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Effects and underlying mechanisms of endotoxemia on post-incisional pain in rats

Takashi Kawano [a,*], Satoru Eguchi [b], Hideki Iwata [a], Daiki Yamanaka [a], Hiroki Tateiwa [a], Fabricio M. Locatelli [a], Masataka Yokoyama [a]

[a] Department of Anesthesiology and Intensive Care Medicine, Kochi Medical School, Nankoku, Japan
[b] Department of Dental Anesthesiology, Tokushima University School of Dentistry, Japan

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ABSTRACT

Aims: The aim of the present study was to investigate the effects and underlying mechanisms of endotoxin (lipopolysaccharide, LPS) on postoperative pain using a rat model of incisional pain.
Main methods: Animals were assigned to one of four groups using a 2 × 2 experimental design: a single intraperitoneal injection of 5 mg/kg LPS *versus* vehicle, by plantar incision *versus* anesthesia alone. Spontaneous pain and mechanical paw withdrawal threshold (PWT) were evaluated using Rat Grimace Scale (RGS) and von Frey fibers, respectively. Analgesic effects of ketoprofen, morphine, and wound infiltration with ropivacaine, as well as the contribution of the Toll-like receptor (TLR) 4 pathway, were also evaluated. *In vivo* single fiber recordings were performed to assess the nociceptive afferent signals from the surgical site.
Key findings: Systemic administration of LPS significantly increased the pain intensity at 2 h after hind paw incision, but did not affect the PWT. The duration of post-incisional pain assessed by both scales did not significantly differ in the presence or absence of LPS. The analgesic efficiency of ketoprofen and morphine was reduced by LPS, while that of wound infiltration with ropivacaine was preserved. On the other hand, *in vivo* single fiber recording failed to demonstrate any significant effects of LPS on the activity of primary afferents due to mechanical stimuli. Pre-treatment with intrathecal LPS from *Rhodobacter sphaeroides*, a TLR-4 antagonist, almost completely inhibited LPS-induced exacerbated post-incisional pain, and decreased analgesic responsiveness.
Significance: The present results suggested that LPS exacerbates post-incisional pain *via* the central TLR-4 pathway.

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1. Introduction

Pain management is an essential part of postoperative care; inadequate pain control may be linked with increased morbidity and mortality [1]. Meanwhile, the prevalence of postsurgical pain remains high, and its treatment suboptimal [2,3]. Consequently, improving the management of postoperative pain is an ongoing challenge in the anesthesia practice. Increased pain sensitivity is now recognized as the main manifestation of moderate to severe postoperative pain, and may contribute to the inter-individual variability in responses to pain and analgesics [4–6]. Postoperative increased pain sensitivity is thought to be mediated by peripheral, spinal, and supra-spinal levels of pain perception, while its exact underlying mechanism remains unclear.

Endotoxin, or lipopolysaccharide (LPS), is a key component of the cell membrane of gram negative bacteria, which can elicit undesirable immune responses via Toll-like receptor (TLR) 4-dependent pathways [7,8]. Previous studies demonstrated that endotoxemia is prevalent in patients after any surgical procedure, although its levels are highly variable [9–11]. Recently, experiments in healthy humans demonstrated that a subclinical low-dose LPS challenge results in increasing sensitivity to visceral and somatic pain [12,13]. These findings imply that surgical procedure-associated endotoxemia, even at a subclinical dose, may contribute to the development of postoperative increased pain sensitivity. However, no research has been conducted to explore this possibility.

To test this hypothesis, we investigated whether low-dose endotoxin could affect the pain intensity and response to analgesics in a rat model of post-incisional pain. *In vivo* single fiber recordings from

* Corresponding author at: Department of Anesthesiology and Intensive Care Medicine, Kochi Medical School, Kohasu, Oko-cho, Nankoku, Kochi 783-8505, Japan.
E-mail address: takashika@kochi-u.ac.jp (T. Kawano).

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primary afferent nerves were also conducted to determine whether peripheral or central mechanisms play a dominant role in endotoxin-induced modulation of pain perception. Furthermore, the possible involvement of TLR-4 signaling in endotoxin activity was examined by pharmacological antagonist experiments.

2. Materials and methods

2.1. Animals and experimental groups

All procedures performed on animals were approved by the Institutional Animal Care and Use Committee of the Kochi Medical School. A total of 325 male Sprague–Dawley rats were used in this study, and maintained individually in humidity (50–60%) and temperature (22 ± 0.5 °C) controlled room with an alternating 12-h light–dark cycle. Both pellet food and tap water were available ad libitum throughout the experiment.

Animals received a single inter-peritoneal (*i.p.*) injection of either 5 mg/kg lipopolysaccharide (LPS, diluted in 0.5 ml of saline) or equivalent volume of saline (control). The dose of LPS (subclinical, but sufficient to induce immune activation) was determined based on a previous study [14] and a pilot experiment conducted beforehand. The animals were further divided into three sets of experiments according to the schema shown in Fig. 1. Experiment 1 was designed for assessment of postoperative pain, and rats were randomly assigned to one of four groups using a 2 × 2 experimental design: LPS versus control, by surgery versus non-surgery. Experiment 2 was conducted to test whether LPS could have an influence on the analgesic efficiency of 3 clinically relevant analgesics: systemic ketoprofen and morphine analgesics, and local wound infiltration with ropivacaine. In this experiment, all animals were anesthetized after measurement of pain (2 h after

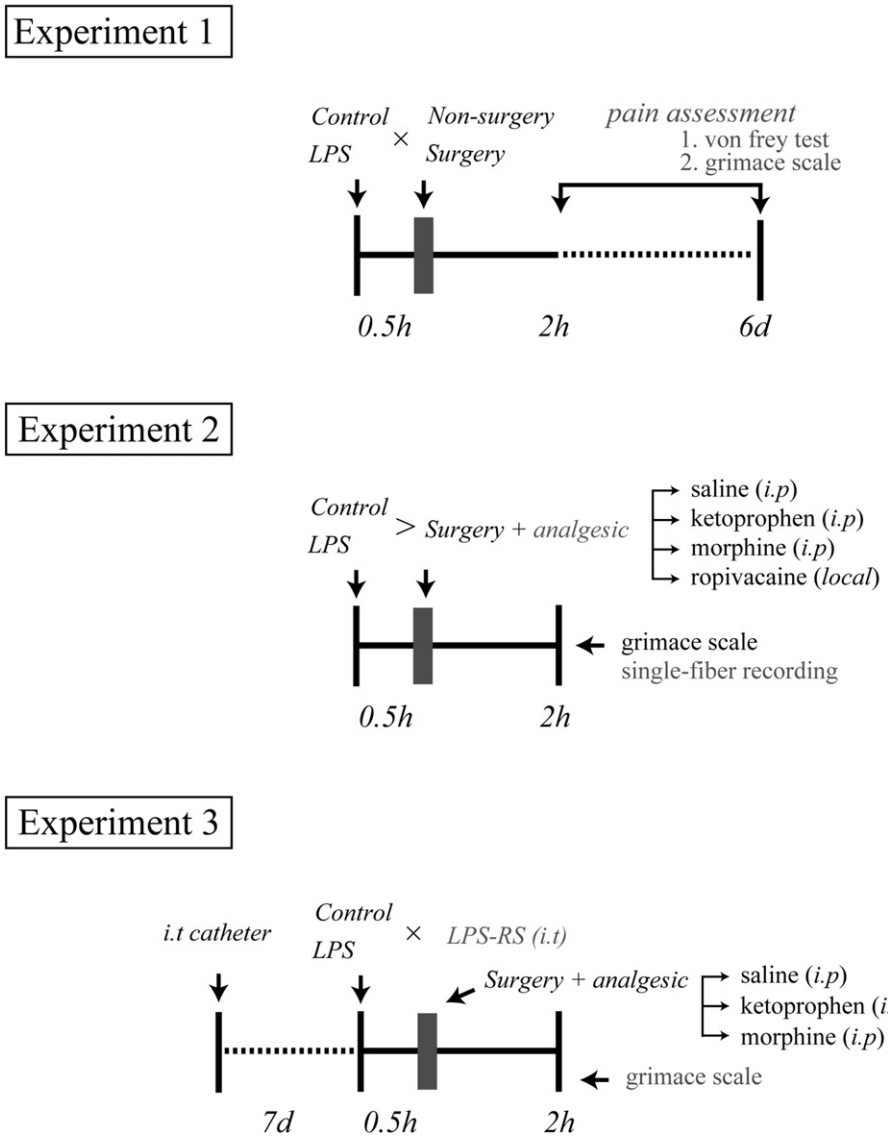

Fig. 1. Experimental protocol and time course. All rats were administered 5 mg/kg lipopolysaccharide (LPS) or an equivalent volume of saline (control) by a single inter-peritoneal (*i.p.*) injection following surgery or non-surgery. Experiment 1: the extent and duration of postoperative pain were assessed using the von Frey test or Rat Grimace Scale. Experiment 2: Analgesic effectiveness of a subcutaneous dose administration of saline, ketoprofen, or morphine, or a single-dose surgical wound infiltration with 0.2% ropivacaine after surgery were evaluated. Following, all animals were anesthetized and the activity of the peripheral primary afferents were evaluated by *in vivo* single fiber recording. Experiment 2: antagonist experiments were conducted using pretreatment with LPS from *Rhodobacter sphaeroides* (LPS-RS, a selective competitive TLR-4 antagonist).

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