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Modulation of Remifentanil-induced Analgesia and Postinfusion Hyperalgesia by Parecoxib in Humans

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Background: **Numerous experimental and clinical studies suggest that brief opioid exposure can enhance pain sensitivity. It is suggested that spinal cyclooxygenase activity may contribute to the development and expression of opioid tolerance. The aim of the investigation was to determine analgesic and antihyperalgesic properties of the cyclooxygenase-2 inhibitor parecoxib on remifentanil-induced hypersensitivity in humans.**

Methods: **Fifteen healthy male volunteers were enrolled in this randomized, double-blind, placebo-controlled study in a crossover design. Transcutaneous electrical stimulation at high current densities was used to induce spontaneous acute pain (numeric rating scale 6 of 10) and stable areas of pinprick hyperalgesia. Pain intensities and areas of hyperalgesia were assessed before, during, and after a 30-min intravenous infusion of remifentanil (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or placebo (saline). Parecoxib (40 mg) was administered intravenously either with onset of electrical stimulation (preventive) or in parallel to the remifentanil infusion.**

Results: **Remifentanil reduced pain and mechanical hyperalgesia during the infusion, but upon withdrawal, pain and hyperalgesia increased significantly above control level. Preventive administration of parecoxib led to an amplification of remifentanil-induced antinociceptive effects during the infusion (71.3 ± 7 *vs.* 46.4 ± 17% of control) and significantly diminished the hyperalgesic response after withdrawal. In contrast, parallel administration of parecoxib did not show any modulatory effects on remifentanil-induced hyperalgesia.**

Conclusion: **The results confirm clinically relevant interaction of μ opioids and prostaglandins in humans. Adequate timing seems to be of particular importance for the antihyperalgesic effect of cyclooxygenase-2 inhibitors.**

OPIOIDS are the drugs of choice for the treatment of moderate to severe acute and chronic pain. However, recent research suggests that opioids can elicit increased sensitivity to noxious stimuli.[1–8] Even brief exposures to μ-receptor agonists can induce long-lasting hyperalgesic effects for days, which rendered clinical significance by observations that large doses of intraoperative μ-receptor agonists increased postoperative pain and morphine consumption.[9–12] Based on the observation that administration of opioids can induce pain inhibitory and pain facilitatory systems, this pain hypersensitivity has been attributed to a relative predominance of pronociceptive mechanisms such as activation of the *N*-methyl-D-aspartate (NMDA) receptor system.[4,5,7,13]

Similarly, prostaglandins—in particular prostaglandin E_2—can stimulate glutamate release from both astrocytes and spinal cord dorsal horns,[14,15] and cyclooxygenase (COX) inhibitors were found to functionally antagonize the NMDA receptor.[16,17] Furthermore, prostaglandins were found to directly sensitize the spinal nociceptive system by depolarizing deep spinal cord dorsal horn neurons[18] and by disinhibiting glycinergic neurotransmission in the superficial layers of spinal cord dorsal horn neurons.[19] The inhibitory neurotransmitter glycine, however, can facilitate NMDA receptor activation and thus transmission of nociceptive input.[20,21]

Therefore, because spinal NMDA receptors are implicated in opioid-induced hypersensitivity, prostaglandins may mediate in part the neural adaptation in which these receptors are involved, and inhibition of prostaglandin production would be expected to block opioid-induced hyperalgesia. The effects of COX-2 inhibitors in this context have not been examined in humans. Although the COX-2 inhibitors have often been used in combination with opioids to improve postoperative pain management, COX-2 inhibitors may ameliorate opioid-induced hyperalgesia by a mechanism independent of the synergy of their analgesic actions.

We therefore compared the time course of analgesic and antihyperalgesic effects of the intravenous COX-2 inhibitor parecoxib on remifentanil, a short-acting μ-receptor agonist, in a human model of electrically evoked pain and secondary hyperalgesia.[22] It has been shown that this experimental model mimics some aspects of clinically observed opioid-induced hypersensitivity.[5–7] Furthermore, it has provided clear experimental evidence for the existence of central antihyperalgesia induced by intravenous infusion of COX inhibitors.[23] Because it is suggested that the timing of the COX inhibitor might play a crucial role for its analgesic and antihyperalgesic effect, the current study was also designed to evaluate possible preventive effects of parecoxib.

Materials and Methods

Fifteen healthy male subjects were enrolled in this randomized, double-blind, placebo-controlled study in a crossover design. The average age was 29 ± 8 yr (range, 20–45 yr; table 1). All subjects underwent a clinical examination including standard blood chemistry and

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Table 1. Demographic Data and Electrical Current

No.	Age, yr	Weight, kg	Height, cm	Current, mA
1	28	70	170	43.3 ± 10.6
2	23	65	177	41.6 ± 5.8
3	43	72	170	15.1 ± 2.1
4	26	66	177	20.6 ± 5.1
5	21	72	196	38.1 ± 11.6
6	33	79	183	29.7 ± 6.8
7	25	66	177	45.2 ± 9.8
8	22	65	173	13.6 ± 2.9
9	45	94	196	44.4 ± 9.3
10	20	92	190	13.9 ± 2.7
11	36	82	180	34.5 ± 4.8
12	33	78	184	26.5 ± 5.6
13	26	75	180	37.1 ± 10.2
14	25	85	186	29.3 ± 4.5
15	24	82	174	48.7 ± 6.3
Mean ± SD	29 ± 8	76 ± 10	181 ± 8	32.1 ± 12.0

The table presents age, weight, and height of the subjects, as well as mean electrical current in the four sessions (mean ± SD).

electrocardiography. No subject had a known drug allergy or was taking medication that may have interfered with pain sensations (*i.e.*, analgetics, antihistamines, calcium, or sodium channel blockers). After giving informed consent to take part in the study, all subjects were familiarized with the stimulation procedures. The experiments were performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical Faculty of the University of Erlangen-Nuremberg.

Experimental Pain Model

Intradermal electrical stimulation was used to induce ongoing pain and secondary mechanical hyperalgesia as described previously.[7,22] Briefly, two microdialysis fibers equipped with internal stainless steel wires were inserted intradermally for approximately 10 mm at a distance of 5 mm in the central volar forearm of the subjects. Monophasic, rectangular electrical pulses of 0.5 ms in duration were applied with alternating polarity *via* a constant current stimulator (Digitimer S7; Digitimer, Hertfordshire, United Kingdom) at 2 Hz. The current was gradually increased during the first 15 min of stimulus administration, targeting a pain rating of 6 on an 11-point numeric rating scale (NRS; 0 = no pain and 10 = maximum tolerable pain) and was then kept constant for the remaining time of the experiment. Thus, this kind of "adjustment procedure" facilitates interindividual comparison of pain ratings.

Beside ongoing pain, this experimental approach has been proven to provoke stable areas of secondary hyperalgesia to punctate stimuli and touch caused by an activation of primarily mechanoinsensitive ("silent") C-nociceptors.[24] This class of nociceptors was shown to be electrically activated preferentially at high current densities as used in this model.[25]

Medication and Side Effects

Four separate treatment trials were performed, at least 2 weeks apart. The subjects received continuous intravenous infusions of remifentanil (Ultiva®; Glaxo Smith-Kline GmbH, Munich, Germany) with weight-adjusted doses of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, or saline 0.9% as a control (fig. 1). These drugs were delivered by a continuous infusion during 30 min, starting 30 min after the onset of the electrical stimulation (fig. 1). In addition, 10-min intravenous infusions of 40 mg parecoxib (Dynastat®; Pfizer GmbH, Karlsruhe, Germany) or saline were administrated before starting the electrical stimulation (parecoxib preventive) or simultaneously to the start of the remifentanil infusion (parecoxib parallel) (fig. 1). The remifentanil and parecoxib doses of were chosen on the basis of clinically used dosages for intravenous administration in adults. Thus, the subject received four different treatments in a randomized order: control, remifentanil, remifentanil + parecoxib preventive, or remifentanil + parecoxib parallel (fig. 1).

During the infusion, an examiner asked the subjects for side effects such as sedation, dizziness, pruritus, and nausea. Pulse oximetry, electrocardiography, and noninvasive arterial blood pressure were monitored continuously during the study.

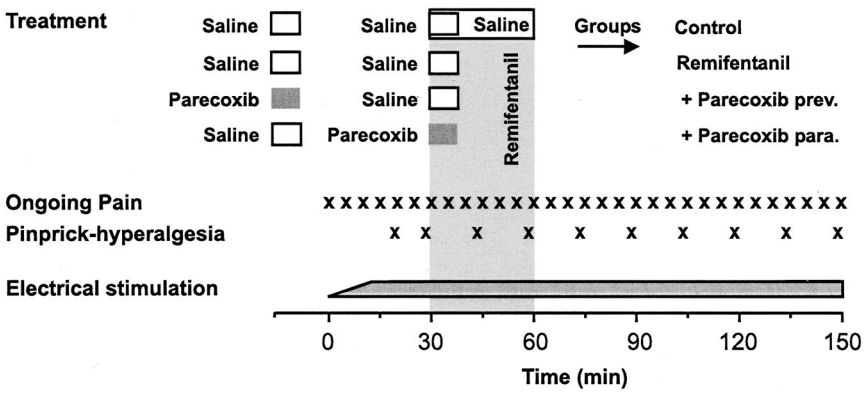

Fig. 1. Schematic illustration of the experimental protocol. Four separate treatment trials were performed. The subjects received intravenous infusions of remifentanil or saline as a control. The drugs were delivered by a continuous infusion during 30 min, starting 30 min after the onset of the electrical stimulation. In addition, intravenous infusions of 40 mg parecoxib or saline were administrated before starting the electrical stimulation (parecoxib prev.) or simultaneously (parecoxib para.) to the start of the remifentanil infusion. Thus, the subject received four different treatments in a randomized order (groups): saline, remifentanil, remifentanil + parecoxib prev., or remifentanil + parecoxib para.

Table 2. Side Effects of Drug Infusions

	Saline	Remifentanil	Remifentanil + Parecoxib Prev.	Remifentanil + Parecoxib Para.
Pruritus		2	1	
Hypacusis/hyperacusis	1	2		1
Dizziness	2	5	4	3
Nausea	1		1	
Sedation	3	11	13	12
Unconsciousness				

The table presents the number of subjects who reported side effects (n = 15). Parecoxib was administered before starting the electrical stimulation (parecoxib prev.) or simultaneously to the start of the remifentanil infusion (parecoxib para.).

Sensory Testing

During the time of the experiment, an examiner asked the subject every 5 min to rate the intensity of ongoing pain induced by the electrical stimulation on the NRS (fig. 1). The area of pinprick hyperalgesia was determined with a 256-mN von Frey filament. The borders of the hyperalgesic areas were delineated by moving along four linear paths parallel and vertically to the axis of the forearm from distant starting points toward the stimulation site (step size 0.5 cm) until the volunteer reported increased pain sensations evoked by the von Frey filament (pinprick hyperalgesia). For further analysis, both diameters were used to estimate the areas of secondary hyperalgesia ($D/2 * d/2 * \pi$). Areas of pinprick hyperalgesia were repeatedly tested in 15-min intervals during the 150-min observation period. After 150 min, the electrical stimulation was switched off (fig. 1).

Comparison with Previous Results

Because it is suggested that COX inhibitors can inhibit opioid-induced hypersensitivity by functionally antagonizing NMDA receptors, modulatory effects of parecoxib on remifentanil-induced hypersensitivity were compared with previous results on *S*-ketamine in the same experimental setup.[7] In this study, subjects received continuous infusions of *S*-ketamine at 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, remifentanil at 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, or a combination of both drugs during 30 min, starting 30 min after the start of electrical stimulation. Furthermore, analgesic and antihyperalgesic effects of a single-dose of 40 mg parecoxib administered 30 min after the start of electrical stimulation[23] were compared with the effects of the remifentanil–parecoxib combinations in the actual study.

Statistical Analysis

Despite the same intensity of electrical stimulation and pain ratings, areas of pinprick hyperalgesia in the electrical hyperalgesia model significantly decrease from session to session.[26] Therefore, before entering statistical analyses, data regarding areas of secondary hyperalgesia were normalized to achieve the same point of reference in subjects from all of the 4 days by setting the mean of both baseline measurements, *i.e.*, 15 and 25 min after onset of electrical stimulation, to 100%. For statistical evaluation, pain ratings as well as data of secondary hyperalgesia were transformed in areas under the curve of subsequent 30-min intervals. Treatment effects over time were evaluated using two-way repeated measures analysis of variance (ANOVA) including the effects "treatment" and "time course." *Post hoc* testing was performed as planned comparisons corrected with the Bonferroni procedure.

For the comparisons with previous results, the area under the curve of analgesic and antihyperalgesic effects of a comparable 60-min interval, immediately after cessation of the continuous infusion, was determined. Differences between the treatments were compared using Student *t* tests corrected with the Bonferroni procedure. Unless stated otherwise, all results are expressed as mean ± SD; significance levels throughout this study were $P \leq 0.05$. The STATISTICA software package (Statsoft, Tulsa, OK) was used for statistical analysis.

Results

Side Effects

Almost all subjects developed subjective side effects during the drug infusion (table 2). Sedation was significantly more pronounced during the infusion of the opioid and was paralleled by a significant decrease in oxygen saturation ($P < 0.001$, by ANOVA and planned comparisons; fig. 2). However, all subjects answered promptly at each time point to the questions of the investigators; the pain ratings and estimations of hyperalgesic areas were accurate and reproducible. At no time did subjects report bothersome side effects or anxiety; respiratory depression and muscular rigidity were not observed. Mean arterial pressure and heart rate remained unchanged during the infusion (nonsignificant, by ANOVA; fig. 2).

Electrical Stimulation

To provoke a pain rating of NRS 6, the average current was increased to 32.1 ± 12.0 mA (range, 12.7–58.8 mA) during the first 15 min of electrical stimulation. After keeping the current constant, the pain ratings decreased significantly, reaching an NRS of 5.4 ± 0.8 at 30 min ($P < 0.001$, by ANOVA; fig. 3A). No significant differences

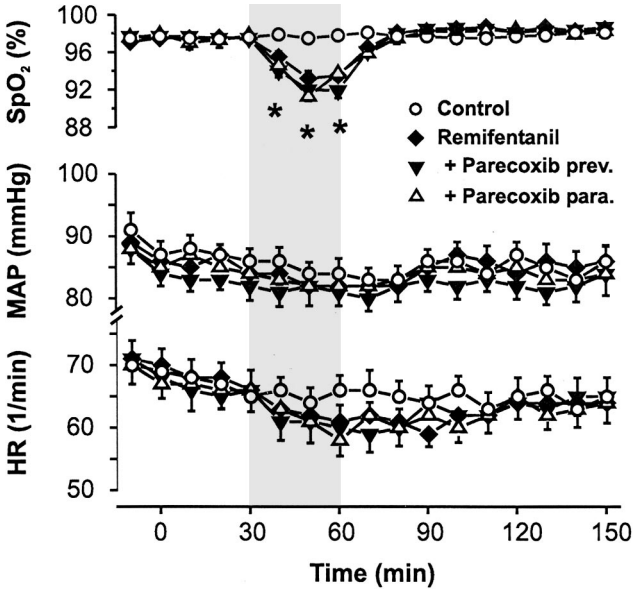

Fig. 2. Infusion of remifentanil resulted in a significant decrease in oxygen saturation (Spo_2), whereas mean arterial pressure (MAP) and heart rate (HR) remained unchanged. No differences were observed when parecoxib was administrated either before starting the electrical stimulation (parecoxib prev.) or simultaneously (parecoxib para.) to the start of the remifentanil infusion. Data are expressed as mean ± SEM (n = 15). * $P < 0.05$, planned comparisons corrected with the Bonferroni procedure.

between the treatment groups were observed until this time point (nonsignificant, by ANOVA; fig. 3A). During the first 30 min of electrical stimulation, areas of pinprick hyperalgesia remained stable at approximately 33.8 (11.2, 49.0) cm^2 in the control group, 18.8 (13.6, 37.1) cm^2 in the remifentanil group, 26.7 (17.4, 45.2) cm^2 in the remifentanil + parecoxib preventive group, and 24.1 (16.2, 31.2) cm^2 in the remifentanil + parecoxib parallel group [median (25%, 75% percentiles)] (100%; fig. 3B). No significant differences between the treatment groups were observed in this early phase of the protocol (nonsignificant, by ANOVA).

Ongoing Pain

Infusion of remifentanil 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ led to a fast onset of analgesia in all groups. Remifentanil significantly decreased pain ratings during the infusion to an NRS of 1.2 ± 0.3 (28 ± 7% of control) ($P < 0.001$, by ANOVA, as compared with control; fig. 3A). However, shortly after cessation of the infusion, pain ratings increased and exceeded control values ($P < 0.001$, by ANOVA). This antianalgesic effect remained stable for the rest of the observation period. Additional administration of intravenous parecoxib did not affect time course and intensity of the pain ratings (nonsignificant, by ANOVA).

Pinprick Hyperalgesia

Infusion of remifentanil significantly reduced the areas of punctate hyperalgesia to 13 ± 4 cm^2 (57% of baseline)

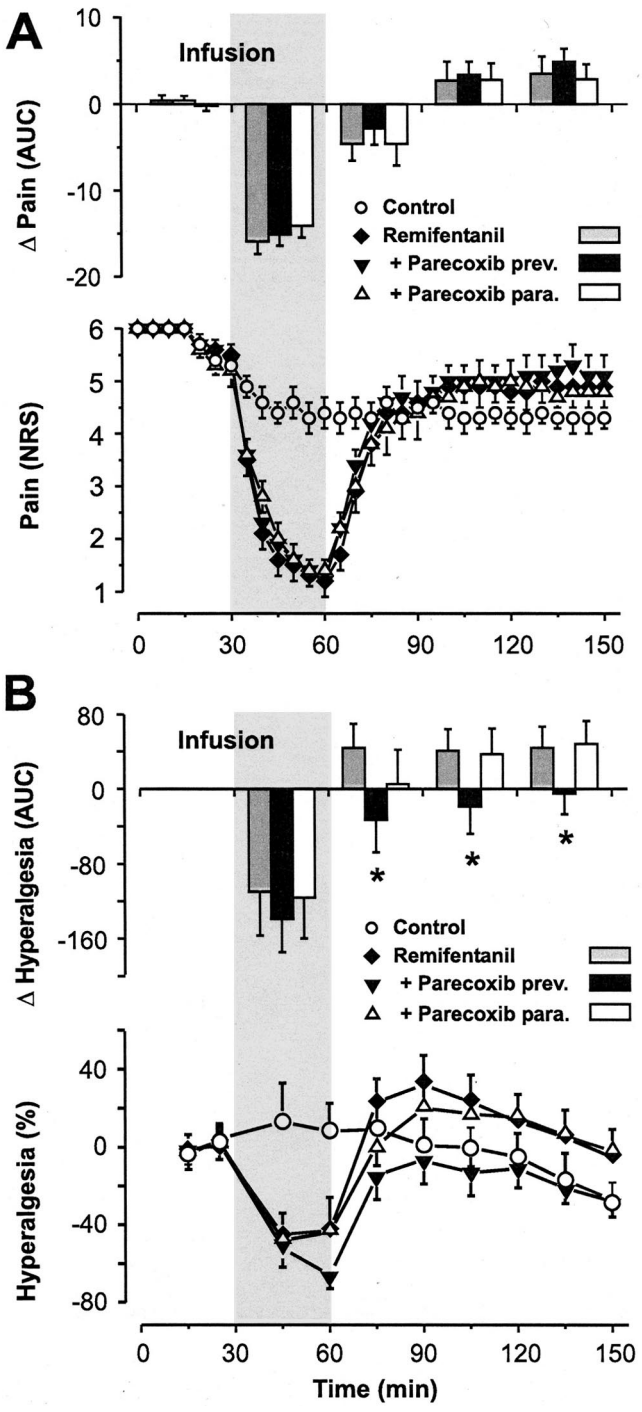

Fig. 3. Pain ratings on the numeric rating scale (NRS) (*A*) as well as areas of pinprick hyperalgesia (*B*) were significant reduced during remifentanil infusion. Pain ratings were not different in the three groups receiving remifentanil (*A*). Preventive administration of parecoxib (parecoxib prev.) significantly diminished the enlarged hyperalgesic areas after cessation of the remifentanil infusion, while parallel administration of parecoxib (parecoxib para.) did not show any modulatory effects on remifentanil-induced hyperalgesia (*B*). Data are expressed as mean ± SEM (*lower panel*) and as mean area under the curve (AUC) ± SEM of 30-min intervals (*upper panel*) (n = 15). Delta pain and delta hyperalgesia are relative changes in pain ratings and hyperalgesic areas as compared with the baseline measurement before drug administration. * $P < 0.05$, planned comparisons corrected with the Bonferroni procedure.

($P < 0.05$, by ANOVA, as compared with control; fig. 3B). However, antihyperalgesic effects were only prominent during infusion: Shortly after cessation of the infusion, areas of pinprick hyperalgesia exceeded control values ($P < 0.05$, by ANOVA) and remained significantly enlarged as compared with control values (fig. 3B). Preventive administration of parecoxib significantly diminished the enlarged hyperalgesic areas after cessation of the remifentanil infusion ($P < 0.05$, by ANOVA and planned comparisons; fig. 3B). In contrast, parallel administration of parecoxib did not show any modulatory effects on time course or size of hyperalgesic areas (nonsignificant, by ANOVA; fig. 3B).

Interactions of Parecoxib and S*-Ketamine with Remifentanil*

Parecoxib as well as *S*-ketamine (data from previous study using the same protocol) did not attenuate the enhanced pain sensitivity after cessation of the remifentanil infusion (fig. 4A). However, pain ratings were not significantly different when compared with parecoxib alone (nonsignificant, by Student *t* test), whereas pain ratings after coadministration of remifentanil and *S*-ketamine remained significantly enhanced as compared with *S*-ketamine alone ($P < 0.05$, by Student *t* test).

In contrast, hyperalgesic areas were significantly reduced after coadministration of *S*-ketamine with remifentanil; no differences were observed to the antihyperalgesic effects of *S*-ketamine alone (nonsignificant, by Student *t* test; fig. 4B). Parecoxib was shown to reduce remifentanil-induced hyperalgesia only after preventive administration; however, even then, hyperalgesic areas remained significantly enlarged when compared with the antihyperalgesic effect of parecoxib alone ($P < 0.05$, by Student *t* test; fig. 4B).

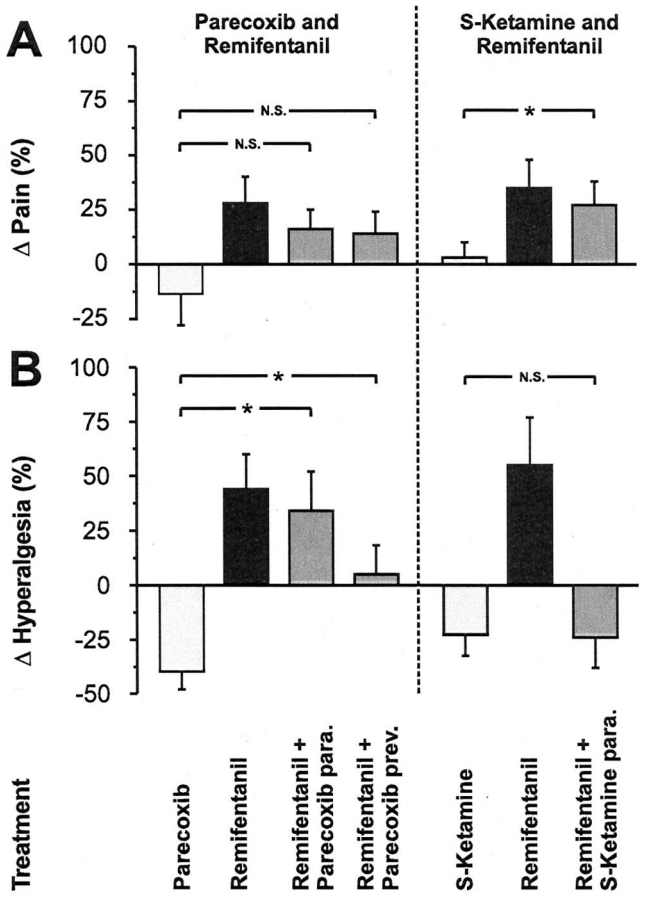

Fig. 4. Overall view of the interactions of parecoxib (40 mg) and *S*-ketamine (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) with remifentanil (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) on pain (*A*) and hyperalgesia (*B*). For details, see text. The data for the single administration of parecoxib and for the interactions of *S*-ketamine and remifentanil were reanalyzed from previous studies.[7,23] Data are expressed as mean and SEM (n = 13–15 each). Δ Pain and Δ hyperalgesia are relative changes in pain ratings and hyperalgesic areas as compared with the baseline measurement before drug administration. * $P < 0.05$, Student *t* tests corrected with the Bonferroni procedure. Parecoxib para. = parallel administration of parecoxib; parecoxib prev. = preventive administration of parecoxib.

Discussion

In the current study, preventive administration of the COX-2 inhibitor parecoxib led to an amplification of remifentanil-induced antinociceptive effects during the infusion and significantly diminished the hyperalgesic response after withdrawal. In contrast, parallel administration of parecoxib did not show any modulatory effects on remifentanil-induced hyperalgesia, suggesting the importance of an adequate timing for its antihyperalgesic efficacy.

Opioid-induced Hyperalgesia

Nonopioid analgesics like nonsteroidal antiinflammatory drugs are increasingly used in postoperative pain management, either alone or as an adjunct to opioid analgesics.[27–29]

Although the inhibition of COX in the periphery is commonly accepted as the primary mechanism, experimental and clinical data suggest a potential role for spinal COX-inhibition to produce antinociception and reduce hypersensitivity.[16,30–32] Recent studies provided clear evidence that up-regulation of prostaglandin E_2 at central sites is an important factor of surgery-induced inflammatory response,[33] and inhibition of prostaglandin E_2 in cerebrospinal fluid is related to the reduction in pain behavior and opioid consumption.[34]

In contrast, μ-receptor agonists show only minor antihyperalgesic properties. Although their profound analgesic effects are highly regarded in general anesthesia, recent clinical evidence suggests that they might elicit increased pain sensitivity in the early postoperative period.[9–11,35] Activation of the NMDA receptor system, acute receptor desensitization *via* uncoupling of the receptor from G proteins, up-regulation of the cyclic adenosine monophosphate pathway, and descending fa-

cilitation have been proposed as potential mechanisms underlying this phenomenon.[4,36–38] A critical role has been attributed to the endogenous pain facilitatory system involving the NMDA receptor: Coadministration of an NMDA receptor antagonist prevented the development of opioid-induced hypersensitivity in animals and humans.[5,7,11,13,39]

In our study, remifentanil provoked enhanced pain intensity and larger hyperalgesic areas as shown before.[5–7] We did not detect any effect of parecoxib on enhanced pain intensity in our study and confirmed that the COX inhibitor did not have direct analgesic effects.[23,40,41] However, parecoxib partially blocked the opioid-induced enlargement of hyperalgesic areas. Antihyperalgesic effects of parecoxib itself has already been shown in the same model: A long-lasting reduction of hyperalgesic areas of approximately 40% was observed as soon as 30 min after intravenous administration of parecoxib when administered 30 min after the onset of the electrical stimulation (fig. 4).[23] This pronounced antihyperalgesic efficacy was significantly reduced when administered in combination with remifentanil: After withdrawal of the opioid, antihyperalgesic effects of the COX-2 inhibitor were no longer detectable. However, preventive administration of parecoxib led to an amplification of remifentanil-induced antihyperalgesic effects during the infusion and significantly diminished the hyperalgesic response after withdrawal. The opposing effects with different time courses suggest independent pronociceptive and antinociceptive pathways of the opioid, with parecoxib supporting the antinociceptive and antagonizing part of the pronociceptive activity.

Interactions of COX Inhibitors and Opioids

Cyclooxygenase inhibitors can reduce the development of opioid tolerance in animals[42,43] and were found to be effective in preventing recurrent morphine withdrawal.[44] However, the exact mechanism of the central analgesic interaction of COX inhibitors and opioids is not clear yet. After COX inhibition, more arachidonic acid can enter the lipoxygenase pathway, and metabolites such as 12-hydroperoxyeicosatetraenoic acid will increase. This metabolite was shown to decrease the duration of action potentials in γ-aminobutyric acid–mediated neurons of the periaqueductal gray by modulating a voltage-dependent potassium conductance, and the resulting inhibition of γ-aminobutyric acid release might be synergistic to the presynaptic inhibition of γ-aminobutyric acid–mediated synaptic currents by opioids.[45,46] Moreover, it is now well established that endogenous cannabinoid levels result from a balance between formation and inactivation of endocannabinoids, and COX-2 is critically involved in endocannabinoid degradation.[47–50] Furthermore, COX-2 was shown to oxygenate 2-arachidonoyl glycerol as efficiently as arachidonic acid, its primary substrate.[51] Therefore, increased endocannabinoids levels after COX-2 inhibition could act synergistically to opioids.[50,52]

Interestingly, only early treatment with parecoxib 30 min before application of remifentanil was effective in reducing the opioid-induced hyperalgesia, whereas upon parallel application, parecoxib was ineffective. This would suggest that the interaction of opioids and COX inhibitors underlying inhibition of opioid-induced hyperalgesia is an early event and depends on whether prostaglandins have already sensitized the nociceptive system. Indeed, μ-receptor agonists are able to enhance prostaglandin-induced hyperalgesia.[53] The signal pathways of G_i protein–coupled μ receptors and G_s protein–coupled prostaglandin receptors converge on adenylyl cyclase, and the βγ subunit of G_i proteins was shown to be able to enhance stimulation of some adenylyl cyclase isoforms if these have already been stimulated by α_s-guanosine triphosphate.[54] On the other hand, E-type prostaglandin 3 receptors are negatively coupled to adenylyl cyclase and might therefore counteract these pronociceptive effects.

Our data did not reveal synergistic *analgesic* effects between parecoxib and remifentanil, possibly because the opioid-induced analgesia during the application was already profound (NRS approximately 1). However, the synergistic *antihyperalgesic* effect between preventive parecoxib and remifentanil would confirm the COX inhibitor–opioid interaction and might contribute to the synergistic antinociceptive effects of COX inhibitors and opioids in the clinical setting.[28,29]

Comparison between Antihyperalgesic Effects of Parecoxib and S*-Ketamine*

In previous experiments, *S*-ketamine presented a similar antihyperalgesic profile, reducing remifentanil-induced hyperalgesic areas to control levels.[5,7] However, parecoxib only partially reduced opioid-induced hyperalgesia, whereas ketamine led to a complete reversal. Therefore, the findings are in line with observations in animals, in which NMDA receptor antagonists were found to be more effective in reducing opioid-induced hyperalgesia than nonsteroidal antiinflammatory drugs.[55–57] However, a direct comparison of the acute postinfusion hyperalgesia investigated in our study with animal models of opioid tolerance is problematic, although the time course in our setting might more closely resemble the clinical situation of postoperative patients in whom opioid-induced hyperalgesia is found.[10,35] Therefore, the clinical implications of opioid-induced hyperalgesia and different treatment options must be clarified in future studies.

In conclusion, our results confirm clinical relevant parallel processing of μ-opioid and prostaglandin signaling in humans. Furthermore, the current study suggests that opioid-induced hypersensitivity is partly mediated by spinal COX activity. However, its contribution to the

induction and maintenance of hyperalgesia seems to be less important than that of spinal NMDA receptor activation. Given the clinical safety and utility of COX-2 inhibitors, their combined use with opioids may present an alternative for the prevention and reversal of hyperalgesia, when the use of NMDA receptor antagonists is limited by the occurrence of side effects.

Interestingly, an adequate timing seems to be of particular importance for the antihyperalgesic effect of COX-2 inhibitors: In the clinical setting, effective concentrations after oral COX-2 inhibitors, especially during preoperative fasting, are reached not until 60 min. Therefore, our findings are in line with clinical studies in which oral COX-2 inhibitors were found to be more effective when given at least 1 or 2 h before surgery. However, suggestions for clinical use should be based on clinical studies rather than solely on volunteer studies. Our data could thus serve as rationale for further clinical studies.

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