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Effects of the NMDA-receptor antagonist ketamine on perceptual correlates of long-term potentiation within the nociceptive system

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Abstract

We recently reported perceptual correlates of long-term potentiation (LTP) of synaptic strength within the nociceptive system demonstrating the functional relevance of LTP for human pain sensation. LTP is generally classified as NMDA-receptor dependent or independent. Here we show that low doses of the NMDA-receptor antagonist ketamine (0.25 mg/kg) prevented the long-term increase in perceived pain to electrical test stimuli, which was induced by high-frequency electrical stimulation (HFS) of nociceptive afferents. Whereas in a control experiment HFS led to a stable increase in perceived pain by 51% for the entire observation period of 1 h HFS given 4 min after i.v. ketamine was ineffective. In contrast, HFS induced a two-fold increase of pinprick-evoked pain surrounding the HFS site (secondary neurogenic hyperalgesia) in both experiments. Pain evoked by light tactile stimuli (allodynia) was also unaffected by ketamine. These data support the concept that homotopic hyperalgesia to electrical stimulation of the conditioned pathway is a perceptual correlate of NMDA-receptor sensitive homosynaptic LTP in the nociceptive system, e.g. in the spinal cord. Although secondary neurogenic hyperalgesia and allodynia are induced by the same HFS protocol, they involve additional NMDA-receptor insensitive mechanisms of heterosynaptic facilitation.

Keywords: Central sensitization; Pain; Hyperalgesia; Spinal cord; Neuropathic pain; Pain memory

1. Introduction

Long-lasting enhancement of synaptic strength (long-term potentiation, LTP) is an ubiquitous phenomenon of synaptic plasticity throughout the central nervous system and is believed to play a major role in learning and memory formation (Bliss and Collingridge, 1993). Within the nociceptive system, LTP has been demonstrated at the first synaptic relay in the spinal cord, both in slice preparations in vitro and in animal experiments in vivo (Randic et al., 1993; Liu and Sandkühler, 1995; Ikeda et al., 2003). High-frequency electrical stimulation of primary nociceptive afferents leads to LTP of excitatory synaptic transmission in the spinal cord resulting in an enhanced responsiveness of spinal projection neurons in the spinal dorsal horn (Liu and Sandkühler, 1997; Ikeda et al., 2003). The perceptual consequence of this use-dependent increase in the excitability of central nociceptive neurons is neurogenic hyperalgesia, i.e. an increase in pain sensitivity caused by the nociceptive input to the spinal cord rather than by tissue damage. If this sensitized state persists, it may contribute to chronic pain (Cervero and Laird, 1991; Treede and Magerl, 1995; Sandkühler, 2000).

However, it has been difficult to find a direct link between neurogenic hyperalgesia and synaptic LTP in humans, because

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the conditioning stimulus protocols used were considerably different (Treede and Magerl, 1995). We have recently reported two distinct perceptual correlates of LTP in human pain pathways after high-frequency electrical stimulation (HFS) of peptidergic primary afferents. (1) An increase of perceived pain when electrical test stimuli were applied to the conditioned pathway (homotopic hyperalgesia); this finding resembles homosynaptic LTP in the spinal cord. (2) An increase of perceived pain when mechanical test stimuli were applied close by but outside the conditioned pathway (heterotopic hyperalgesia); this finding resembles secondary neurogenic hyperalgesia surrounding an injury site and has been suggested to be a perceptual correlate of heterosynaptic nociceptive LTP (Klein et al., 2004). Both phenomena were induced by the same conditioning HFS stimulus, but it remained unclear, if they were caused by similar cellular mechanisms.

In other parts of the central nervous system, complex interactions of different LTP types have been described, including strictly homosynaptic events as well as long-lasting heterosynaptic facilitations (Bailey et al., 2000). One fundamental distinction is between NMDA-receptor dependent and independent types of LTP (Bliss and Collingridge, 1993). The LTP induced in spinal cord slices by HFS belongs to the NMDA-receptor dependent type (Ji et al., 2003), and can be prevented by low doses of NMDA-receptor antagonists (Liu and Sandkühler, 1995; Ikeda et al., 2003; Benrath et al., 2005). Thus, to investigate the relationship of both homotopic and heterotopic hyperalgesia to nociceptive LTP in the spinal cord, we tested the ability of the non-competitive, low affinity NMDA-receptor antagonist ketamine to prevent the induction of either or both perceptual correlates of nociceptive LTP. Ketamine has been shown to be effective in several animal models of spinal plasticity (e.g. Laird et al., 1995; Chizh et al., 1997; Benrath et al., 2005).

2. Methods

2.1. Subjects

Experiments were performed in eight healthy subjects (four females and four males, mean age 25 ± 3 years, range 22–31 years), who participated in two sessions (with and without ketamine). Each subject was familiarized beforehand with the experimental procedures and gave written, informed consent. The study was approved by the local ethics committee.

2.2. Conditioning stimuli

Conditioning electrical pulse trains were applied by simultaneous stimulation through a circular array (diameter 6 mm) of 10 punctate electrodes (0.25 mm diameter each) mounted in a small circular plastic frame and attached to the skin by double-adhesive tape on the forearm 5 cm distal to the cubital fossa (Fig. 1A). This electrode configuration favours activation of superficial nociceptive Aδ- and C-fiber afferents already at low stimulus intensities due to high current density in the epidermis. Cathodal electrical stimuli were applied via a constant current stimulator (model DS7H, Digitimer Ltd., Welwyn Garden City, England), and a large surface electrode on the ipsilateral upper arm served as the anode.

Conditioning stimulation consisted high-frequency stimulation (HFS) trains of 100 Hz for 1 s (pulse width 2 ms, stimulus intensity 2 mA), repeated five times at 10 s intervals. This protocol has previously been shown to induce LTP at primary afferent synapses with rat spinal cord neurons (Randic et al., 1993; Liu and Sandkühler, 1997; Svendsen et al., 1998) and corresponding perceptual correlates in the human nociceptive system (Klein et al., 2004). Another circular array of punctate electrodes on the contralateral forearm served as the unconditioned control site, which received single electrical test stimuli but no HFS.

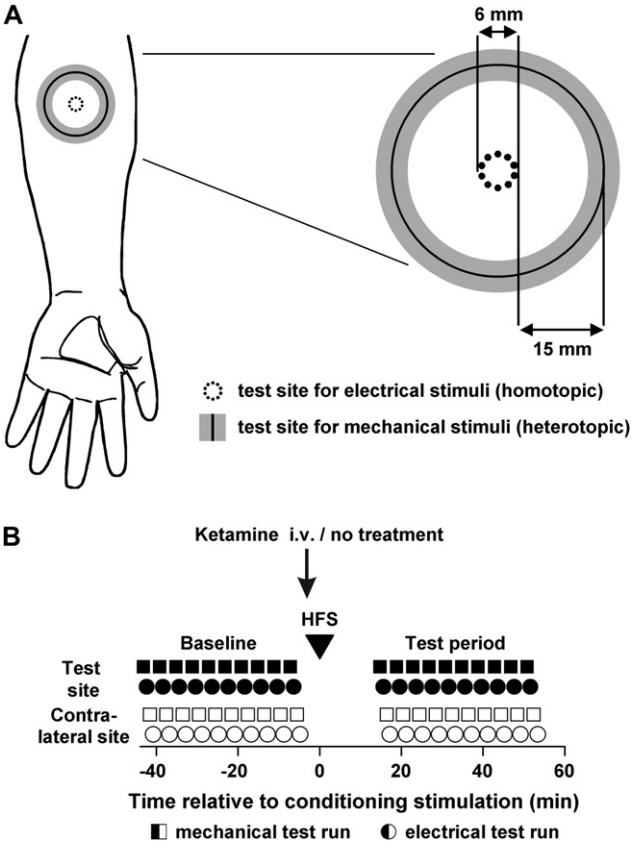

Fig. 1. Experimental protocol for testing the effects of ketamine on LTP of human pain perception. (A) Conditioning electrical HFS was applied to the proximal volar forearm via a circular array of punctate electrodes. Homotopic effect of HFS on the conditioned pathway was tested by pain ratings to single pulses through the conditioning electrode. Heterotopic effects outside of the conditioned pathway were tested by pain ratings to mechanical stimuli at a mean distance of 15 ± 5 mm from the electrode array. (B) Testing of mechanical sensitivity consisted of stimulus-response functions for pricking pain with punctate probes and soft stroking. Tests were arranged in runs comprising all 10 mechanical stimuli in a randomized order (black and white squares) followed by three electrical pulses (black and white circles) with 5–10 s interstimulus intervals. Runs were alternated between the conditioned skin site and the contralateral control site for 40 min before and up to 55 min after HFS.

2.3. Study design

The trial was designed as an open-label cross over study. Blinding was not possible because of the psychomimetic side effects of ketamine (sedation, dizziness), which are obvious to both subject and experimenter. Moreover, all drugs, which potentially might serve as an active placebo such as benzodiazepines or dopamine-receptor antagonists, have been shown to interfere with synaptic plasticity in the CNS (e.g. Ziemann et al., 1997; Yang et al., 2005; Hu et al., 2006). Subjects were, however, naïve with respect to the scientific framework and hypothesis tested. Electrical and mechanical test stimuli were applied in runs alternating between the conditioned skin site and a contralateral unconditioned control site during a period of 60 min before (baseline)

and 55 min after conditioning electrical stimulation (Fig. 1B). Low-dose ketamine (0.25 mg/kg i.v. Ketanest®, Parke–Davis, Karlsruhe, Germany) was slowly injected over 1 min immediately after the baseline period. The dose of 0.25 mg/kg ketamine was the maximum dose considered subanaesthetic. Conditioning stimulation was applied 4 min after ketamine injection because the central nervous system effects of ketamine (increase in EEG theta power, decrease in alpha power) are maximal at this time (Kochs et al., 1996). Electrical and mechanical testings were resumed 15 min after conditioning stimulation to await the decay of the psychomimetic effect of ketamine as tested by a mental arithmetic task. Each subject underwent a separate control experiment without ketamine with the same stimulation and test parameters as used in the ketamine experiment separated by at least 7 days. The order of the two experiments and the site of conditioning stimulation (right vs. left forearm) were balanced across subjects.

2.4. Test stimuli

Pain perception was tested by two different approaches:

- single electrical test pulses for testing modulation of human pain perception at the site of conditioning stimulation (test for homotopic hyperalgesia). Stimulus intensity was adjusted at 10× individual detection threshold (T) determined by single electrical pulses in the first experiment to adjust potential interindividual differences in sensitivity to electrical stimuli. In the second experiment, we used the same stimulus intensity (1.54 ± 1.01 mA, mean ± SD) to obtain similar painfulness to electrical test stimuli at baseline over the experiments.
- two sets of mechanical test stimuli for testing modulation of human pain perception adjacent to the site of conditioning stimulation (test for heterotopic hyperalgesia). One set consisted of seven punctate probes (forces of 8, 16, 32, 64, 128, 256 and 512 mN), which were cylindrical stainless steel wires (0.25 mm tip diameter) mounted on plastic rods that moved freely within a wider hand-held tube. They preferentially activate nociceptive primary afferents (Greenspan and McGillis, 1994) and were sensitive to detect modulation of neurogenic secondary hyperalgesia in humans (Magerl et al., 2001).

  Pain to light touch (dynamic mechanical allodynia) was tested with a second set of mechanical stimuli consisting of a short stroke (1 cm) of a soft cotton wisp (3 mN), a cotton-tipped applicator (100 mN) fixed alongside a flexible strip of plastic and a soft make-up brush (200–400 mN). These three stimuli only activate low-threshold mechanoreceptors (Leem et al., 1993) and are not painful in normal skin. They were applied in balanced order within a circular area surrounding the electrode array at 15 ± 2.5 mm distance (Fig. 1A and B).

2.5. Pain ratings

Subjects rated the magnitude of pain to mechanical and electrical test stimuli as well as to conditioning stimulation on a numerical rating scale (NRS) ranging from 0 (non-painful) to 100 (most intense pain imaginable).

2.6. Data evaluation and statistics

Ratings were transformed into decadic logarithmic values in order to get a normal distribution. To avoid loss of zero-values, a small constant (0.1) was added to all ratings (Magerl et al., 1998; Magerl et al., 2001). Except for touch-evoked pain (absent at baseline), ratings were normalized to baseline by building the difference of log-transformed pain ratings obtained before (baseline) and after conditioning HFS. This procedure is equivalent to building the ratio of original pain ratings, but avoids the skewed non-normal distribution of ratio data. Hyperalgesia to electrical and pinprick stimuli was quantified as the difference of log-transformed normalized pain ratings between the test and the contralateral sites. In the following, we referred to this parameter as the "log ratio" between test and contralateral sites. The log ratios were included in a paired t-test to determine differences between treatments. Since no normal distribution of touch-evoked pain ratings was achieved, allodynia data were analyzed by non-parametrical Friedman analysis of variance (ANOVA). Data are expressed as mean ± SEM in logarithmic space. To improve comprehensibility the means of the log ratios were re-transformed into percentage changes. p-Values < 0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

Pain to electrical stimuli (6.0/100 vs. 6.2/100 NRS equivalent to 0.780 ± 0.147 vs. 0.790 ± 0.146 log units; $p = 0.79$) and mechanical stimuli (both 1.2/100 NRS equivalent to 0.074 ± 0.093 vs. 0.080 ± 0.083 log units; $p = 0.87$) did not differ significantly at baseline between the two experimental days suggesting similar conditions.

3.2. Conditioning process

In the control experiment, a single train of HFS evoked moderate pain (40/100 NRS equivalent to 1.600 ± 0.068 log units). Repetition of such trains (five times at 10 s intervals) resulted in a gradual increase in perceived pain by 67% (0.224 ± 0.056 log ratio between the 1st and 5th train). In the ketamine experiment, three of the eight subjects were not able to judge pain evoked by conditioning HFS due to sedation for more than 4 min. In the remaining five subjects, there was no significant difference in pain ratings between control and ketamine experiments, neither for the first HFS train ($p = 0.94$) nor for the increase with repetition of HFS trains ($p = 0.47$). Thus, we found no evidence for suppression of the perception of the conditioning nociceptive input by pre-treatment with ketamine.

3.3. Perceptual correlates of LTP at the site of conditioning stimulation (homotopic hyperalgesia)

In the control experiment, HFS led to a significant increase of normalized pain ratings evoked by single electrical test stimuli by 51% (0.180 ± 0.055 log ratio, $p < 0.05$), which lasted for the entire observation period of 1 h (Fig. 2A). In the ketamine experiment, HFS was ineffective (+9%/0.039 ± 0.037 log ratio, n.s.). Thus, pre-treatment with ketamine significantly reduced the homotopic effects of HFS by 82% ($p < 0.05$, Fig. 2B).

3.4. Perceptual correlates of LTP adjacent to the site of conditioning stimulation (heterotopic hyperalgesia)

In the control experiment, HFS led to a significant increase in pain evoked by pinprick stimuli adjacent to the conditioning electrode (+206%/0.314 ± 0.057 log ratio, $p < 0.001$, secondary hyperalgesia) that persisted throughout the observation period (Fig. 3A). In the ketamine experiment, HFS also induced a significant secondary hyperalgesia (+229%/0.359 ± 0.103 log ratio, $p < 0.05$). The stimulus-response function for pinpricks was approximately linear in log–log coordinates in

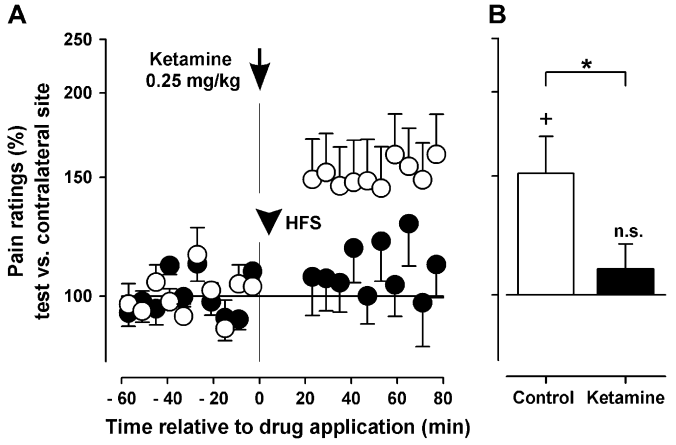

Fig. 2. Effect of ketamine on pain to homotopic electrical test stimuli. (A) The HFS-induced significant increase of electrically-evoked pain in the control experiment (open circles) was abolished by pre-treatment with 0.25 mg/kg ketamine 4 min before conditioning HFS stimulation (filled circles). Each circle represents the log ratio between test and control sites of pain ratings to electrical test stimuli averaged over a 6-min time window. (B) Electrically-evoked pain averaged over 60 min after HFS showing a 82% reduction in homotopic hyperalgesia to electrically-evoked pain compared to the control experiment. Mean values ± SEM across eight subjects. $^{*}p < 0.05$ (vs. ketamine experiment); $+\ p < 0.05$ (vs. contralateral site).

normal skin and did not differ across the two experiments (Fig. 3C). Following conditioning HFS there was a parallel upward shift of this function that was undistinguishable between the control experiment and the ketamine experiment. Thus, pre-treatment with ketamine did not prevent the development of secondary neurogenic hyperalgesia (Fig. 3B).

HFS also induced a significant pain to light touch (allodynia) in the control experiment (Fig. 4A, test vs. contralateral site; $p < 0.05$). Ketamine did not prevent the development of allodynia (-0.761 ± 0.153 vs. -0.800 ± 0.091 log NRS, $n = 8$; Fig. 4B). The magnitude of allodynia was independent of the test stimulus intensities (Fig. 4C).

4. Discussion

This study has shown that low doses of the NMDA-receptor antagonist ketamine prevented the enhanced pain perception following high-frequency electrical stimulation of nociceptive afferents when pain perception was tested with the same electrical stimuli that activated the conditioned pathway (homotopic hyperalgesia). In contrast, the induction of enhanced pain perception to pinpricks and light tactile stimuli in an area adjacent to the conditioned skin site (heterotopic hyperalgesia) was unaffected. These findings suggest that the facilitation of the conditioned pathway resembles the NMDA-sensitive homosynaptic type of LTP in the spinal cord reported in animal experiments (Randic et al., 1993; Ikeda et al., 2003) and that the spread of facilitation to previously unstimulated adjacent (heterosynaptic) inputs involves other NMDA-receptor insensitive mechanisms.

4.1. Homotopic hyperalgesia and NMDA-receptor sensitive homosynaptic LTP

Five trains of conditioning HFS (100 Hz for 1 s) of nociceptive cutaneous afferents were sufficient to induce a long-term increase of pain evoked by single electrical test stimuli (undiminished for 1 h), confirming our previous report (Klein et al., 2004). Since both, conditioning HFS and electrical test stimuli were given through the same electrode, this type of hyperalgesia is as close as possible to a model of homosynaptic LTP in human subjects. We call this phenomenon homotopic hyperalgesia. LTP induced by the same HFS protocol in spinal cord slices belongs to the NMDA-receptor sensitive type of LTP (Liu and Sandkühler, 1995; Ikeda et al., 2003). The nearly complete prevention of homotopic hyperalgesia by pre-treatment with low-dose ketamine indicates that this phenomenon is NMDA-receptor sensitive, may be even at lower doses.

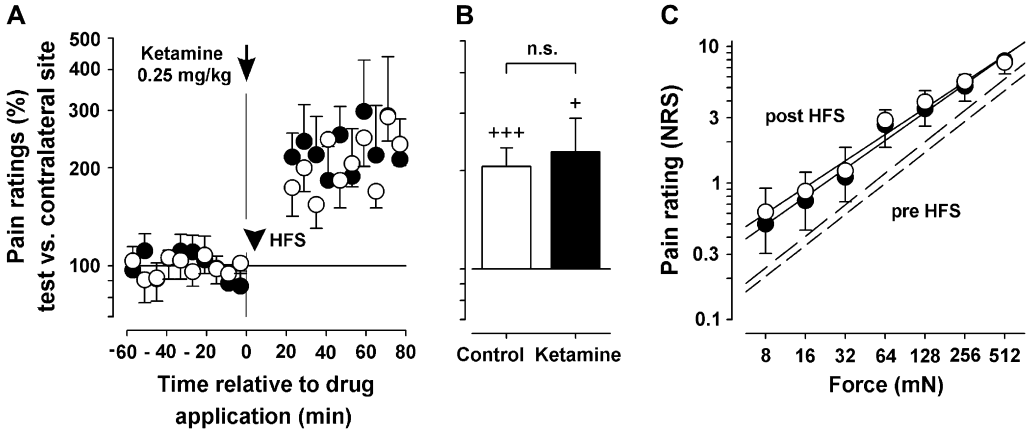

Fig. 3. Effect of ketamine on pain to heterotopic pinprick stimuli. (A) The HFS-induced significant increase of pinprick-evoked pain adjacent to the conditioned skin site (secondary hyperalgesia) was observed both in the control experiment (open circles) and in the ketamine experiment (filled circles). Each circle represents the log ratio between test and control site of pain ratings to pinprick averaged over a 6-min time window (i.e. the mean over one stimulus-response function consisting of pain ratings to seven stimulus intensities). (B) Secondary hyperalgesia averaged over 60 min after HFS was not prevented by ketamine pre-treatment. Ratings were normalized to the baseline values. (C) Stimulus-response functions for pinprick-evoked pain at baseline (dashed linear regression lines, values omitted for clarity) and after conditioning HFS (solid lines; control experiment: open circles, ketamine experiment: filled circles). Each circle represents pain ratings to one stimulus intensity averaged over the 60 min observation period. Mean value ± SEM across eight subjects. $+\ p < 0.05$, $+++\ p < 0.001$ (vs. contralateral site).

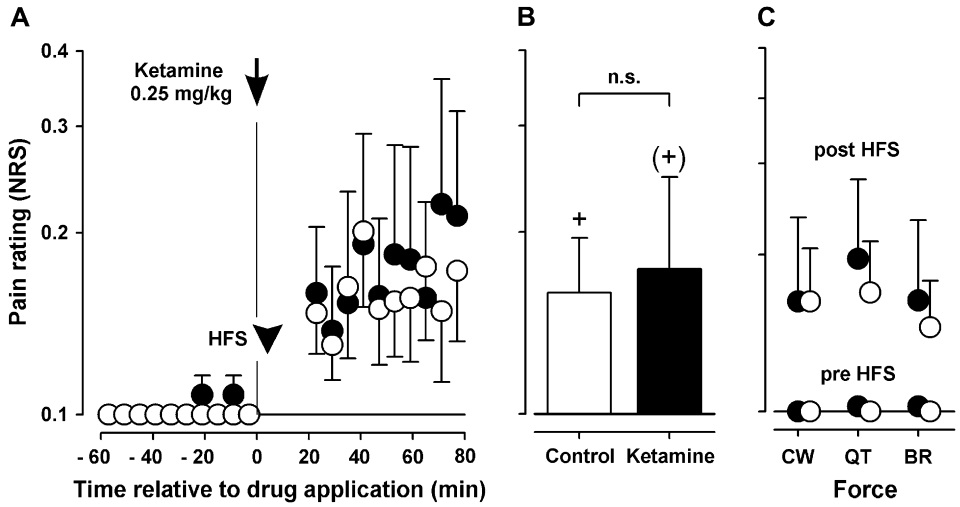

Fig. 4. Effect of ketamine on pain to heterotopic light tactile stimuli. (A) HFS induced significant pain to light tactile stimuli (allodynia) adjacent to the conditioned skin site, both in the control experiment (open circles) and in the ketamine experiment (filled circles). Each circle represents the average pain ratings across all three stimulus intensities over a 6-min time window. (B) Allodynia at the test site averaged over the 60 min after HFS was not reduced by pre-treatment with ketamine. (C) Stimulus-response functions for light tactile stimuli adjacent to the HFS site. Each circle represents average pain ratings to one stimulus intensity over a 60 min time window. CW: cotton wisp 3 mN, QT: cotton-tipped applicator 100 mN, BR: make-up brush 400 mN. Mean value ± SEM across eight subjects. (+) $p = 0.08$, + $p < 0.05$ (vs. contralateral site).

This finding supports the concept that homotopic hyperalgesia is a perceptual correlate of homosynaptic LTP in the human nociceptive system (cf. Willis, 2002; Ji et al., 2003; Klein et al., 2004). Although NMDA-receptor sensitive plasticity at supraspinal sites may contribute to homotopic hyperalgesia (e.g. in the brainstem, Terayama et al., 2000), the known mechanisms of plasticity in the spinal cord are sufficient to explain the observed findings, even with respect to magnitude and duration (Randic et al., 1993).

In addition to the non-competitive blockade of NMDA-receptors, ketamine can act on non-NMDA type glutamate receptors, on nicotinic and muscarinic acetylcholine-receptors, on 5-HT_3-receptors, μ-opiate receptors as well as Na^+- and L-type Ca^{2+}-channels (Hirota and Lambert, 1996; Kohrs and Durieux, 1998). Several of these receptors also play a role in the nociceptive system. In contrast to memantine and other open channel NMDA-receptor blockers, which almost equipotently block 5-HT_3- and NMDA-receptors, the affinity of ketamine to 5-HT_3-receptors (Rammes et al., 2001) as well as μ-receptors (Kohrs and Durieux, 1998) is much lower than its affinity to the NMDA-receptor. Hence, the dosage given in this study is considered specific for NMDA-receptors.

4.2. Heterotopic hyperalgesia and NMDA-receptor insensitive heterosynaptic facilitation

In line with our previous study (Klein et al., 2004), the HFS protocol also induced a long-term increase of pain to pinpricks and light touch adjacent to the conditioning electrode (secondary hyperalgesia and allodynia). These heterotopic types of hyperalgesia depend on heterosynaptic interaction of two input pathways: whereas the conditioning input is carried by capsaicin-sensitive C-fibers, the facilitated input is carried by capsaicin-insensitive A-fibers (Aδ high-threshold mechanoreceptors for secondary hyperalgesia and Aβ low-threshold mechanoreceptors for allodynia; Magerl et al., 2001). Thus, we suggested that they are perceptual correlates of heterosynaptic LTP (Klein et al., 2004).

Low-dose ketamine abolished homotopic hyperalgesia, but did not affect heterotopic hyperalgesia. This differential sensitivity to NMDA-receptor blockade adds to the list of differences between the two phenomena. Whereas pain to homotopic electrical test stimuli was increased by 40–50% following the HFS protocol, the pain to heterotopic pinprick stimuli increased to about 200% and more (Klein et al., 2004 and this study). Moreover, heterotopic hyperalgesia can also be induced by low-frequency stimulation (5 Hz: Koppert et al., 2001; 1 Hz: Klein et al., 2004), which does not lead to facilitation of pain to homotopic test stimuli but to its long-term depression (Klein et al., 2004).

Because ketamine has a relatively low affinity to the NMDA-receptor and there may be a voltage-dependent relief of blockade by ketamine at higher synaptic concentrations of glutamate (Chizh et al., 1997; Parsons, 2001) we cannot fully exclude a contribution of NMDA-receptors to the development of secondary hyperalgesia. It therefore may be that a higher dose of ketamine providing a full block of NMDA-receptors could interfere with the induction of secondary hyperalgesia. Indeed several previous studies in human experimental models of secondary hyperalgesia have suggested the prevention of secondary hyperalgesia by ketamine when given prior to the conditioning stimulus (Park et al., 1995; Ilkjaer et al., 1996; Wallace et al., 2002). However, these studies used the reduction in sizes of hyperalgesic areas as the outcome parameter, which in principle can be achieved by a general reduction of

nociceptive processing (analgesia), which should affect pain perception in both sensitized and non-sensitized pain states or by prevention of neurogenic hyperalgesia (i.e. prevention of sensitization, anti-hyperalgesia) or both. Thus analgesic and specific anti-hyperalgesic effects are not clearly discriminated and may have been confounded in these studies. Notably, ketamine given *after* induction of secondary hyperalgesia reduced the area of secondary hyperalgesia only during treatment reflecting the pharmacokinetic properties of ketamine (Park et al., 1995; Mikkelsen et al., 1999; Koppert et al., 2001; Schulte et al., 2004). These findings suggest that the reduction of the area of secondary hyperalgesia may have predominantly depended on a general analgesic rather than a specific anti-hyperalgesic effect. In contrast to these previous studies, we used a normalization procedure (log ratio between conditioned skin site and an unconditioned contralateral site) to quantify hyperalgesia, which eliminates a confounding general analgesic effect of ketamine (cf. Kochs et al., 1996).

Our findings also seem to be at variance with Stubhaug et al. (1997), who reported prevention of postoperative secondary hyperalgesia by perioperative ketamine. In this study, an analgesic effect of ketamine can be excluded at the time of assessment because of the long follow-up (4 days after the end of the ketamine infusion). However, in contrast to our study, the dosage used was 25 times higher (6.26 mg/kg) and action on other receptor types or more complete NMDA-receptor blockade, as discussed above, may have become more relevant. For example, activation of μ-opiate receptors by DAMGO prevented the induction of spinal LTP presumably by decreasing the release of glutamate from presynaptic terminals and thus counteracting the conditioning nociceptive input (Terman et al., 2001). In addition, 5-HT_3-receptors are also involved in the initiation of use-dependent increase in the excitability of central nociceptive neurons (Suzuki et al., 2002; Zeitz et al., 2002). Another explanation may be that heterosynaptic facilitation is much more resistant to NMDA-receptor blockade and that more NMDA-receptors have to be blocked to prevent heterosynaptic facilitation when compared to homosynaptic processes.

Our data, however, clearly show that secondary hyperalgesia and allodynia do not develop secondary to changes within the conditioned pathway. Instead, there must be parallel and at least partly NMDA-receptor insensitive mechanisms how HFS induces both phenomena. These mechanisms are still poorly understood. Nociceptive neuropeptides co-released with glutamate may serve as diffusible factors that reach extrasynaptic receptors and remote neurons. In animal experiments, substance P (Liu and Sandkühler, 1997; Laird et al., 2001), calcitonin-gene related peptide (CGRP; Sun et al., 2004) and brain-derived neurotrophic factor (BDNF; Malcangio and Lessmann, 2003) are involved in the induction of nociceptive LTP in spinal cord neurons and are potential candidates when heterosynaptic facilitation of synaptic transmission encompasses adjacent neurons. The activation of those peptidergic afferents by electrical HFS has been verified in our previous study by Laser Doppler imaging (Klein et al., 2004).

5. Conclusions

Conditioning HFS of nociceptive primary afferents induces homotopic hyperalgesia, a perceptual correlate of nociceptive, NMDA-receptor sensitive LTP and heterotopic hyperalgesia, which involves other NMDA-receptor insensitive mechanisms of heterosynaptic facilitation. Heterosynaptic types of facilitation are more robust and can be more easily induced than homosynaptic types of facilitation, and therefore play a prominent role in the dorsal horn. The two manifestations of heterotopic hyperalgesia, secondary hyperalgesia and allodynia, are highly conserved features of injury-related behaviour (Walters, 1994) and therefore redundant mechanisms with high safety factors may have emerged during evolution.

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