Section 1

Psychophysical studies

Chapter 2

Effect of Ketamine on Endogenous Pain Modulation in Healthy Volunteers

M. Niesters, A. Dahan, M. Swartjes, I.M. Noppers,
R.B. Fillingim, L.P.H.J. Aarts, E.Y. Sarton
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Introduction

The number of patients affected by chronic pain is growing. Various mechanisms may underlie the process of chronification of pain. Important mechanisms include NMDAR activation and up-regulation and inflammatory responses in the spinal cord;[1-3] both cause central sensitization and are related to repeated afferent excitation.[1] Another mechanism involved in pain chronification is dysfunction of inhibitory pathways or a shift in the balance between pain inhibition and pain facilitation. In the last decades the role of central pain modulation in the control of nociception been investigated intensively.[4,5] Inhibitory and facilitatory descending pathways, originating at higher central nervous system sites, such as the cerebral cortex, nucleus raphe magnus, periaquaductal grey (PAG), locus coeruleus and rostraventral medulla (RVM), modulate activity of dorsal horn nociceptive neurons.[4,6] Alterations in endogenous pain modulation have been observed in chronic pain diseases like irritable bowel syndrome, fibromyalgia, chronic tension headache, temporomandibular disorder and complex regional pain syndrome type 1 (CRPS-1).[5,7-9] Seifert et al. showed a shift from inhibition towards facilitation of nociceptive input in CRPS patients.[9]

Recent studies indicate that treatment of chronic pain patients with the NMDAR antagonist ketamine has a prolonged beneficial effect on spontaneous pain reporting and is effective when used in combinations with opioids in the treatment of acute postoperative pain and cancer pain management.[10-15] Ketamine may produce prolonged analgesia through multiple mechanisms. Most important and most frequently studied is its desensitizing effect on sensitized nociceptive neurons in the spinal cord by blocking the NMDAR.[1] As a result, ketamine blocks the enhanced signal transmission in the pain circuitry. The effect of ketamine on endogenous inhibitory pain control remains unknown. Since ketamine ameliorates chronic pain (such as occurs in CRPS patients) an effect on endogenous pain modulation is plausible. In the current study we address this issue by examining the effect of low-dose ketamine (40 mg/h) on two expressions of endogenous control of pain: Diffuse Noxious Inhibitory Controls (DNIC) and Offset Analgesia (OA).[5,7,16-20]

DNIC has been investigated in both animals and humans, showing central inhibition of a focal pain stimulus by administering a noxious stimulus at a remote area, thereby reducing the perception of the focal pain stimulus.[5,21] OA has recently been proposed as a second endogenous analgesia mechanism. This mechanism demonstrates profound analgesia during slight incremental decreases of a noxious heat stimulus, which is more rapid than would be predicted by the rate of temperature decrease.[16,19,20] Recent studies indicate that OA coincides with activation of the PAG, RVM and locus coeruleus, areas with substantial roles in descending inhibition of pain.[19]

The main aim of the present study is to explore whether ketamine interacts with pathways involved in endogenous pain modulation and whether it enhances

inhibitory control. To that end we studied the effect of low-dose ketamine on DNIC and OA in healthy volunteers. We hypothesize that ketamine enhances both DNIC and OA and by that contributes to the prolonged analgesic effect of ketamine in chronic pain patients.

Methods

Subjects
Ten healthy volunteers (4 men/6 women) were recruited for participation in the study, after approval of the protocol by the local medical ethics committee (Commissie Medische Ethiek LUMC). Informed written consent was obtained according to the Declaration of Helsinki from all participants. The study was registered in the Dutch trial register (www.trialregister.nl) under number NTR2005. Before participation all subjects received a physical examination and their medical history was taken. Exclusion criteria were: age < 18 years or > 75; presence or history of a medical disease such as renal, liver, cardiac, vascular (incl. hypertension) or infectious disease; presence or history of a neurological and psychiatric disease (*e.g.* increased cranial pressure, epilepsy, psychosis); glaucoma; pregnancy; obesity (BMI > 30) and any use of pain medication.

Pain assessment, DNIC and offset analgesia
Heat pain was induced using the Pathway Neurosensory Analyzer (Medoc Ltd, Ramat Yishai, Israel). Using a 3 x 3 cm thermal probe, the skin on the volar side of the arm was stimulated with a preset and computer controlled temperature scheme. Baseline temperature was set at 32 °C. During heat pain stimulation, subjects quantified the pain intensity of the noxious stimulus using the slider on an electrical potentiometer connected to a computer, allowing continuous monitoring of the Visual Analogue Scale (eVAS), that ranged from 0 (no pain) to 100 (worst pain imaginable). To overcome adaptation, the volar side of the arm was divided into three zones. The thermode was moved from zone to zone between stimuli. Prior to the study, the test temperature was determined by applying a series of heat stimuli, ranging from 42 °C to 49 °C with increments of 1 °C; each stimulus was applied for 10 seconds, with 5-10 min intervals between stimuli. The temperature evoking an eVAS of at least 50 mm was used during the remainder of the study (this is the test temperature).

Cold pain was induced by cold water immersion of the subject's foot and lower leg into a reservoir with cold water. Water with a predetermined temperature was produced by a rapid water-cooling system (IcyDip, IcySolutions BV, Delft, The Netherlands). The cold water temperature could be set at any value ranging from 6 °C to 18 °C. Prior to the study various water temperatures were tested. The temperature that produced an eVAS of at least 30 mm was used in the remainder of the study. After each exposure to cold water, the subject's foot was warmed to room temperature using the warm water reservoir of the IcyDip.

DNIC was determined according to the protocol described by King et al.[7] In short, for the experimental stimulus focal heat pain was applied to the subject's volar side of the left arm as follows: the temperature gradually increased from baseline (32 °C) to the test temperature (at 1.5 °C/s) and was held constant for 30 seconds. Next, the temperature decreased rapidly (at 6 °C/s) to baseline. Each heat stimulus was repeated for a total of three times, after which the same stimulus was applied for another three times but now in combination with the conditioned stimulus (immersion of foot and lower leg in cold water). The conditioned stimulus was applied 25 seconds before the start of the experimental stimulus and ending simultaneously with the end of the experimental stimulus. Between each heat stimulus there was a 3 minute rest period. During the heat stimulation the subjects rated pain intensity using the eVAS slider.

Offset analgesia was determined as described by Yelle et al.[20] In short, a focal heat stimulus was applied to the subject's volar side of the arm. The thermode positioned on the arm was ramped (1.5 °C/s) from baseline temperature to the individual's test temperature. The test temperature was kept constant for 5 seconds after which it was raised by 1 °C for 5 seconds and next decreased by 1 °C to the test temperature and kept constant for 20 seconds. Next, the temperature quickly returned (6 °C/s) to baseline. Subjects rated the intensity of the heat stimulus using the eVAS slider. Offset analgesia was determined three times with a 3 minute rest period between tests.

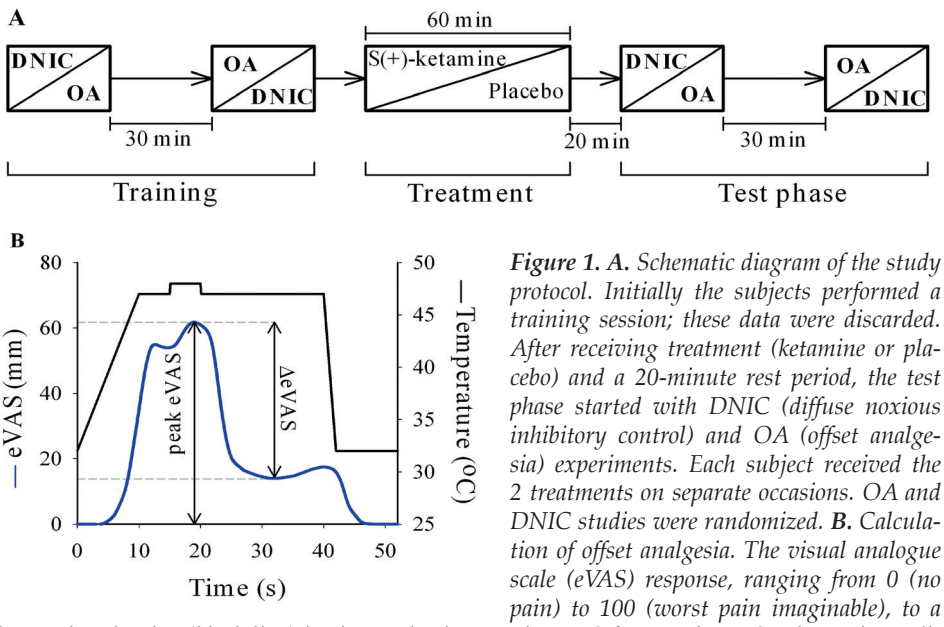

Figure 1. A. *Schematic diagram of the study protocol. Initially the subjects performed a training session; these data were discarded. After receiving treatment (ketamine or placebo) and a 20-minute rest period, the test phase started with DNIC (diffuse noxious inhibitory control) and OA (offset analgesia) experiments. Each subject received the 2 treatments on separate occasions. OA and DNIC studies were randomized.* ***B.*** *Calculation of offset analgesia. The visual analogue scale (eVAS) response, ranging from 0 (no pain) to 100 (worst pain imaginable), to a heat pain stimulus (black line) is given. The decrease in eVAS from peak eVAS value to its nadir following the 1 °C decrease of the heat pain stimulus (at t = 20 seconds) is calculated (ΔeVAS). To correct for the value of the peak eVAS, the ΔeVAS is divided by the peak eVAS giving the 'corrected' ΔeVAS or ΔeVAScc (= ΔeVAS/[peak eVAS]).*

Study design
The study had a single-blinded, cross-over design. Subjects were randomized for treatments (intravenous S(+)-ketamine (Ketanest-S, Pfizer BV, Capelle a/d IJssel, The Netherlands) or placebo (NaCl 0.9%)) and pain test order (offset analgesia or DNIC, experiment with and without conditioning stimulus). Randomization for studies with and without water immersion was performed to avoid a distraction or learning effect.[22] There were at least two weeks in between the placebo and ketamine sessions. On both experiment days, individual test temperatures for the experimental and conditioned stimulus were determined first. Next, the subjects were trained by performing DNIC and offset analgesia studies, as described above. Subsequently, the subjects received a 1-h infusion of either S(+)-ketamine (40 mg per 70 kg) or placebo. After a 20-minute wash-out period the test phase began with studies to determine DNIC and offset analgesia after placebo or ketamine treatment (with a 30-minute interval between studies). See also figure 1A.

Side effects
During ketamine and placebo treatment the occurrence of nausea and vomiting was recorded (yes/no), and drug high and drowsiness were scored using an 11-point numerical rating scale ranging from 0 (= no effect) to 10 (= most severe effect).

Data and statistical analyses
The DNIC and offset analgesia data collected during training were discarded. The eVAS data were averaged over 1-second periods. To quantify the DNIC data, the area-under-the-curve (AUC) of each eVAS response curve was calculated. A linear mixed model was used to compare the AUCs without and with conditioning stimulus after ketamine and placebo infusions. Group differences were tested by a chi-square test. To quantify offset analgesia the decrease in eVAS from peak eVAS value to the eVAS nadir following the 1 °C decrease of the test stimulus was measured (ΔeVAS; Fig. 1B) corrected for the value of the peak eVAS (ΔeVASc = ΔeVAS/[peak eVAS]). ΔeVASc values observed after ketamine and placebo treatment were compared using a linear mixed model. p-values < 0.05 were considered significant. Data are presented as mean (SEM) unless otherwise stated.

Results

Baseline values
All subjects completed the protocol without unexpected or major side effects. Baseline subject characteristics are listed in table 1. Between treatment days no significant differences were observed in test temperatures of the conditioning and experimental stimuli. Mean testing temperatures were 46.1 ± 2.5 °C (mean ± SD) and 45.9 ± 2.9 °C for placebo and ketamine study days, respectively (t-test: p = 0.908). The corresponding mean baseline eVAS scores were 52.1 ± 9.8 mm (placebo) and 51.7 ± 12.9 mm (ketamine; p = 0.942). The temperatures of the con-

Table 1. *Subject characteristics*

Number of subjects (M/F)	10 (4/6)
Age (year)	24.1 ± 3.7
Weight (kg)	76.5 ± 13.8
Baseline heat temperature in placebo/ketamine studies (°C)	46.1 ± 2.5/45.9 ± 2.9 (ns)
Baseline water temperature in placebo/ketamine studies (°C)	10.3 ± 3.9/10.7 ± 3.8 (ns)

Values are mean ± SD; ns = not significantly different.

ditioning stimulus were 10.3 ± 3.9 °C (placebo) and 10.7 ± 3.8 °C (ketamine; p = 0.838) with mean baseline eVAS scores of 29.9 ± 16.7 mm (placebo) and 32.6 ± 20.6 mm (ketamine; p = 0.764). The baseline or training eVAS responses to the two heat stimuli paradigms, DNIC and OA obtained prior to placebo and ketamine treatment, are given in figure 2 (the DNIC response is given without conditioning stimulus). It shows that the baseline eVAS responses were similar for the two treatment sessions.

Ketamine-induced analgesia and side effects

Despite an average 1-hour interval between the end of the ketamine infusion and the eVAS responses, ketamine analgesia persisted: eVAS (obtained at identical temperatures) were significantly lower after ketamine treatment compared to placebo treatment by 10 to 12 mm ($p < 0.01$). In order to get an indication of the analgesic effect of ketamine, we plotted the first 13 seconds of the eVAS responses following ketamine and placebo treatment for the 2 heat stimuli paradigms in figure 3. We present only the initial part of the response in relation to

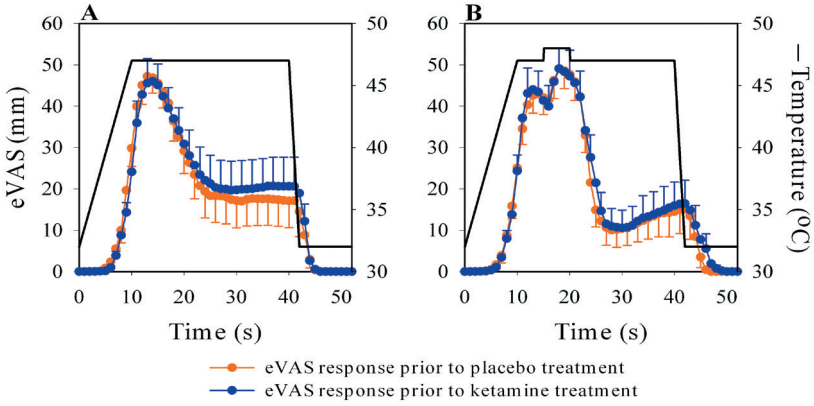

Figure 2. *Baseline eVAS (visual analogue scale ranging from 0 (no pain) to 100 (worst imaginable pain)) responses (obtained during training):* ***A.*** *responses obtained during the 30-second continuous heat stimulus and* ***B.*** *the varying heat stimulus used to induce offset analgesia. Orange circles are the eVAS response prior to placebo treatment; blue circles prior to ketamine treatment. Values are mean ± SEM. No differences in baseline responses were obtained between treatment sessions.*

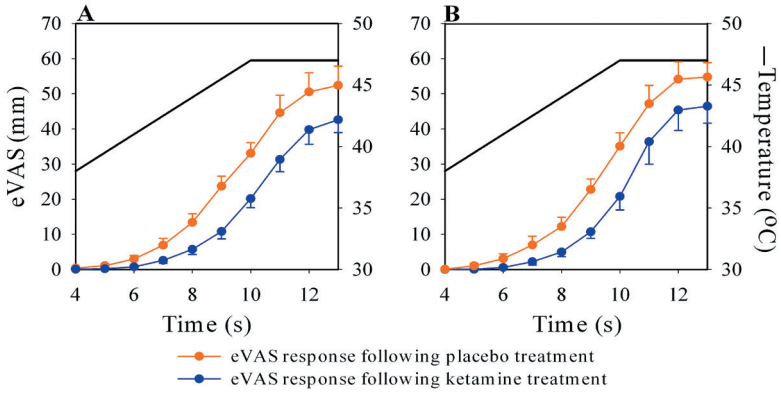

Figure 3. *Ketamine's analgesic effect. First 13 seconds of the eVAS (visual analogue scale ranging from 0 (no pain) to 100 (worst pain imaginable)) responses without conditioning stimulus after placebo (orange circles) and ketamine treatment (blue circles) for studies performed in the* ***A.*** *DNIC paradigm and* ***B.*** *offset analgesia paradigm. Ketamine produced a significant analgesic effect with a reduction in eVAS of 10-12 mm at t = 13 seconds.*

ketamine analgesia as it may be argued that other phenomena (*e.g.* adaptation, endogenous analgesic effects) influence the remainder of the response. Consequently, DNIC and OA eVAS responses (and their respective AUCs) in studies following ketamine treatment were smaller compared to responses obtained following placebo treatment. Ketamine produced nausea in six subjects and vomiting in three. Numerical rating scores for drug high were 6.0 ± 1.2 *versus* 1.2 ± 0.8 ($p < 0.05$) and for drowsiness 4.7 ± 0.8 *versus* 0.8 ± 0.6 ($p < 0.05$) during ketamine *versus* placebo treatment.

Diffuse noxious inhibitory control

eVAS responses (DNIC and OA) without conditioning stimulus were obtained 59 minutes (95% confidence interval 44 – 79 minutes) following the end of the ketamine or placebo infusion. eVAS responses (DNIC) with conditioning stimulus were obtained 56 minutes (41 – 76 minutes) following ketamine infusion. Mean DNIC responses are presented in figure 4. Heat pain stimulation for a period of 30 seconds gave an eVAS response with rapid temporal sensitization (0-10 seconds) followed by a phase of adaptation (10-30 seconds). After placebo and ketamine infusions, significant effects of the conditioning stimuli were observed ($p < 0.0001$). After placebo infusion significant inhibitory control (*i.e.* DNIC) was activated in all subjects. Experimental heat pain applied simultaneously with the conditioned stimulus resulted in eVAS values below those observed during testing just experimental heat pain (AUCs 764.3 ± 139.9 *versus* 1008.9 ± 178.2; $p < 0.001$). In contrast, after ketamine infusion, no DNIC was observed, but rather a significant facilitatory pain response occurred when heat pain was combined with the conditioning stimulus (AUCs 889.8 ± 201.5 *versus* 708.4 ± 155.9; $p < 0.01$).

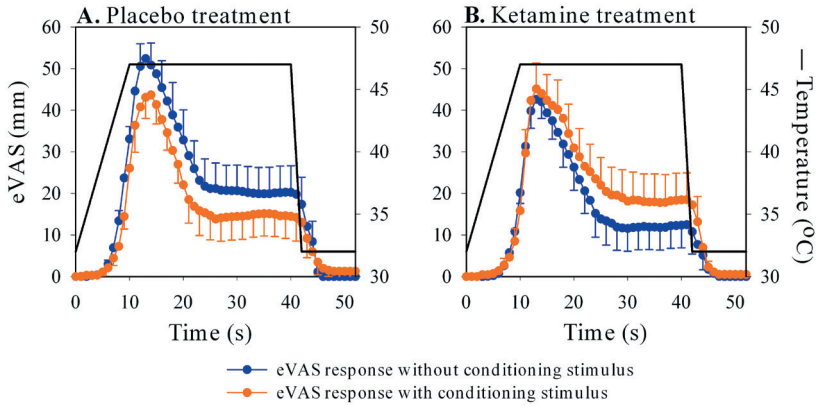

Figure 4. *Effect of* ***A.*** *placebo and* ***B.*** *ketamine treatment on endogenous pain modulation as determined by a diffuse noxious inhibitory control paradigm, that is, a heat pain stimulus (black line) applied without and with a conditioning stimulus (leg immersion in cold water). After placebo treatment the eVAS (visual analogue scale ranging from 0 (no pain) to 100 (worst pain imaginable)) response to experimental heat pain with the conditioning stimulus was significantly inhibited compared to the response without the conditioning stimulus ($p < 0.001$). After ketamine treatment the eVAS response to the noxious heat stimulus was increased when the conditioning stimulus was applied ($p < 0.01$). The data are the population mean of the subjects' mean eVAS values (SEM).*

In figure 5 the individual magnitudes of the eVAS responses without conditioning stimulus *versus* responses with stimulus are presented in a scatter plot. It shows that while the mean AUC without conditioning stimulus (x-axis) after ketamine treatment is reduced compared to placebo the individual data overlap. The plot further shows that magnitude of the eVAS response without con-

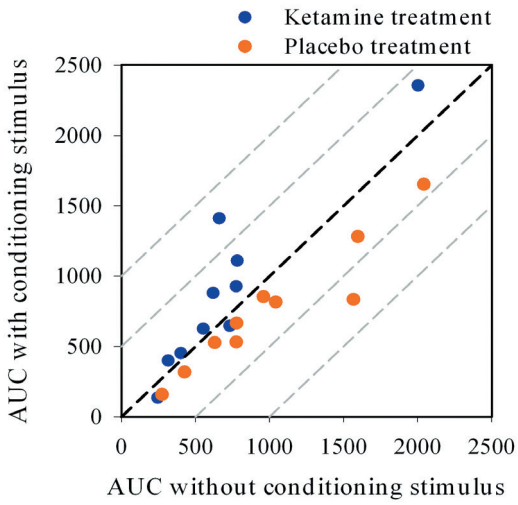

Figure 5. *Scatter plot of the effect of the conditioning stimulus on eVAS (visual analogue scale ranging from 0 (no pain) to 100 (worst pain imaginable)) responses after placebo treatment (orange circles) and ketamine treatment (blue circles). The dashed lines are lines of identity. On the x-axis the areas-under-the curve (AUC) of the eVAS responses without conditioning stimulus; on the y-axis the AUCs of the eVAS responses with conditioning stimulus.*

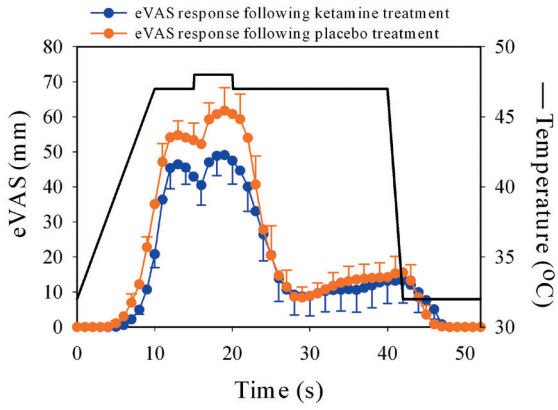

Figure 6. *Effect of placebo and ketamine treatment on endogenous pain modulation as determined by the offset analgesia paradigm. The ΔeVAS values (decrease in eVAS (visual analogue scale ranging from 0 (no pain) to 100 (worst pain imaginable)) from peak eVAS value to its nadir following the 1 °C decrease of the heat pain stimulus (at t = 20 seconds)) corrected for the difference in peak ΔeVAS did not differ between treatments. The data are the population mean of the subjects' mean eVAS values (SEM).*

ditioning stimulus had just limited effect on the magnitude of the response with stimulus (slope of linear regression on the ketamine data = 1.19; on the placebo data 0.75).

Offset analgesia

Mean OA responses are shown in figure 6. The response after ketamine treatment was smaller than after placebo treatment; a sign of persistent analgesic effect of ketamine in the hours following treatment. Offset analgesia was observed in all subjects after both placebo and ketamine infusion. The placebo ΔeVASc (0.91 ± 0.03) did not differ significantly from the ketamine ΔeVASc (0.86 ± 0.06), indicating no effect of ketamine on OA. No correlation was observed between placebo ΔeVASc and DNIC responses (inhibition determined by subtracting AUCs) ($p > 0.05$, correlation coefficient = 0.11).

Absence of sex differences

No sex differences in the response of ketamine relative to placebo were observed in the effects of ketamine on analgesia, DNIC and OA responses.

Discussion

Descending control of nociceptive spinal responses has both inhibitory and facilitatory components.[6] Diffuse noxious inhibitory control and offset analgesia are examples of dynamic inhibitory processes. DNIC is a spinal-medullary-spinal feedback loop that is activated when two painful stimuli are applied simultaneously.[5,17,18] A heterotopic noxious stimulus modifies the perception of another noxious stimulus, and, in case of DNIC, inhibits the perception of the primary (*i.e.* test) stimulus. It has been suggested that DNIC serves as a filter that helps to extract nociceptive signals from the background noise by inhibiting basal somatosensory activity of the population nociceptive neurons (*i.e.* increasing the signal-to-noise ratio).[17] In our current study we generated inhibition of a heat pain stimulus applied to the arm, by immersion of the foot and lower leg in cold

water (placebo data; Fig. 4A). An infusion with ketamine resulted in a blocked inhibitory pain response with more pain when a conditioning stimulus was combined with the test stimulus rather than an increase in DNIC (Fig. 4B; *i.e.* the null-hypothesis was rejected). Our data indicate that the balance between pain inhibition and pain facilitation (that normally has predominance for pain inhibition) was shifted by ketamine towards blocking DNIC, resulting in some form of pain facilitation. Similar alterations in endogenous pain modulation have been observed with acute and chronic morphine treatment.[23,24]

Ketamine analgesia *versus* anti-analgesia

The effect of ketamine on DNIC was not expected and is, at present, difficult to explain. Ketamine is usually associated with analgesia in chronic pain and in combination with opioids in cancer pain and perioperative pain.[10-15,25,26] Pain relief occurs due to blockade of excitatory NMDARs, which results in a reduced or even blocked signal transmission in the pain circuitry towards the thalamus and cerebral cortex. Still, there are several multiple, converging lines of evidence showing that ketamine and other NMDAR antagonists are associated with pain facilitation and antagonism of opioid-induced pain relief. We recently showed in healthy volunteers that while ketamine had a dose-dependent antinociceptive effect on static nociceptive pain (repetitive noxious heat pain stimuli), pain responses following infusion were perceived as more painful (by about 1 cm VAS) for more than 3 hours compared to pre-drug pain responses.[26,27] In agreement with these findings, Mitchell described a cancer patient that developed severe hyperalgesia and allodynia directly following treatment with ketamine.[28] During treatment, the noncompetitive NMDA receptor antagonist MK801 can cause an anti-analgesic effect in mice, where it significantly reduced morphine and stress-induced analgesia (an effect which displayed sex-dependency).[29-32] In another study, MK801 induced hyperalgesia in an acute pain model in the rat.[33] Interestingly, in the anesthetized rat, the NMDAR has been implicated in inhibition of chronic inflammatory pain. High dose (but not low dose) NMDA microinjected into the RVM inhibited primary hyperalgesia 3 hours following injection of complete Freund's adjuvant into a hind paw.[34] In total, these data indicate that apart from a potent analgesic effect, NMDAR antagonists, including ketamine, may, under specific circumstances, produce anti-analgesic and pain facilitatory effects.

Mechanisms of ketamine effect on DNIC

Multiple, non-exclusive mechanisms may cause anti-analgesic or pain facilitatory responses during and/or following ketamine treatment. (i) It has been argued that excitatory amino acids accumulate at spinal and supraspinal sites during effective blockade of the NMDAR.[30,33] These amino acids may activate non-NMDA excitatory receptors (metabotropic or non-NMDA ionotropic glutamate receptors) and consequently produce anti-analgesia and increased pain responses. (ii) Ketamine may recruit different nociceptive mechanisms (compare the mechanism proposed for the block of DNIC by morphine)[23] or additionally activate non-NMDA receptor systems, such as the opioid system causing a

net inhibitory effect on DNIC.[35] (iii) DNIC may require supraspinal processing, which is effectively disrupted by ketamine (*e.g.* a dissociative effect of ketamine between the limbic system and cerebral cortex).[1] And (iv), because we performed our experiments following ketamine infusion, a direct effect at the NMDAR is not excluded, for example by actions of accumulated excitatory amino acids (see "i"), which during the loss of NMDAR blockade from the decrease in ketamine concentration causes a rebound increase in NMDAR activity and consequently enhanced transmission of afferent nociceptive stimuli (*i.e.* pain facilitation).[26]

Because the link of excitatory receptor systems and the process of endogenous pain inhibition/facilitation (and its neurotransmitters such as serotonin and norepinephrine) remains understudied, further studies are needed to investigate the specific role of the excitatory receptors in the balance between pain inhibition and facilitation under physiological and chronic pain conditions.

Offset analgesia

Apart from DNIC, we tested the effect of ketamine on offset analgesia. OA is considered an inhibitory mechanism that increases the temporal contrast between stimuli (*i.e.* a temporal sharpening filter).[16,19,20] OA is defined as the decrease in pain intensity following a decrease in stimulus temperature that is disproportionate compared to a similar increase in temperature. After placebo infusion, we observed an increment in eVAS of 6 mm going from 46 to 47 °C while a subsequent similar decrease in temperature caused a drop in eVAS of 33 mm (a ratio of 5.5; Fig. 3). A similar ratio was observed after ketamine infusion. Furthermore, the drop in eVAS was twice as fast (average 6 mm/s) in OA experiments compared with the adaptation seen in DNIC experiments (3 mm/s). Ketamine had no effect on OA development, *i.e.* the enhanced and robust analgesia following the 1 °C decrease in noxious stimulus intensity remained unaffected by ketamine (drop in eVAS relative to peak eVAS = 0.91 ± 0.03 after placebo *versus* 0.86 ± 0.06 after ketamine treatment). These data contrast the observations in the DNIC experiments. As previously discussed, both in their generation and probably also in their neuroanatomic pathways the inhibitory processes OA and DNIC are distinct: OA relates inhibition to the offset of a noxious stimulus, while DNIC is related to the onset of a heterotopic stimulus.[16,19,20] In agreement with this is the observation that there was no correlation between ΔeVASc and DNIC. We further show that OA and DNIC are dissimilar in their interaction with the glutamatergic receptor system.

Critique of methods

We tested the effect of ketamine and placebo using a single-blind study design as we expected to become unblinded during the treatment of the subjects. Also the subjects noted more severe side effects during ketamine treatment but were not made aware that this was specific to the test treatment. We cannot exclude that specific a priori expectations may have influenced the study outcome at some level. For example, it was shown that the subject's expectation of hyperalgesia completely blocked the analgesic effect of descending inhibition on spinal no-

ciceptive reflexes.[36] To our advantage is that our subjects remained uninformed regarding a possible effect of ketamine on DNIC or OA and the a priori expectations of the investigators were towards an increase in inhibitory control. Furthermore, we observed that treatment sequence had no effect on outcome parameters (DNIC and OA, experiment with and without water immersion) and therefore we do not think that our approach influenced the study outcome significantly.

Finally, it may be argued that the ketamine effect on DNIC is related to the smaller magnitude of the eVAS responses following ketamine treatment and that, for example, the increase in eVAS responses during water immersion is due to a drift towards pre-ketamine baseline values (due to the loss of ketamine analgesic effect). There are several arguments opposing this assumption. DNIC eVAS responses without and with conditioning stimulus were randomized and on average occurred both about 60 min following the end of the ketamine infusion. Hence ketamine's analgesic effect was of similar magnitude in the 2 experiments. Furthermore, the magnitude of the eVAS responses with conditioning stimulus is minimally related to the magnitude of the responses without stimulus (Fig. 5). A small effect (ranging from 0 to 20%) cannot be excluded with larger eVAS responses with conditioning stimulus associated with larger responses without water stimulation. The reverse would be expected when the response would have drifted back to pre-ketamine baseline values.

Conclusions

In conclusion, our data suggest that ketamine treatment effects endogenous modulation of nociceptive stimuli as examined by the DNIC paradigm. DNIC responses following a 1-hour low-dose ketamine treatment displayed a modulated (blocked or even facilitated) DNIC. These findings suggest a modulatory involvement of the NMDA and/or other glutamatergic receptors at some level within the endogenous pain system. No effect of ketamine treatment was observed on the inhibitory effects of subsequent OA responses. This suggests that OA and DNIC differ in their susceptibility for glutamatergic influences. The enduring pain relief of chronic pain during and following ketamine treatment[10-15] cannot be explained by our current findings and suggests the absence between DNIC alterations and relief of spontaneous chronic pain from ketamine. However, it may well be that the effect of ketamine on descending pain modulation is different in chronic pain patients and cannot be addressed by performing ketamine studies in volunteers.

References

1. Petrenko AB, Yamakura T, baba H et al. The role of *N*-methyl-D-aspartate (NMDA) receptors in pain; A review. *Anesth Analg* 2003; 97: 1108-16
2. Roberts J, Ossipov MH, Porreca F. Glial activation in the rostroventromedial medulla promotes descending facilitation to mediate inflammatory hypersensitivity. *Eur J Neurosci* 2009; 30: 229-41
3. Wieseler-Frank J, Maier SF, Watkins LR. Central proinflammatory cytokines pain enhancement. *Neurosigmals* 2005; 14: 166-74

4. Millan M.J. Descending control of pain. *Prog Neurobiol* 2002; 66: 355-474
5. Van Wijk G, Veldhuijzen DS. Perspective on diffuse noxious inhibitory controls as a model of endogenous modulation in clinical pain syndromes. *J Pain* 2010; 11: 408-19
6. Vanegas H, Schaible HG. Descending control of persistent pain: inhibitory or facilitatory? *Brain Res Rev* 2004; 46: 295-309
7. King CD, Wong F, Currie T et al. Deficiency in endogenous modulation of prolonged heat pain in patients with irritable bowel syndrome and temporomandibular disorder. *Pain* 2009; 143: 172-78
8. Lautenbacher S, Rollman GB. Possible deficiencies of pain modulation in fibromyalgia. *Clin J Pain* 1997; 13: 189-96
9. Seifert F, Kiefer G, deCol R et al. Differential endogenous pain modulation in complex-regional pain syndrome. *Brain* 2009; 132: 788-800
10. Amr YM. Multi-day low dose ketamine infusion as adjuvant to oral gabapentin in spinal cord injury related chronic pain: A prospective, randomized, double blind trial. *Pain Physician* 2010; 13: 245-9
11. Bell R, Eckleston C, Kalso E. Ketamine as an adjuvant to opioids for cancer pain. *Cochrane Database Syst Rev* 2003: CD003351
12. Mercadante S, Arcuri E, Tirelli W et al. Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: a randomized, controlled, double-blind, crossover, double-dose study. *J Pain Symptom Manage* 2000; 20:246-52
13. Schwartzman RJ, Alexander GM, Grothusen JR et al. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: A double-blind placebo controlled study. *Pain* 2009; 147: 107-115
14. Sigtermans MJ, van Hilten JJ, Bauer MCR et al. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. *Pain* 2009; 145: 304-11
15. Sörensen J, Bengtsson A, Ahlner J et al. Fibromyalgia – Are there different mechanisms in the processing of pain? A double blind crossover comparison of analgesic drugs. *J Rheumatol* 1997; 24: 1615-21
16. Grill JD, Coghill RC. Transient analgesia evoked by noxious stimulus offset. *J Neurophysiol* 2002; 87: 2205-8
17. Le Bars D, Villanueva L, Bouhassira D et al. Diffuse noxious inhibitory controls (DNIC) in animals and in man. *Path Physiol Exp Ther* 1992; 4: 55-65
18. Talbot JD, Duncan GH, Bushnell MC et al. Diffuse Noxious Inhibitory Controls (DNICs): psychophysical evidence in man for intersegmental suppression of noxious heat perception by cold pressor pain. *Pain* 1987; 30: 221-32
19. Yelle MD, Oshiro Y, Kraft RA et al. Temporal filtering of nociceptive information by dynamic activation of endogenous pain modulatory systems. *J Neurosci* 2009; 29: 10264-71
20. Yelle MD, Rogers JM, Coghill RC. Offset analgesia: A temporal contrast mechanism for nociceptive information. *Pain* 2008; 134: 174-86.
21. Pud D, Granovsky Y, Yarnitsky D. The methodology of experimentally induced diffuse noxious inhibitory control (DNIC)-like effect in humans. *Pain* 2009; 144: 16-9
22. Moont R, Pud D, Sprecher E et al. 'Pain inhibits pain' mechanisms: Is pain modulation simply due to distraction? *Pain* 2010;150: 113 -20
23. Le Bars D, Willer JC, De Broucker T. Morphine blocks descending inhibitory controls in humans. *Pain* 1992; 13-20
24. Ram KC, Eisenberg E, Haddad M et al. Oral opioid use alters DNIC but not cold pain perception in patients with chronic pain — New perspective of opioid-induced hyperalgesia. *Pain* 2009; 139: 431-8
25. Nesher N, Serovian I, Marouani N et al. Ketamine spares morphine consumption after transthoracic lung and heart surgery without adverse hemodynamic effects. *Pharmacol Res* 2008; 58: 38-44
26. Sigtermans M, Noppers I, Sarton E et al. An observational study on the effect of S(+)-ketamine on chronic versus experimental acute pain in Complex Regional Pain Syndrome type 1 patients. *Eur J Pain* 2010; 14: 302-7
27. Sigtermans M, Dahan A, Mooren R et al. S(+)-ketamine effect on experimental pain and cardiac output: a population pharmacokinetic-pharmacodynamic modeling study in healthy volunteers. *Anesthesiology* 2009; 111: 892-903

28. Mitchell AC. Generalized hyperalgesia and allodynia following abrupt cessation of subcutaneous ketamine infusion. *Palliat Medicine* 1999; 13: 427-8
29. Lipa SM, Kavaliers M. Sex differences in the inhibitory effects of the NMDA antagonist, MK-801, on morphine and stress-induced analgesia. *Brain Res Bull* 1990; 24: 627-30
30. Lomas LM, Terner JM, Picker MJ. Sex differences in NMDA antagonist enhancement of morphine antihyperalgesia in a capsaicin model of persistent pain: Comparison to two models of acute pain. *Pharmacol Biochem Behav* 2008; 89: 127-36
31. Lutfy K, Hurlbut DE, Weber E. Blockade of morphine-induced analgesia and tolerance by MK-801. *Brain Res* 1993; 616: 83-8
32. Nemmani KVS, Grisel JE, Stowe JR et al. Modulation of morphine analgesia by site-specific *N*-methyl-D-aspartate receptor antagonists: dependence on sex, site of antagonism, morphine dose, and time. *Pain* 2004; 109: 274-83
33. Schmidt AP, Tort AB, Silveira PP et al. The NMDA antagonist MK-801 induces hyperalgesia and increases CSF excitatory amino acids in rats: Reversal by guanosine. *Pharmacol Biochem Behav* 2009; 91: 549-53
34. Guan Y, Tereyama R, Dubner R et al. Plasticity in excitatory amino acid receptor-mediated descending pain modulation and inflammation. *J Pharmacol Exp Ther* 2002; 300: 513-20
35. Sarton E, Teppema LJ, Olievier CN et al. The involvement of the μ-opioid receptor in ketamine-induced respiratory depression and antinociception. *Anesth Analg* 2001; 93: 1495-1500
36. Goffaux P, Redmond WJ, Rainville P et al. Descending analgesia — when the spine echoes what the brain expects. *Pain* 2007; 130: 137-43