol intravenoso, tramadol intraplantar-naloxona intravenosa, tramadol intraplantar-naloxona intraplantar, tramadol intravenoso-naloxona intravenosa e naloxona intravenosa. Após receberem os medicamentos designados (5 mg de tramadol, 200 mg de naloxona ou NaCl a 0,9%, os ratos foram submetidos à incisão plantar, e os limiares de retirada após estímulos mecânicos com filamentos de von Frey foram avaliados no início do estudo e nos minutos 10, 15, 30, 45 e 60 após a incisão.
Resultados: A incisão plantar levou à hiperalgesia mecânica acentuada durante todo o período de observação no grupo controle; hiperalgesia mecânica não foi observada nos grupos tramadol intraplantar, tramadol intraplantar-naloxona intraplantar e tramadol intraplantar-naloxona intravenosa. No grupo tramadol intravenoso, um aumento tardio do limiar de retirada (após 45 minutos) foi observado, os grupos tramadol intravenoso-naloxona intravenosa e naloxona intravenosa permaneceram hiperalgésicos durante todo o período.
Conclusões: Tramadol apresentou efeito analgésico local inicial, diminuindo a hiperalgesia mecânica induzida pela incisão plantar. Esse efeito analgésico não foi mediado por receptores opioides periféricos.

Introduction

Tramadol, (1-RS,2RS)-2-[(dimethyl-amino)-methyl]-1-(3-methoxyphenyl)-cyclohexanol hydrochloride, is an analgesic drug used mainly for treatment of moderate to severe, as well as acute and chronic pain.[1,2] It presents a weak opioid effect and has other different mechanism of action through the decrease of the reuptake of monoaminergic neurotransmitters (5-hydroxy-tryptamine and noradrenaline).[3] Additionally it presents an analgesic effect in peripheral nerves, which is, in part, local anesthetic-like.[4–6]

The peripheral analgesic effect of tramadol has been also showed in humans after infiltration for third molar extraction, minor surgical procedures in children and as adjuvant to local anesthetics to reduce postoperative pain.[7–12] Peripheral opioid receptors have long been described and their role in analgesia in animals and humans demonstrated,[13–20] but little is known about peripheral opioid mediated effect of tramadol.

This study aimed to evaluate the role of opioid receptors in the analgesic effects of intraplantar tramadol in a model of postoperative pain.

Materials and methods

Animals

The experiments were performed after the approval of the Bioethics Committee of the Hospital of Clinics of The University of São Paulo Faculty of Medicine and according to the Committee for Research and Ethical Issues of the IASP.[21] All experiments were performed on Wistar male rats, weighing 250 g, supplied by own breeding facilities of the University of São Paulo Faculty of Medicine. The total number of animals used in the study was 35 rats. All behavioral experiments were conducted between 9:00 am and 12:00 pm. All animals were housed in pairs, in cages with bedding and free access to food and water.

Plantar incision

The rat hind paw plantar incision model was performed as previously described.[22] Briefly, rats were anesthetized with 2% to 3% isoflurane delivered *via* nose cone. The plantar aspect of the right hind paw was prepared in a sterile manner with a 10% povidone-iodine solution and draped. A 1 cm longitudinal incision was made with a number 11 blade through skin and fascia of the plantar aspect of the paw of the rat, starting 0.5 cm from the proximal edge of the heel and extending toward the toes. The flexor muscle was elevated and incised longitudinally and the muscle origin and insertion remain intact. After hemostasis with gentle pressure, the skin was opposed with two simple sutures of 5–0 mononylon.

Mechanical hyperalgesia

Rats were placed on an elevated plastic mesh floor covered with a clear plastic cage top. The animals were allowed to