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Low dose of S(+)-ketamine prevents long-term potentiation in pain pathways under strong opioid analgesia in the rat spinal cord *in vivo*

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Background. μ-Opioid receptor (MOR) agonists are strong antinociceptive drugs. Low, but not high doses of the MOR agonist fentanyl prevent synaptic long-term potentiation (LTP) in pain pathways. Block of spinal *N*-methyl-D-aspartate (NMDA) receptors prevent central sensitization. Here we tested whether the NMDA receptor antagonist S(+)-ketamine reduces C-fibre-evoked potentials and prevents induction of LTP despite high doses of fentanyl.

Methods. C-fibre-evoked field potentials were recorded in the superficial laminae I/II of the rat lumbar spinal cord. High-frequency stimulation (HFS) was applied to the sciatic nerve at C-fibre strength to induce LTP. S(+)-ketamine 5 mg kg^{-1} was given 1 h before or after HFS. S(+)-ketamine 5 mg kg^{-1} and fentanyl as a bolus (40 μg kg^{-1}) followed by an infusion (96 μg kg^{-1} h^{-1}) were given before HFS to test the action of the combination of these drugs.

Results. HFS potentiated C-fibre-evoked field potentials to mean 173 (SEM 15)% of control (n=7) for at least 1 h. Low-dose S(+)-ketamine given before HFS blocked the induction of LTP. S(+)-ketamine given after HFS had no effect on the maintenance of LTP. Low-dose S(+)-ketamine prevented induction of LTP under fentanyl-infusion.

Conclusions. Low-dose S(+)-ketamine does not affect C-fibre-evoked potentials alone but blocks LTP induction in pain pathways. In contrast, high doses of opioids strongly reduce C-fibre-evoked potentials, but do not fully prevent LTP induction. In this animal study the combination of S(+)-ketamine with fentanyl reveals both a reduction of C-fibre-evoked potentials and prevention of LTP and seem therefore a better choice for perioperative pain management compared with the sole administration.

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Surgical damage is able to induce hyperalgesia (abnormal intense pain elicited by noxious stimulation) and allodynia (pain induced by normally non-painful stimuli). These enhanced responses to noxious or non-noxious stimuli result from peripheral[1] and/or central sensitization.[2 3] Twenty per cent of patients attending chronic pain clinics implicated surgery as one of the causes of their chronic pain and, in about half of these cases, surgery was the sole cause.[4] Thus, during surgery both strong analgesia is required and the surgical injury should not produce central sensitization.

Opioids are widely used, both for intra-operative use and for the treatment of moderate to severe pain. Our previous data show that low-doses of the clinically used μ-opioid receptor agonist (MOP) fentanyl not only reveal analgesic effects but also a block of long-term potentiation (LTP) of synaptic strength in pain pathways, a form of central sensitization in the rat spinal cord *in vivo*[5] and *in vitro*.[6] High doses of opioids, however, fail to prevent LTP induction in

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pain pathways[5] and can even cause opioid-induced hyperalgesia[7] in animal studies[8 9] and in humans.[10] Therefore, opioids not only demonstrate beneficial effects but also may reveal unwanted side-effects on pain.

From our previous studies we know that the block of spinal *N*-methyl-D-aspartate (NMDA) receptors prevents the induction of LTP of synaptic strength in nociceptive pathways.[11] For clinical routine use the NMDA receptor antagonist S(+)-ketamine is available. To pre-empt post-surgical central sensitization a dose of ketamine should be used that is sufficient to prevent central sensitization without causing psychotomimetic or cardiovascular side-effects. Here we provide evidence that with the combination of low-dose S(+)-ketamine and high-dose fentanyl not only is C-fibre activity diminished but LTP induction is also blocked and this is probably related to an analgesic effect and a prevention of central sensitization.

Methods

Animals

After obtaining approval from the Institutional Animal Care Committee (Regierungspräsidium Karlsruhe, Germany), the experiments were performed on male Sprague–Dawley rats weighing 250–320 g (Charles River Deutschland, Sulzfeld, Germany). Animals were kept in temperature-controlled environmental conditions on a 12:12 h light:dark cycle and were a fed standard diet (Altromin C 1000; Altromin, Lage, Germany) with access to food and water *ad libitum*.

Animal preparation

Isoflurane in two-thirds nitrous oxide and one-third oxygen was used to induce (3.5 vol% inspiratory) and maintain (1.0 vol% expiratory) anaesthesia. The right femoral vein was cannulated for application of drugs and the right femoral artery was cannulated in order to monitor arterial pressure and heart rate. The trachea was intubated with a 14 gauge i.v. cannula to allow mechanical ventilation. Muscle relaxation was achieved with pancuronium bromide 1 mg kg^{-1} h^{-1}. Atropine (0.05 mg kg^{-1}) was given once at the beginning of the preparation to reduce tracheal secretion. Glucose (5%, 10 ml kg^{-1}) was injected subcutaneously for nutrition of the animals during the 8–12 h experimental procedure. Blood gas analysis was performed at regular intervals during the experiment and ventilation parameters were adapted if necessary. Body temperature was kept constant between 37 and 38°C by means of a feedback-controlled heating blanket. The left sciatic nerve was dissected free for bipolar electrical stimulation with a silver hook-electrode. Lumbar segments L4 and L5 of the spinal cord were exposed by laminectomy and the dura mater was incised longitudinally. All exposed tissue was covered with warm agar (1.6%) except the recording segments of the spinal cord column. For each experiment one animal was used. Animals were randomly assigned to the different experimental protocols. Animals were killed with saturated potassium chloride at the end of each experiment.

Electrophysiological recordings and nerve stimulation

In response to electrical stimulation of the sciatic nerve, field sum potentials were recorded with glass microelectrodes (3–5 MW) 300–600 μm from the dorsal surface of the spinal cord dorsal horn (laminae I and II). Microelectrodes were moved into the spinal cord by an electronically controlled microstepper. Recordings were made with an ISO-DAM-amplifier (World Precision Instruments, Inc., Sarasota, FL, USA). Corner frequencies of the band-pass filter were set to 1 kHz and 0.1 Hz, respectively. The signal output was monitored on a digital oscilloscope (Hameg HM 250, Oceanside, CA, USA) and digitized at a sampling rate of 5 kHz by an A/D-converter card (DT281-F-16SE). Data were stored in a personal computer for off-line analysis. Test stimuli were 10–25 V, 0.5 ms and were applied at intervals of 5 min to the sciatic nerve. Intensity for the test stimulus was adjusted for each animal to achieve a stable C-fibre-evoked potential. For induction of LTP a high-frequency stimulus (HFS) consisting of four trains of 100 Hz, 40–50 V, 0.5 ms pulses for 1 s at 10 s intervals was applied. Conditioning stimulation was given at 40 V when intensity of test stimuli were lower than 20 V. Conditioning stimulation consisted of 50 V when the intensity of test stimuli was higher than 20 V. The distance between the stimulation site at the sciatic nerve and the recording site in the lumbar spinal dorsal horn was approximately 8 cm.

Behavioural testing

In order to ensure that the dose of 5 mg kg^{-1} S(+)-ketamine in the rat is in a subanaesthetic dose range, S(+)-ketamine was injected intraperitoneally in three otherwise drug-free rats. After injection of 5 mg kg^{-1} S(+)-ketamine the behaviour of the rats was observed carefully for 60 min. Rats were especially observed for sleepiness, staggered locomotion, or repetitive arching of the neck.

Experimental procedures

Test stimuli (10–25 V, 0.5 ms) were applied to the sciatic nerve for 60 min at intervals of 5 min. The following experimental protocols were performed.

- In order to test the effect of S(+)-ketamine at a low dose on established LTP, baseline recordings were performed for 60 min. Then the conditioning HFS was applied to the sciatic nerve to induce LTP and recordings were continued for another 60 min. After that time period a bolus of 5 mg kg^{-1} S(+)-ketamine was given intravenously and recordings were continued for another 120 min (n=6).
- The effect of low-dose S(+)-ketamine was investigated both on C-fibre-evoked potentials and on the induction of

LTP. After baseline recordings were performed for 60 min, a bolus of 5 mg kg^{-1} S(+)-ketamine was given intravenously and recordings were continued for another 60 min. Then HFS was applied to the sciatic nerve to induce LTP and recordings were continued for another 60 min (n=7).

- The combination of fentanyl and S(+)-ketamine was tested on both the C-fibre-evoked potentials and the induction of LTP. After 60 min of baseline recordings a bolus of 5 mg kg^{-1} S(+)-ketamine together with a bolus of 40 μg kg^{-1} fentanyl was injected intravenously. The bolus was followed by a fentanyl infusion of 96 μg kg^{-1} h^{-1}. After 60 min HFS was applied to the sciatic nerve. Recordings were continued for another 60 min after the application of HFS during continuous fentanyl infusion (n=5).

Data analysis and statistics

The area under the curve of the C-fibre-evoked field potentials was determined off-line by parameter extraction using the software Experimenter's Workbench (DataWave, Colorado, USA). The area of the C-fibre-evoked field potentials was determined as the integral of the waveform. Measurements were standardized for each rat such that the mean of the respective baseline values is equal to 100.

For the comparison of fentanyl alone (data taken from Benrath and colleagues[5]) *vs* fentanyl and S(+)-ketamine before HFS (Fig. 2A and B) post minus baseline differences were calculated (mean of the 11 baseline values compared with the 11 values after injection of fentanyl or S(+)-ketamine and fentanyl). These differences were compared using unpaired t-tests. The grand mean and its corresponding 95% confidence interval (CI) were estimated to test whether there was an effect of HFS on C-fibre-evoked potentials after the combined injection of fentanyl and S(+)-ketamine. A (95%) CI that does not overlap 0 is equivalent to a statistically significant difference (at the 5% level).

Calculations were performed using the SAS software system V8.2 (SAS Institute, Inc., 2002, Cary, NC). A significant difference was considered when P<0.05. All values are expressed as mean (SEM).

Results

After i.p. injection of 5 mg kg^{-1} S(+)-ketamine in three otherwise drug-free rats the behaviour of the animals was observed for 60 min. Rats were not sleepy at any time. Only one rat showed light side-to-side head-wagging. Neither staggered locomotion nor repetitive arching of the neck occurred in any animal at any time.

Aβ- and C-fibre-evoked field potentials could be clearly distinguished after stimulation of the sciatic nerve. C-fibre-evoked field potentials that were characterized by a negative focus in superficial spinal dorsal horn, long latencies (90–120 ms, corresponding to conduction velocities <1.2 m s^{-1}) and by high thresholds (10–25 V) were investigated further.

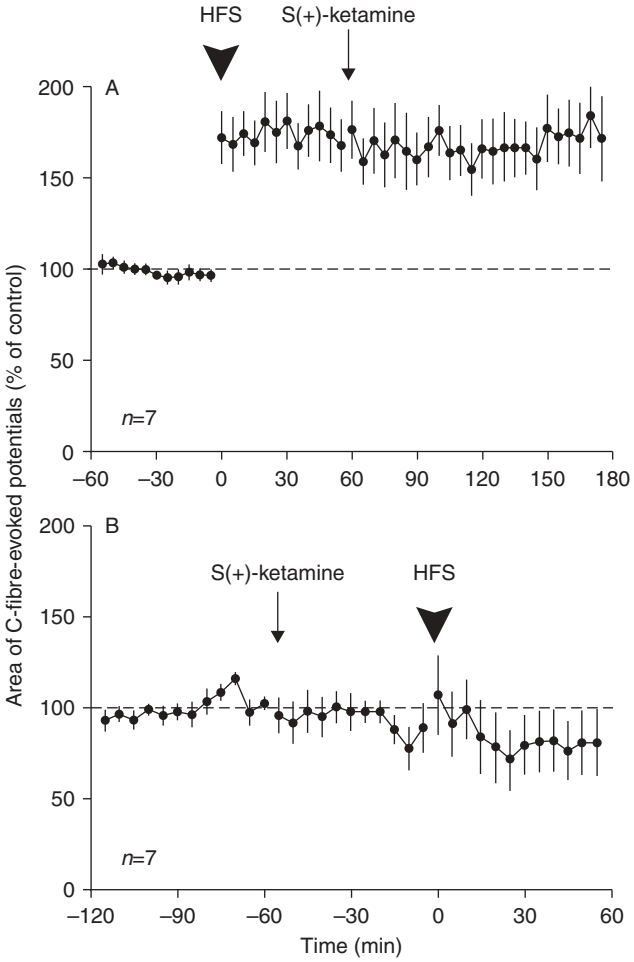

Fig 1 In isoflurane anaesthetized rats HFS induced LTP of synaptic strength between primary afferent C-fibres and neurones in the superficial spinal dorsal horn (A). Test stimuli were taken for 60 min as control. The NMDA-antagonist S(+)-ketamine (5 mg kg^{-1}) given 1 h after the induction of LTP did not reveal any effect on the maintenance of LTP (A). S(+)-ketamine (5 mg kg^{-1}) did not affect the magnitude of C-fibre-evoked potentials but prevented the induction of LTP (B).

HFS of the sciatic nerve at C-fibre strength consistently induced LTP in isoflurane anaesthetized rats to 173 (15)% of control (n=7; Fig. 1A).

When 5 mg kg^{-1} S(+)-ketamine was injected 1 h after LTP had been induced, C-fibre-evoked potentials remained unaffected [164 (14)% of control, n=7, Fig. 1A]. S(+)-ketamine 5 mg kg^{-1} was injected intravenously after 60 min of stable recording of C-fibre-evoked field potentials. S(+)-ketamine 5 mg kg^{-1} did not significantly affect the magnitude of the C-fibre-evoked potentials [89 (13)% of control, n=7, Fig. 1B]. HFS failed to induce LTP after bolus injection of low-dose S(+)-ketamine [81 (18)%, n=7, 60 min after HFS, Fig. 1B].

Bolus of S(+)-ketamine (5 mg) given in combination with a bolus of 40 μg kg^{-1} followed by an infusion of 96 μg kg^{-1} h^{-1} reduced C-fibre-evoked potentials to 40 (6)% of control,

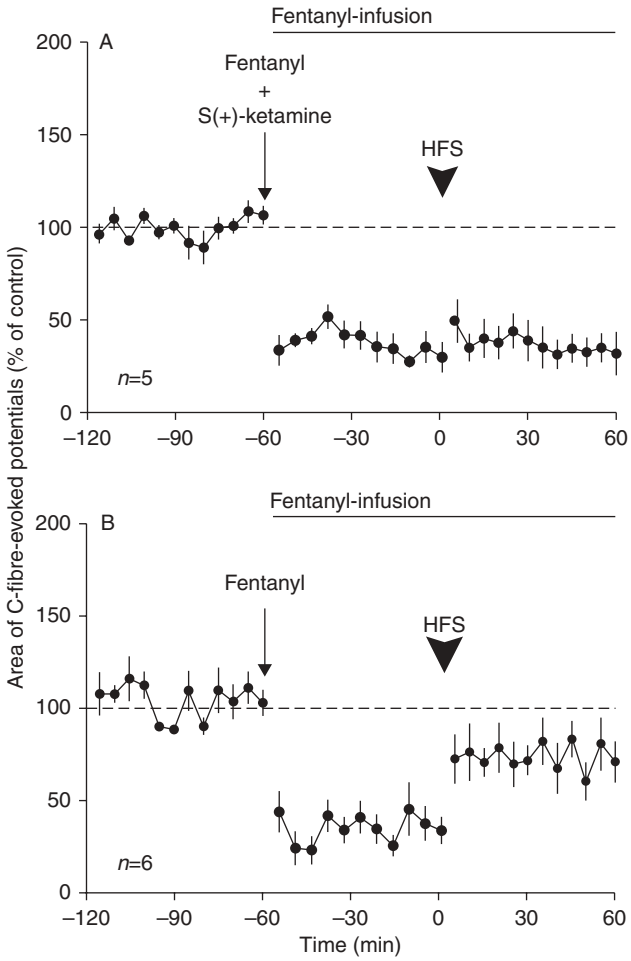

Fig 2 High-dose fentanyl in combination with the NMDA receptor-antagonist S(+)-ketamine reduced C-fibre-evoked potentials and blocked the induction of LTP. In (A) a bolus of S(+)-ketamine (5 mg kg^{-1}) was given in combination with a bolus of 40 μg kg^{-1} fentanyl followed by an infusion of 96 μg kg^{-1} h^{-1}. One hour after start of infusion HFS was applied to the sciatic nerve but no LTP was induced (cf. Fig. 1B). In (B), for comparison, a figure taken from Benrath and colleagues[5] shows that HFS induced long-term potentiation of reduced C-fibre-evoked potentials under high doses of fentanyl alone.

n=5 (Fig. 2A). Compared with the results from our previous study[5] the reduction of C-fibre-evoked potentials as a result of fentanyl alone [37 (8)% of control; *n*=6[5]] was not different from the combination of both drugs (Fig. 2B taken from Benrath and colleagues[5] for comparison).

One hour after the combined bolus injection of S(+)-ketamine with fentanyl and start of fentanyl-infusion HFS was applied to the sciatic nerve. The induction of LTP was fully blocked by the combination of S(+)-ketamine and fentanyl (Fig. 2A). The mean changes of the combined application of fentanyl and S(+)-ketamine on C-fibre-evoked potentials was 37 (95% CI: −23; 26) In our previous study,[5] however, we have shown that C-fibre-evoked potentials were significantly potentiated under fentanyl-infusion as a result of HFS (Fig. 2B taken from Benrath and colleagues[5] for comparison).

Discussion

The main results of this study are that neither the NMDA receptor antagonist S(+)-ketamine nor the MOR agonist fentanyl alone can provide both powerful inhibition of C-fibre-evoked potentials and prevention of LTP when used separately. In contrast, the combination of low-dose S(+)-ketamine with high-dose fentanyl reveals not only inhibition of C-fibre-evoked potentials but also prevention of LTP.

Ketamine is a non-competitive NMDA receptor antagonist and is a well established clinical drug used as a racemate or the S(+)-enantiomer. Ketamine reveals different actions depending on the dosage used. Ketamine in low dosages seems to have pre-emptive analgesic effects.[12,13] In higher dosages ketamine is also antinociceptive and at the highest dosages it induces anaesthesia. However, NMDA receptor block may lead to unwanted psychotomimetic and haemodynamic effects, which limits the use of high-dose ketamine in the clinical setting. Ketamine is not a selective pharmacological agent and has been shown to interact with many proteins. Nevertheless, it is the only clinically available NMDA receptor antagonist for i.v. application and is therefore routinely used to study the involvement of NMDA receptor in animals[8,9,14] and humans.[15]

Opioids have dose-dependent antinociceptive effects. Additionally MOR agonists may reveal pre-emptive action in low but not high doses,[5] which may cause opioid-induced hyperalgesia.[7] This is a potential cause for apparent acute opioid tolerance even after a single opioid administration.[16] For surgery, however, both strong antinociception and prevention of central sensitization is required.

In the present study a subanaesthetic dose of S(+)-ketamine was used, which also did not affect the C-fibre-evoked potentials in the superficial spinal dorsal horn, that is, it was not antinociceptive. In behavioural experiments neither racemic ketamine nor its enantiomers reveal any significant effect on the tail-flick test.[17] At 4 and 8 mg kg^{-1} i.v. racemic ketamine inhibit the C-fibre-evoked response of dorsal horn neurones to electrical stimulation in the rat.[18] This single cell study reflects polysynaptic nociceptive transmission, which seems to be more sensitive to NMDA receptor antagonists. Here, C-fibre-evoked field potentials were recorded, which reflect the net effect of monosynaptic transmission in a large number of neurones. The present data support previous findings that the monosynaptic nociceptive transmission is relatively insensitive to NMDA receptor antagonists.[11]

Here we show for the first time that the clinically used S(+)-ketamine applied in a subanaesthetic dose 1 h before HFS blocks the induction of LTP in the rat spinal cord *in vivo*. This result is in line with our previous findings, that superfusion of the spinal cord with the NMDA receptor antagonist D-CPP prevents the induction of LTP in the rat *in vivo*.[11] It is well known that other forms of central sensitization in the rat spinal dorsal horn are also NMDA receptor antagonist sensitive.[6,19]

Synaptic LTP in pain pathways is a cellular model of inflammatory and postoperative pain.[3] It is, therefore, of clinical interest to prevent LTP by the means of a clinically used drug such as the NMDA receptor antagonist S(+)-ketamine. This is the concept of pre-emptive analgesia,[20 21] which is an antinociceptive treatment given before, during, and after surgery in an attempt to prevent or reduce post-surgical hyperalgesia.[22] In numerous clinical studies low-doses of ketamine, so called 'subanaesthetic ketamine'[13] were used for the management of acute postoperative pain[23 24] and in the prevention of post-surgical hyperalgesia.[12]

In our study the i.v. application of low-dose S(+)-ketamine did not affect the maintenance of established LTP. This finding reflects the clinical situation where the use of NMDA receptor antagonists in the treatment of some forms of established chronic pain is unsatisfying.[25] Their adverse side effects limit the use of high dosages.[26] Although the evidence of ketamine for the treatment of chronic pain is moderate to weak, ketamine is successfully used in situations where standard analgesic options have failed.[25 27 28] Oral NMDA receptor antagonists are used as co-medication with opioids in the treatment of chronic pain.[27]

As shown in our previous study, the MOR agonist fentanyl dose dependently reduces C-fibre-evoked potentials.[5] Given at low doses fentanyl blocks LTP, whereas at high doses fentanyl fails to prevent LTP induction. This phenomenon may be explained by facilitated currents through NMDA receptor as a result of the activation of protein kinase C by high doses of opioids[29] and is discussed in detail elsewhere.[5] Here, a high dose of fentanyl was combined with a low-dose of S(+)-ketamine. At this low dose S(+)-ketamine did not affect C-fibre-evoked potentials but abolished the induction of LTP.

In the clinical situation the beneficial effect of the co-administration of ketamine to opioid analgesia is still under discussion, although there is clear evidence for the advantage of low-dose ketamine to standard practice opioid-analgesia in postoperative pain control.[12 13 30 31] The pre-emptive effect of low-dose ketamine seems to be dependent on the time and duration of administration perioperatively.[32] Whereas Stubhaug and colleagues[33] clearly showed reduction of central sensitization as a result of perioperative low-dose ketamine treatment, there was no statistically significant reduction in the incidence of phantom pain 6 months after amputation in the ketamine group.[34]

In addition to the proposed reduction of postoperative pain and the prevention of central sensitization co-administration of MOR agonists and NMDA receptor antagonists may have another beneficial effect: MOR agonists lead to tolerance, which is thought to occur over a period of days or weeks with repeated administration of the drug[35] through NMDA receptor-dependent mechanisms.[15 36] Acute tolerance may even occur after a single opioid administration.[16] Animal[8 9 14] and clinical[15] studies demonstrate that acute opioid tolerance can be prevented by co-administration of NMDA receptor antagonists.[8 15]

Thus, the presently described results and previous studies suggest combining a low-dose of S(+)-ketamine with high doses of MOP agonists to achieve both sufficient analgesia and prevention of central sensitization.

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