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Analgesic Efficacy of Low-dose Ketamine

Somatosensory-evoked Responses in Relation to Subjective Pain Ratings

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Background: **Low-dose ketamine has been shown to exert analgesic effects. Whether ketamine-induced pain relief may be quantitated by somatosensory evoked cerebral potentials has not been established.**

Methods: **Thirty healthy volunteers were assigned randomly to one of three groups. Subjects of group 1 (n = 10, control) were given saline as placebo. In groups 2 (n = 10) and 3 (n = 10), intravenous ketamine (0.25 mg · kg^{-1} and 0.50 mg · kg^{-1}, respectively) was administered. The following variables were recorded at baseline and for 50 min after drug administration: electroencephalographic (EEG) data, somatosensory-evoked late cortical responses (SEP) elicited by intracutaneous stimulation of the fingertip (2–3 fold pain threshold), heart rate, mean arterial blood pressure, and end-tidal $P_{ET_{CO_2}}$ *via* a tight-fitting mask. Electroencephalographic spectral power in selected frequency bands and frequency percentiles were calculated from the spontaneous EEG segment preceding each somatosensory stimulus. Somatosensory-evoked late cortical response parameters were calculated from the respective poststimulus EEG segments. After recording of each EEG response, subjects were asked to rate the individual pain sensation.**

Results: **In group 1, all variables did not change over time. Ketamine administration resulted in dose-dependent decreases in alpha-activity and increases in theta power (group 2: 190%, group 3: 440%). Electroencephalographic changes were not related to changes in pain perception. For the first 30 min after ketamine injection, a dose-dependent decrease of the long-latency N_{150}-P_{250} somatosensory-evoked late cortical response component was observed (group 2: 15–20%; group 3: 25–30%). Subjective pain ratings were also different between groups, with a higher degree of pain relief in group 3 for the first 30 min. At the end of the observation period, pain relief and the N_{150}-P_{250} amplitude were comparable in both ketamine groups.**

Conclusions: **These data indicate that pain relief induced by low-dose ketamine is dose-dependent for the first 30 min after bolus injection. Changes in pain perception may be quantitated by somatosensory-evoked cortical responses. Also, EEG changes are not specific for changes in nociception, but the increase in theta power may reflect the hypnotic effect of low-dose ketamine. (Key words: Anesthetics, intravenous: ketamine; pain evoked responses; Measurement techniques: SSEP, electroencephalography.)**

LOW-DOSE ketamine (0.25–0.50 mg · kg^{-1}) has been shown to provide adequate analgesia for postoperative pain treatment[1–3] and in critically injured patients.[4] This analgesic effect was assessed by clinical measures. A recent study in volunteers showed that 0.50 mg · kg^{-1} ketamine may increase pressure pain detection and tolerance thresholds, as well as pain after electrical stimulation.[5] It is unknown whether the pain relief after ketamine can be quantified by electrophysiologic methods. If neurophysiologic variables specific for pain relief or analgesic treatment effects could be defined, the analgesic component of anesthesia could be assessed more accurately. Measures of the spontaneous electroencephalogram (EEG) have been proposed for the assessment of depth of anesthesia and drug-induced sedative effects.[6–8] However, the EEG response to different anesthetics given at equipotent doses may be variable and agent specific. Because pain sensation involves cortical signal processing and cognitive function, by definition, adequately anesthetized patients

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cannot experience pain. However, increased nociceptive input may result in changes in a variety of physiologic variables (*e.g.,* heart rate (HR), blood pressure, organ blood flow, sympathetic outflow). These changes cannot be taken as a specific marker for nociception. In unconscious subjects, analgesia may be defined as a blockade of nociceptive pathways at different levels (*e.g.,* peripheral nerve, spinal cord, thalamus, *etc.*). For the assessment of the analgesic component of general anesthesia, no simple parameter for routine use in clinical practice has been identified. Experimental pain research makes use of recordings of late components of cerebral potentials evoked by pain-inducing somatosensory stimuli (SEP).[9–12] In humans, late cortical SEP waves were shown to correlate with subjective pain ratings.[13,14] From this, it was concluded that these pain-related SEP may be used for the assessment of changes in nociceptive transmission. This study investigated the analgesic and hypnotic effects of low-dose ketamine (0.25 $mg \cdot kg^{-1}$; 0.50 $mg \cdot kg^{-1}$ intravenously). Changes in late cortical SEP in response to intracutaneous phasic pain stimuli and the spontaneous EEG were correlated to subjective pain ratings.

Methods

After institutional approval and written informed consent had been obtained, 30 adult volunteers (ASA-physical status 1; 16 females, 14 males; aged 27 ± 6 yr) were studied. All subjects were free from neurologic, psychiatric, cardiovascular, renal, or hepatic diseases and had not taken any drug known to interfere with central nervous system function for at least 3 months before the study. Subjects were assigned randomly to one of three groups. Subjects of group 1 (n = 10) received 5 ml saline intravenously as placebo. In groups 2 (n = 10) and 3 (n = 10), intravenous ketamine (0.25 $mg \cdot kg^{-1}$ and 0.50 $mg \cdot kg^{-1}$, respectively) was administered intravenously for 30 sec. The following variables were recorded at baseline and for 50 min after placebo or ketamine administration: EEG, SEP, HR, (beats per min, RM300, Honeywell, Germany), mean arterial blood pressure (MAP, mmHg; Dinamap, Critikon), end-tidal P_{CO_2} ($P_{ET}CO_2$, mmHg, Datex, Hoyer, Germany).

Electroencephalogram, Somatosensory-evoked Late Cortical Responses

Electroencephalogram and SEP were recorded continuously with Ag/AgCl electrodes by means of an EEG-amplifier (Biosignalverstaerker, nbn-electronics, Germany) from vertex (Cz) *versus* linked earlobes (A1-A2). The electrooculogram was recorded from supra- and infraorbital leads. For all recordings, the system bandpass was set at 0.5 and 30 Hz (3 dB cut-off points, 24 dB/octave). The electrode impedances were kept below 5 kOhm (at 12 Hz). The stimulus and the raw EEG signals were monitored on an oscillograph (Hameg) and stored on an analog tape (Store 7DS, Racal, England). Peristimulus EEG segments from 5 s before to 3.5 s after stimulus onset were digitized off-line, with a sampling rate of 200 Hz and a resolution of 12 bit (CED 1401, Cambridge Electronics, Cambridge, England).

Somatosensory stimuli were given to the tip of the left index finger by the intracutaneous technique described by Bromm and Meier.[15] Briefly, the superficial epidermal layers of the glabrous skin are carefully removed, using a small stainless steel drill comparable to a drill used by a dentist (diameter: 1.5 mm). Constant current stimuli (train-of-four 5 msec square waves) with intensities of 2- and 3-fold above the individual pain threshold are passed through an inserted and fixed metal electrode, with a large return electrode placed at the middle finger. This procedure ensures a high current density at the superficial nociceptive nerve terminals. The elicited sensation is described as a stinging pain similar to that evoked by electrical tooth pulp stimulation. With this technique, pain thresholds are one order of magnitude lower than with conventional electrical stimuli.[15] Before medication and before EEG and SEP recordings, individual detection and pain thresholds were determined by four series of increasing and decreasing stimulus intensities. Pain sensation was rated verbally on a numerical scale ranging from "0" (no sensation) to "10" (unbearable pain). The first sensation of any pain was defined as "4" (individual pain threshold). The individually determined intensities ensured pain ratings between "4" and "6." The subjects were allowed to familiarize themselves with the experimental setup for 30 min before the first two stimulus blocks were recorded. Three seconds after each stimulus, a tone prompted the subject to rate his sensation. Because stimulus randomization and long intervals are essential to minimize effects of habituation and distraction,[11] stimuli were given in blocks that consisted of 40 stimuli with randomized intensities (20 stimuli of 2- and 3-fold pain intensity each) with varying interstimulus intervals between 10 and 20 s, resulting in a block length of 10 min. Seven blocks were

applied, from which the first block was not evaluated, to exclude major habituation effects. The second block was taken as baseline. The following five blocks were recorded after drug treatment. The time interval between each block was 1 min.

From the spontaneous EEG segment (epoch length: 5 s) preceding each somatosensory stimulus, the spectral power was calculated for selected frequency bands: delta: 1.0–4.0 Hz; theta: 4.0–8.0 Hz; alpha: 8.0–12.0 Hz; and beta: 12.0–30 Hz after Fast Fourier Transformation (Kaiser window, 40 dB sidelobe depression).[16] In addition, the spontaneous EEG was also quantified by the most commonly used percentile frequencies: $f_{25\%}$, $f_{50\%}$, $f_{75\%}$, and $f_{95\%}$. The percentile frequencies are defined as that frequency f [Hz] below which a certain percentage of power is located; $f_{50\%}$ is also denoted as median frequency and $f_{95\%}$ as spectral edge frequency. Electroencephalographic parameters were calculated after averaging single-trial spectra of four successive prestimulus EEG segments, resulting in one value per minute. After this, EEG variables were averaged for all subjects. Trials with electrooculogram artifacts were discarded. SEP amplitudes and latencies were calculated from the respective poststimulus EEG segments of 500 msec duration. Evaluated SEP components consisted of a negativity at approximately 150 msec after stimulus onset (N_{150}) and a positivity (P_{250}) with a latency of approximately 250 msec. The SEP amplitudes were quantified by the peak-to-peak values between these two components.

Statistical Analysis

Treatment effects for the total period of measurements were analyzed using the respective mean values of all variables for each recording block (10 min recording each; one pre- and 5 posttreatment blocks). At first, differences in the posttreatment values between the groups due to inhomogeneities between groups were eliminated by subtracting the mean pretreatment value from the posttreatment values. Changes in values were then subjected to a two-way analysis of variance, with one within-subjects factor (posttreatment blocks) and one between-subjects factor (treatments) to detect "overall" effects over time, treatment, and their interaction. The Huynh-Feldt correction was used to take into account differences between variances.[17] In case of a significant treatment or interaction effect, differences between groups were evaluated at each time point by two-sample *t* tests, with Bonferroni corrections. In addition, the stability of changes in values during the five posttreatment blocks was tested for the placebo group by a one-way analysis of variance. The Pearson correlation coefficient was used to quantify the relation between variables, including pain scores.[18] Data are given as mean ± SD, if not stated otherwise. Significance was assumed at $P < 0.05$. Statistics were performed by the SPSS package.#

Results

Cardiovascular and Respiratory Parameters

Four subjects of group 2 and all subjects of group 3 became unconscious after ketamine administration and were unresponsive for 3 ± 2 min (group 2) or 6 ± 5 min (group 3), respectively. Data for HR, MAP, and $P_{ET_{CO_2}}$ are shown in figure 1. Using analysis of variance, significant treatment effects for HR and MAP were noted in groups 2 and 3 (see table 1 for a summary of the analyses of variance). $P_{ET_{CO_2}}$ was not significantly affected by the treatments and did not change over time.

Neurophysiologic Parameters

Pain Ratings. The mean detection threshold for the intracutaneous stimuli was 0.16 ± 0.06 mA, and the mean pain threshold was 0.34 ± 0.08 mA. Pain ratings exhibited a significant treatment effect and were changed over time (table 1), although the pain ratings in the placebo group were stable over the entire observation period ($P < 0.05$). Four subjects of group 2 and all subjects of group 3 became unresponsive after ketamine administration, and no pain ratings could be obtained over an individually varying time period of 1–11 min. Thereafter, pain ratings from all subjects could be recorded. In both ketamine groups, pain ratings were decreased below the placebo level over the whole observation period. A summary of the Bonferroni corrected *t* test comparisons is given in table 2. A ketamine-induced dose-dependent effect on pain relief was seen during the first three posttreatment periods. In the last two experimental blocks, no differences in the analgesic efficacy between both ketamine doses were found.

Electroencephalogram. An example of smoothed EEG single trial spectra of one subject from group 1 (control) is given in figure 2 (left). The drug (placebo)

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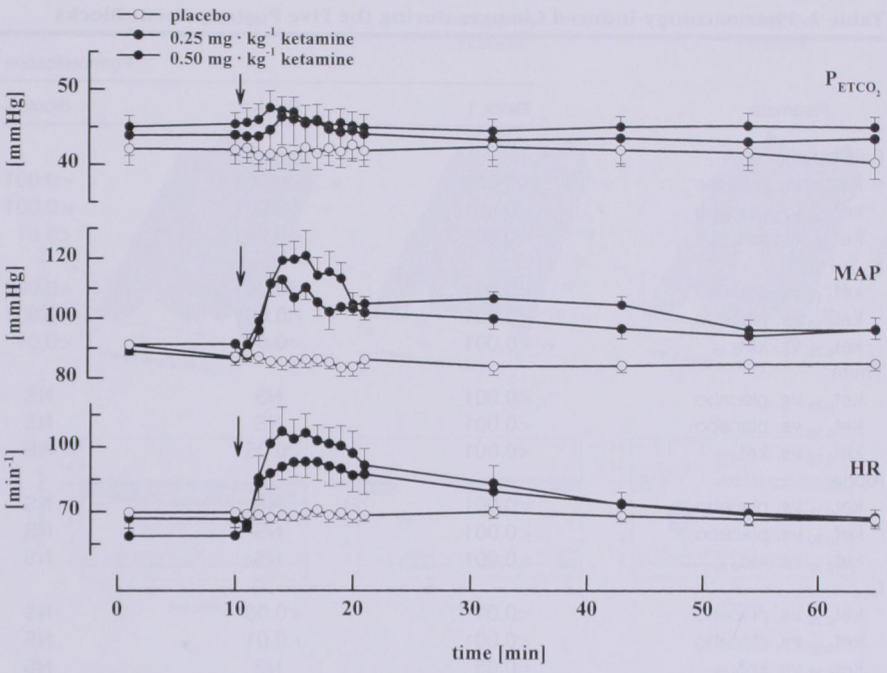

Fig. 1. End-tidal ($P_{ET_{CO_2}}$), mean arterial blood pressure (MAP), and heart rate (HR) for all groups before and after drug treatment (means ± SE). Data were sampled before and after each stimulus block of 10-min duration and every minute during the first block after medication.

was given after 10 min of baseline recordings. Alpha activity was dominant over time. Corresponding single trial EEG spectra for two subjects given 0.25 mg · kg^{-1} and 0.5 mg · kg^{-1} ketamine, respectively, are shown in figure 2 (middle, right). The time course of changes in frequency bands and computed EEG variables for all groups is presented in figure 3.

Ketamine administration resulted in a transient loss of alpha-activity ($P < 0.001$). As much as a fivefold increase in theta power ($P < 0.001$, group 3) was observed during the first postmedication stimulus block. Delta and beta activities did not change over time. Changes in theta and alpha activities or other EEG variables were not correlated to reduction in pain perception (fig. 4).

Somatosensory-evoked Potentials. At baseline, SEP consisted of a large biphasic deflection, with a vertex negativity at 150 msec (N_{150}) and a vertex positivity

Table 1. Summary of the Two-way Analysis of Variance: Pharmacology-induced Changes during the Five Posttreatment Blocks

	Treatment		Block		Treatment × Block	
Parameter	$F_{df = 2,27}$	p(F)	$F_{df = 4,108}$	p(F)	$F_{df = 8,108}$	p(F)
Pain ratings	13.96	<0.001	12.68	<0.001	5.59	<0.001
N_{150}–P_{250}	5.90	<0.01	5.81	<0.001	0.98	NS
Delta	0.92	NS	1.53	NS	1.22	NS
Theta	9.78	<0.001	12.75	<0.001	18.77	<0.001
Alpha	5.87	<0.01	3.02	<0.05	2.43	<0.05
Beta	2.59	NS	1.01	NS	1.61	NS
$f_{95\%}$	5.62	<0.01	3.10	<0.05	3.48	<0.01
$f_{75\%}$	4.55	<0.05	2.98	<0.05	3.24	<0.01
$f_{50\%}$	2.98	NS	2.72	NS	2.53	<0.05
$f_{25\%}$	1.88	NS	1.52	NS	1.76	NS
$P_{ET_{CO_2}}$	1.21	NS	0.91	NS	1.43	NS
MAP	10.21	<0.001	3.61	<0.01	1.84	NS
HR	9.80	<0.001	9.37	<0.001	2.37	<0.01

MAP = mean arterial pressure; HR = heart rate; NS = not significant.

Table 2. Pharmacology-induced Changes during the Five Posttreatment Blocks

Parameter	Postmedication Period				
	Block 1	Block 2	Block 3	Block 4	Block 5
Pain ratings					
$ket_{0.25}$ *vs.* placebo	<0.001	<0.001	<0.001	<0.001	<0.001
$ket_{0.50}$ *vs.* placebo	<0.001	<0.001	<0.001	<0.001	<0.001
$ket_{0.25}$ *vs.* $ket_{0.50}$	<0.001	<0.001	<0.01	NS	NS
N_{150}–P_{250}					
$ket_{0.25}$ *vs.* placebo	<0.001	<0.001	<0.001	<0.001	<0.001
$ket_{0.50}$ *vs.* placebo	<0.001	<0.001	<0.001	<0.001	<0.001
$ket_{0.25}$ *vs.* $ket_{0.50}$	<0.001	<0.01	<0.01	NS	NS
Theta					
$ket_{0.25}$ *vs.* placebo	<0.001	NS	NS	NS	NS
$ket_{0.50}$ *vs.* placebo	<0.001	NS	NS	NS	NS
$ket_{0.25}$ *vs.* $ket_{0.50}$	<0.001	<0.05	NS	NS	NS
Alpha					
$ket_{0.25}$ *vs.* placebo	<0.001	NS	NS	NS	NS
$ket_{0.50}$ *vs.* placebo	<0.001	NS	NS	NS	NS
$ket_{0.25}$ *vs.* $ket_{0.50}$	<0.001	NS	NS	NS	NS
$f_{95\%}$					
$ket_{0.25}$ *vs.* placebo	<0.01	<0.05	NS	NS	NS
$ket_{0.50}$ *vs.* placebo	<0.001	<0.01	NS	NS	NS
$ket_{0.25}$ *vs.* $ket_{0.50}$	<0.05	NS	NS	NS	NS
$f_{75\%}$					
$ket_{0.25}$ *vs.* placebo	<0.05	NS	NS	NS	NS
$ket_{0.50}$ *vs.* placebo	<0.01	NS	NS	NS	NS
$ket_{0.25}$ *vs.* $ket_{0.50}$	NS	NS	NS	NS	NS
$f_{50\%}$					
$ket_{0.25}$ *vs.* placebo	<0.05	<0.05	NS	NS	NS
$ket_{0.50}$ *vs.* placebo	<0.01	<0.05	NS	NS	NS
$ket_{0.25}$ *vs.* $ket_{0.50}$	NS	NS	NS	NS	NS
MAP					
$ket_{0.25}$ *vs.* placebo	<0.001	<0.001	<0.001	<0.05	<0.01
$ket_{0.50}$ *vs.* placebo	<0.001	<0.001	<0.001	<0.01	<0.01
$ket_{0.25}$ *vs.* $ket_{0.50}$	<0.05	NS	NS	NS	NS
HR					
$ket_{0.25}$ *vs.* placebo	<0.001	NS	NS	NS	NS
$ket_{0.50}$ *vs.* placebo	<0.001	NS	NS	NS	NS
$ket_{0.25}$ *vs.* $ket_{0.50}$	<0.05	NS	NS	NS	NS

$ket_{0.25}$ = 0.25 $mg \cdot kg^{-1}$ ketamine, $ket_{0.50}$ = 0.50 $mg \cdot kg^{-1}$ ketamine. Summary of Bonferroni corrected *t* tests for independent samples. Comparisons of means between treatments were performed only in case of significant effects in the corresponding analysis of variance (see table 1). NS = not significant.

at 250 msec (P_{250}). In all groups, baseline pain ratings were in the range of 4 to 7. In group 1, SEP and pain ratings did not change over time. Ketamine administration resulted in a dose-dependent attenuation of SEP amplitudes. Even in unresponsive subjects, SEP could be recorded. Pain ratings and averaged SEP components of a subject of group 2 are shown in figure 5. Data for grand mean SEP amplitudes and subjective pain ratings for all groups are shown in figure 6. Ketamine administration resulted in decreases in SEP amplitudes, which were different between groups for the first 30 min after bolus injection. At the end of the observation period in both groups, SEP amplitudes were 25–30% less than baseline values ($P < 0.05$). The correlations between duration of unresponsiveness or reduction in pain relief and EEG/SEP variables are shown in figure 4. Ketamine-induced changes in the N_{150}-P_{250} SEP amplitude were significantly correlated with attenuation of pain perception ($r = 0.61$; $P(r) < 0.01$) but not with the time of unresponsiveness ($r = 0.36$; $P(r) > 0.05$). Conversely, increases in EEG theta power exceeding more than 20% of baseline values were significantly related

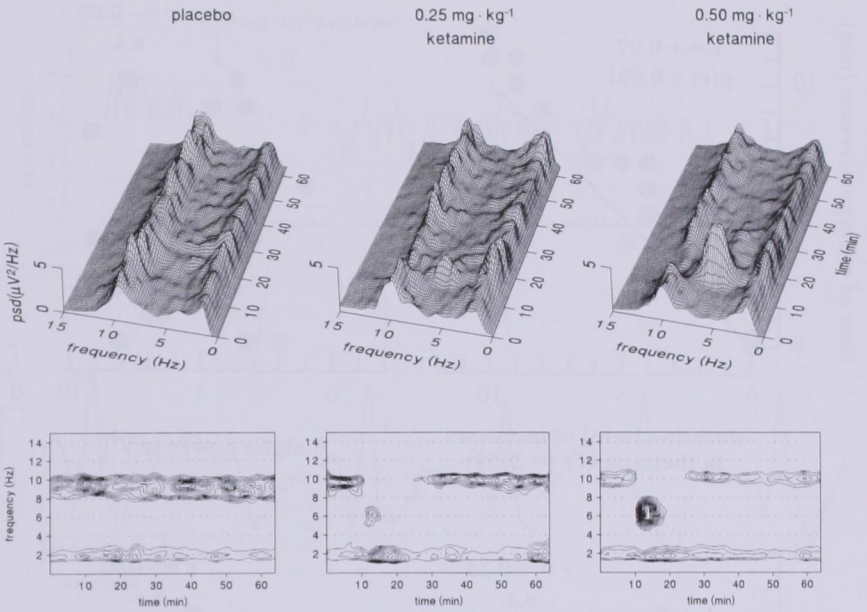

Fig. 2. *Upper graphs:* Mean power spectral density (PSD) functions of spontaneous electroencephalogram activity in three subjects before and after medication (bandpass: 0.5–30 Hz; epoch length: 5 s; the single-trial spectra were smoothed by a running median filter and a moving average filter, each with a length of 5 points). The injections were given 10 min after start of recordings. *Bottom:* Iso-contour line plots representing different levels of the PSD functions given above. The lowest iso-contour line corresponds to a power spectral density of 20% above the mean power in the premedication period. The difference between two successive contour lines amounts to 0.25 μV^2/Hz. Alpha activity was dominant over time in the placebo group. After ketamine injection, alpha activity was transiently replaced by a dose-dependent increase in theta activity.

to the time of unresponsiveness ($r = 0.97$; $P(r) < 0.001$)

Discussion

This study demonstrates a dose-dependent correlation of pain relief and decreases in late cortical SEP components after low-dose ketamine. The dose-dependent decrease in SEP amplitudes seen in the first 30 min after ketamine injection was paralleled by a dose-dependent decrease in pain ratings in all subjects. In contrast, the changes in the spontaneous EEG did not correlate with pain sensation. Within 1 min after ketamine injection, the alpha rhythm disappeared, and a synchronous high-voltage theta-activity was noted. The duration of the dose-dependent increase in theta activ-

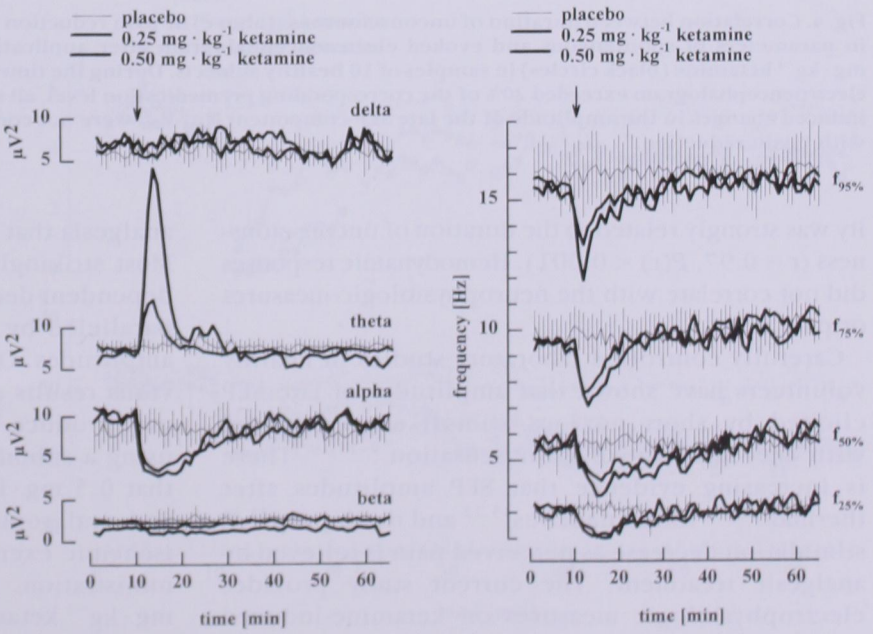

Fig. 3. Treatment effects on parameters of spontaneous electroencephalogram activity before and after medication for all treatment groups. ***Left:*** **Time course of the power in different frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), and beta (12–30 Hz).** ***Right:*** **time course of four frequency percentiles. Given are mean values and their standard errors for 1-min intervals. The most obvious effects were a marked increase in theta power after injection of 0.5 mg · kg^{-1} ketamine and a decrease in alpha power. Corresponding to changes in theta activity, spectral edge ($f_{95\%}$) was significantly reduced. Although the mean median frequency ($f_{50\%}$) was significantly reduced immediately after ketamine injection, for subjects who showed low baseline alpha power, ketamine-induced theta activation sometimes resulted in an increase of the median frequency, even in periods in which the subjects were unresponsive.**

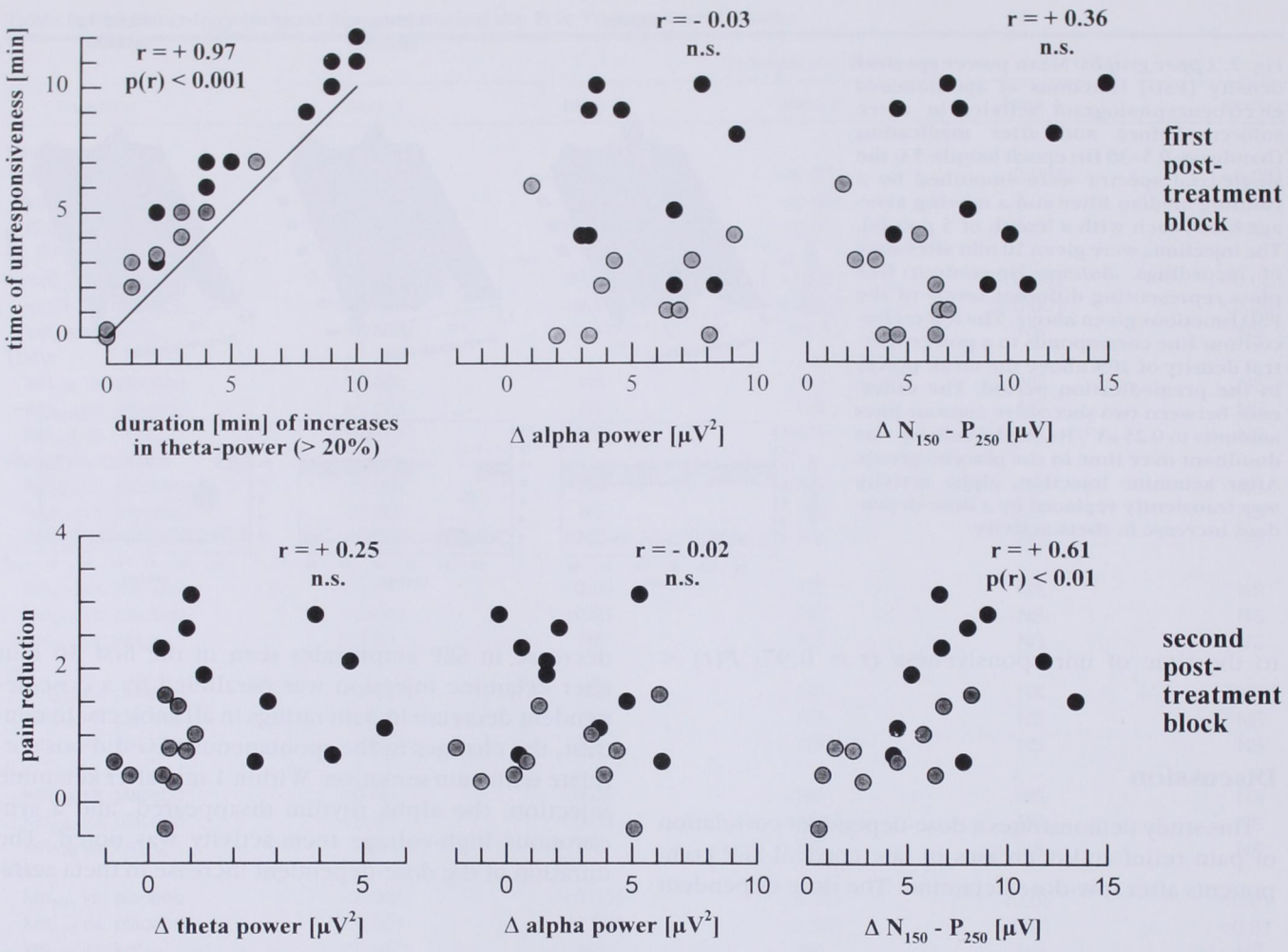

Fig. 4. Correlation between duration of unconsciousness (above) or pain reduction (below) and pharmacologic-induced changes in parameters of spontaneous and evoked electroencephalogram after application of 0.25 mg · kg^{-1} (gray circles) and 0.50 mg · kg^{-1} ketamine (black circles) in samples of 10 healthy subjects. During the time in which the theta power of the spontaneous electroencephalogram exceeded 20% of the corresponding premedication level, all subjects were unconsciousness. The ketamine-induced changes in the amplitude of the late SEP-component N_{150}-P_{250} were not correlated with "time of unresponsiveness" but with "pain reduction."

ity was strongly related to the duration of unconsciousness ($r = 0.97$, $P(r) < 0.001$). Hemodynamic responses did not correlate with the neurophysiologic measures or pain relief.

Carefully controlled laboratory studies in healthy volunteers have shown that amplitudes of late SEP elicited by short noxious stimuli are correlated with the intensity of pain sensation.[9–13,19] There is increasing evidence that SEP amplitudes after thermal[9,20,21] intracutaneous[15,22] and tooth pulp[23,24] stimulation decrease as perceived pain is relieved by analgesic treatment. The current study provides electrophysiologic measures on ketamine-induced analgesia that can supplement clinical observations. Most strikingly, after low-dose ketamine, the dose-dependent decrease in subjective pain sensation was paralleled by a dose-dependent attenuation in SEP amplitudes. Our findings are in agreement with previous results showing that 0.44 mg · kg^{-1} ketamine may produce long-lasting analgesia.[25] Grant *et al.*,[2] using a submaximal tourniquet technique, showed that 0.5 mg · kg^{-1} ketamine given by intramuscular and oral route prolonged the period of pain-free ischemic exercise for at least 30 min after drug administration. In addition, it was shown that 0.5 mg · kg^{-1} ketamine increases pressure pain detection

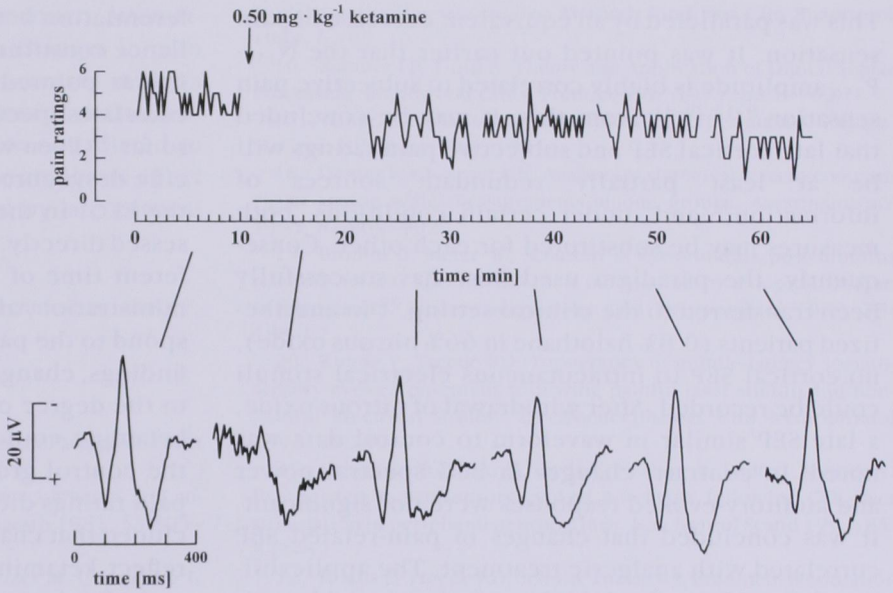

Fig. 5. Example of pain ratings (upper graph) in response to intracutaneous electrical stimuli before and after administration of 0.5 mg · kg $^{-1}$ ketamine in one subject. After ketamine injection, the subject became unconscious, and no pain ratings could be obtained for 10 min. In contrast, SEP were attenuated but still recordable. On awakening, pain ratings were lower when compared with the premedication level during the whole observation period. This long-lasting analgesic effect was reflected by a comparable decrease in the amplitude of the cerebral potential.

and tolerance thresholds and attenuates pain sensation induced by electrical stimuli.[5]

Although we did not compare the effect of ketamine to that of other analgesics, our results suggest that the effect of ketamine on late cortical SEP is less depressant than that observed with narcotic analgesics like morphine, fentanyl, or alfentanil.[23,26] From these findings, it may be concluded that the analgesic potency of 0.25–0.5 mg · kg^{-1} ketamine with a significant reduction in pain sensation elicited by electrical stimuli is superior to that of aspirin[27] and less than the analgesic effects of centrally acting opioids like tilidine.[28]

Our results are similar to previous findings from *Buchsbaum et al.*,[29] who studied the effects of 5 mg morphine on cortical SEP. In their study, cortical SEP amplitudes were depressed by approximately 15%.

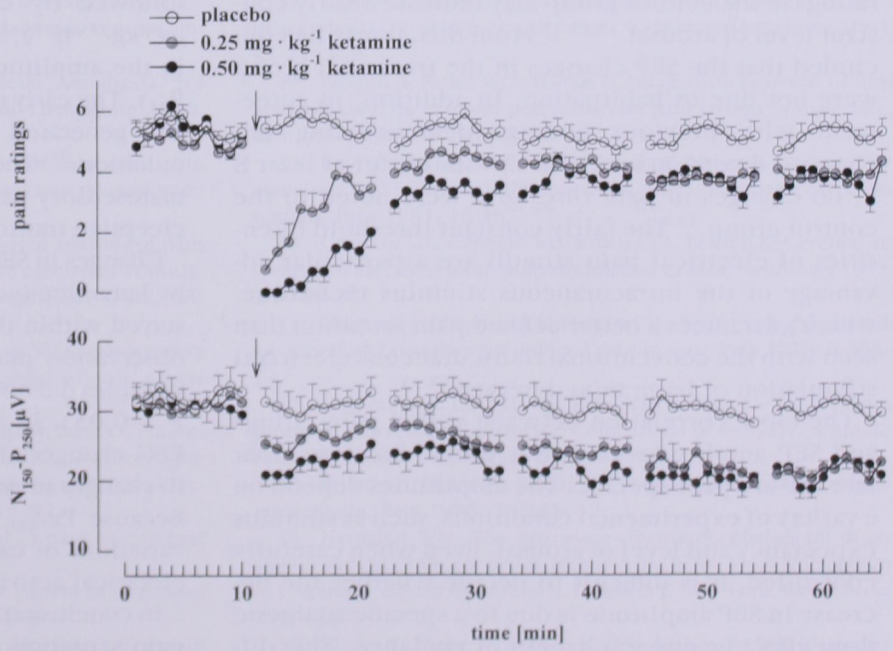

Fig. 6. Pain ratings (upper graph) and amplitude differences (lower graph) of pain-relevant cerebral potentials components in response to the intracutaneous stimuli before and after medication for all treatment groups. Given are mean values and their standard errors for 1-min intervals. Injection of ketamine resulted in a dose-dependent attenuation of the SEP amplitude and a corresponding reduction of pain sensation throughout the whole observation period.

This was paralleled by an equivalent decrease in pain sensation. It was pointed out earlier that the N_{150}-P_{250} amplitude is highly correlated to subjective pain sensation.[9–12,29–31] From this, it may be concluded that late cortical SEP and subjective pain ratings will be at least partially redundant sources of information[32] and, under certain conditions, both measures may be substituted for each other. Consequently, the paradigm used here has successfully been transferred to the clinical setting.[22] In anesthetized patients (0.8% halothane in 66% nitrous oxide), no cortical SEP to intracutaneous electrical stimuli could be recorded. After withdrawal of nitrous oxide, a late SEP similar in waveform to control data was noted. In contrast, changes in EEG spectral power and auditory-evoked responses were not significant. It was concluded that changes in pain-related SEP correlated with analgesic treatment. The applicability of the electrophysiologic technique used here is supported by its intraindividual reliability and its consistency with previous reports on the sensitivity to analgesic treatment effects.[19,29]

Habituation and changes in vigilance are known to affect evoked cortical responses. Randomization of stimulus conditions (intensity and interstimulus intervals) was shown to be of importance to minimize habituation and sensitization effects.[11] No arousal scores were measured in the current study. However, it was shown previously that unchanged SEP and pain ratings in the control group may indicate a fairly constant level of arousal.[10,11,15] From this, it may be concluded that the SEP changes in the treatment group were not due to habituation. In addition, in agreement with previous findings demonstrating unchanged detection and pain thresholds for at least 8 h, no changes in pain threshold were noted in the control group.[15] The fairly constant threshold intensities of electrical pain stimuli are a particular advantage of the intracutaneous stimulus technique, which guarantees a better defined pain sensation than seen with the conventional transcutaneous electrical stimulation of large mixed nerves.[15,33]

The close correlation between verbal pain ratings and SEP amplitudes does not prove, however, that late SEP are pain-specific. The amplitudes depend on a variety of experimental conditions, such as stimulus expectancy and level of arousal. Even when carefully controlled, it is difficult to decide whether the decrease in SEP amplitude is due to a specific analgesic drug effect or due to changes in vigilance. This differentiation between pain relief and decrease in vigilance constitutes a basic problem in pain research.[26] It was pointed out previously that in the EEG, no correlates specific for pain sensation have been found so far.[34] Even with severe pain stimuli, only nonspecific desynchronization patterns may be observed in the EEG. In the current study, vigilance was not assessed directly. However, after an intraindividual different time of unresponsiveness after ketamine administration, all subjects were vigilant enough to respond to the pain stimulus. Consistent with previous findings, changes in EEG parameters were not related to the degree of pain relief.[34] Because the effects of ketamine could clearly be separated from those of the control group, in which EEG activity, SEP, and pain ratings did not change over time, it may be concluded that changes in electrophysiologic parameters reflect ketamine effects. The time of unresponsiveness after ketamine was significantly correlated to increases in theta power, but not to SEP amplitudes. Conversely, SEP but not EEG were highly correlated to pain ratings. It may be concluded that cortical SEP may serve as an indicator of pain relief even in periods when no subjective pain report is available.

The effects of ketamine on early cortical SEP were studied previously.[35,36] Low-dose ketamine (0.5 $mg \cdot kg^{-1}$) did not change subcortical or early cortical (N_{20}-P_{25}) SEP components after median nerve stimulation. Using larger ketamine doses (2 $mg \cdot kg^{-1}$ bolus followed by continuous infusion at a rate of 30 $\mu g \cdot kg^{-1} \cdot h^{-1}$), Schubert *et al.*[36] demonstrated increases in the amplitude of the early cortical response (N_{19}-P_{22}). The early cortical SEP components are most probably generated in the thalamus or the thalamocortical radiation.[37] They reflect the integrity of afferent somatosensory pathways but may not be specific for nociceptive transmission.

Changes in SEP or EEG seen here cannot be explained by ketamine-induced alterations in HR or MAP, which stayed within the physiologic range during the entire observation period. These changes in hemodynamic variables did not correlate to changes in SEP ($r = -0.14$; $P > 0.05$). In addition, it was shown previously that EEG changes after low-dose ketamine are not related to changes in systemic or intracranial hemodynamics.[38] Because $P_{ET_{CO_2}}$ was constant over time, an effect of variations of carbon dioxide concentrations on brain electrical activity also can be excluded.

In conclusion, the current study shows that subjective pain sensation is reduced by bolus injection of low-

dose ketamine in a dose-dependent manner. Attenuation of late cortical SEP correlated to changes in pain sensation. In the spontaneous EEG, increases in theta activity coincided to the duration of loss of consciousness. Changes in EEG parameters were not related to pain relief. These data indicate that the analgesic effect of low-dose ketamine may be assessed by late cortical SEP.

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