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Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients

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Abstract

Central mechanisms related to referred muscle pain and temporal summation of muscular nociceptive activity are facilitated in fibromyalgia syndrome (FMS) patients. The present study assessed the effects of an NMDA-antagonist (ketamine) on these central mechanisms. FMS patients received either i.v. placebo or ketamine (0.3 mg/kg, Ketalar®) given over 30 min on two separate occasions. Habitual pain intensity was assessed on a visual analogue scale (VAS). Initially, 29 FMS patients received ketamine or isotonic saline to determine which patients were ketamine responders (>50% decrease in pain intensity at rest by active drug on two consecutive VAS assessments). Fifteen out of 17 ketamine-responders were included in the second part of the study. Before and after ketamine or placebo, experimental local and referred pain was induced by intramuscular (i.m.) infusion of hypertonic saline (0.7 ml, 5%) into the tibialis anterior (TA) muscle. The saline-induced pain intensity was assessed on an electronic VAS, and the distribution of pain drawn by the subject. In addition, the pain threshold (PT) to i.m. electrical stimulation was determined for single stimulus and five repeated (2 Hz, temporal summation) stimuli. The pressure PT of the TA muscle was determined, and the pressure PT and pressure pain tolerance threshold were determined at three bilaterally located tenderpoints (knee, epicondyle, and mid upper trapezius). VAS scores of pain at rest were progressively reduced during ketamine infusion compared with placebo infusion. Pain intensity (area under the VAS curve) to the post-drug infusion of hypertonic saline was reduced by ketamine ($-18.4 \pm 0.3\%$ of pre-drug VAS area) compared with placebo ($29.9 \pm 18.8\%$, $P < 0.02$). Local and referred pain areas were reduced by ketamine ($-12.0 \pm 14.6\%$ of pre-drug pain areas) compared with placebo ($126.3 \pm 83.2\%$, $P < 0.03$). Ketamine had no significant effect on the PT to single i.m. electrical stimulation. However, the span between the PT to single and repeated i.m. stimuli was significantly decreased by the ketamine ($-42.3 \pm 15.0\%$ of pre-drug PT) compared with placebo ($50.5 \pm 49.2\%$, $P < 0.03$) indicating a predominant effect on temporal summation. Mean pressure pain tolerance from the three paired tenderpoints was increased by ketamine ($16.6 \pm 6.2\%$ of pre-drug thresholds) compared with placebo ($-2.3 \pm 4.9\%$, $P < 0.009$). The pressure PT at the TA muscle was increased after ketamine ($42.4 \pm 9.2\%$ of pre-drug PT) compared with placebo ($7.0 \pm 6.6\%$, $P < 0.011$). The present study showed that mechanisms involved in referred pain, temporal summation, muscular hyperalgesia, and muscle pain at rest were attenuated by the NMDA-antagonist in FMS patients. It suggested a link between central hyperexcitability and the mechanisms for facilitated referred pain and temporal summation in a sub-group of the fibromyalgia syndrome patients. Whether this is specific for FMS patients or a general phenomena in painful musculoskeletal disorders is not known.

Keywords: Fibromyalgia; NMDA-antagonist; Referred pain; Temporal summation; Muscular hyperalgesia

1. Introduction

Muscle pain and widespread deep hyperalgesia characterize the symptoms of fibromyalgia syndrome (FMS) (Wolfe et al., 1990). Recently, it was found that the gain of temporal summation was increased in FMS patients because the pain threshold for repeated intramuscular electrical stimuli, and not single stimulus, was decreased significantly in FMS patients compared with controls (Sörensen et al., 1998).

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Moreover, experimental painful stimulation of the tibialis anterior (TA) muscle by hypertonic saline gave extended areas of referred pain in FMS patients compared with a control group (Sörensen et al., 1998). A similar phenomenon has recently been shown to exist also in whiplash patients (Johansen et al., 1999). The referred pain area was not only exaggerated compared with controls, but referred pain also appeared at completely different structures (proximal referred pain) in patients compared with controls (mainly distally referred pain). This suggested that the central processing of nociceptive stimuli from the muscles might be up-regulated in FMS patients. Several lines of evidence suggest that central hyperexcitability can be induced by a nociceptive barrage from muscles. Intense stimulation of muscle afferents in animals is followed by hyperexcitability of dorsal horn neurones (Wall and Woolf, 1984; Hoheisel et al., 1993, 1997) and expansion of their receptive fields (Cook et al., 1987; Hoheisel et al., 1993, 1997). Therefore, it is likely that clinical muscle pain conditions can evoke central hyperexcitability (Mense, 1994).

Repeated stimulation of C-fibres leads to a progressive increase in the firing rates of dorsal horn neurones (wind-up) which are reduced by application of an NMDA-antagonist (Davies and Lodge, 1987; Dickenson and Sullivan, 1987). Involvement of NMDA-receptors in temporal summation of heat and electrical cutaneous pain stimuli has been shown in human studies (Price et al., 1994; Arendt-Nielsen and Petersen-Felix, 1995; Andersen et al., 1996). Moreover, temporal summation is facilitated in areas of secondary cutaneous hyperalgesia (central hyperexcitability), and this facilitation is reduced by ketamine (Andersen et al., 1996). Thus, the facilitated temporal summation of muscle pain in FMS patients (Sörensen et al., 1998) may be reduced by an NMDA-antagonist.

Animal studies have shown that NMDA-receptors are involved in the generation of central hyperexcitability (Haley et al., 1990; Woolf and Thompson, 1991). Myositis-induced central hyperexcitability can be explained by an increased efficacy of synapses on converging dorsal horn neurones. This increased efficacy can be normalized by an NMDA-antagonist (Hoheisel et al., 1997). Therefore, it is suggested that NMDA-receptors could be involved in maintaining muscular hyperalgesia in muscle pain patients (Hoheisel et al., 1997). It is not clear if the NMDA-receptor plays a role for muscle pain at rest since the spontaneous activity of dorsal horn neurones is not increased by myositis-induced central hyperexcitability or decreased by an NMDA-antagonist (Hoheisel et al., 1997). It is possible, however, that non-nociceptive muscle afferents (e.g. proprioceptors) may cause pain at rest (allodynia) through increased central excitability (Kramis et al., 1996). It has been shown that chronic musculoskeletal pain responds better to an NMDA-antagonist (ketamine) compared with morphine management (Sörensen et al., 1995) indicating a role of central hyperexcitability in these patients.

In the present double-blinded, placebo-controlled study on FMS patients, we investigated the effect of ketamine on muscle pain at rest (experiment 1), muscular hyperalgesia, temporal summation of muscle pain, and referred pain pattern (experiment 2). The patients included in experiment 2 were those responding to the ketamine treatment in experiment 1.

2. Material and methods

2.1. Subjects

Twenty-nine FMS females (mean age: 45 years; age range: 31–64; mean duration of FMS diagnosis: 3.2 years) completed experiment 1, and 15 (mean age: 43 years; age range: 31–58; mean duration of FMS diagnosis: 3.7 years) of these participated in experiment 2. The patients had been referred to the Department of Rheumatology or the Pain and Rehabilitation Centre at the University Hospital of Linköping. They all fulfilled the classification criteria for FMS proposed by the American College of Rheumatology 1990 (Wolfe et al., 1990). The study was conducted in accordance with the Declaration of Helsinki, approved by the local Ethics Committee, and written informed consent was obtained from all participants before inclusion.

2.2. Pharmacological intervention

2.2.1. Drugs

In both experiments 1 and 2, ketamine hydrochloride (0.3 mg/kg, Ketalar®, Park Davis) or isotonic saline (9 mg/ml NaCl) were administrated intravenously over 30 min in a randomized, double-blind, cross-over design. The infusions were accomplished with a syringe pump (SP-100, JMS, Hiroshima, Japan). Each session was separated by one week. Electrocardiography and blood pressure were monitored. In experiment 2, blood samples were collected by vein puncture of the contralateral arm. The samples were centrifuged, the plasma were separated and frozen (−70°C). The plasma samples were analysed for ketamine and norketamine by a solid phase extraction method and ion-pair high-performance liquid chromatography (HPLC) (Geisslinger et al., 1991; Josefsson et al., 1995).

2.2.2. Assessment of pain at rest and reaction times

Sedation and how well the patients could co-operate were assessed by the reaction time determined by the reaction to 15 consecutive beeps (1000 Hz tone computer delivered) with 4–6 s interval. The subject was asked to press a button as fast as possible after the beep. A mean of the 15 trials was used.

Pain intensity at rest was assessed on a VAS scale where 0 cm indicated ‘no pain’ and 10 cm ‘worse pain imaginable’. VAS scores of the widespread pain and of the pain in the most painful area were obtained. The patients were classified into three different groups according to the VAS scores of the widespread pain: responders, placebo-responders, and

non-responders. The criterion for (1) a placebo-responder was a 50% reduction of two consecutive widespread pain VAS-scores (minimum 1.5 cm on a VAS) in the placebo session compared with baseline VAS scores, (2) a ketamine-responder was a 50% reduction of two consecutive widespread pain VAS-scores (minimum 1.5 cm on a VAS) in the ketamine session compared with baseline VAS scores and in addition not characterized as a placebo-responder, and (3) non-responders were not characterized as placebo-responder or ketamine-responder (Sörensen et al., 1997). The pain intensity should be reduced by minimum 1.5 cm on a VAS to ensure a reliable characterisation for patients with low intensity of widespread pain.

2.3. Assessment of somatosensory sensibility and referred pain

Pressure pain threshold (PT) and tolerance (PTOL) threshold were determined at three bilaterally located tenderpoints (medial fat pad of the knee, 2 cm distal to the medial epicondyle, and mid-upper trapezius). Secondly, the pressure PT was tested on the belly of the right TA muscle. Thirdly, the PT to electrical single and repeated stimuli of the left TA muscle and of the skin above the TA muscle was assessed. Fourthly, muscular sensibility and pattern of referred pain were assessed by infusion of hypertonic saline into the right TA muscle.

2.3.1. Pressure algometry

Pressure PT and PTOL threshold were determined with an electronic algometer (Somedic AB, Sweden) mounted with a 1 cm^2 probe. The pressure was increased with 50 kPa/s until the subject detected the pressure PT or PTOL. At the tenderpoints, the PT and PTOL were only determined once, but for the TA muscle the PT was found as the mean of three trials.

2.3.2. Cutaneous and intramuscular electrical stimulation

Two insulated needle electrodes (13R27, Dantec, Skovlunde, Denmark) with a 3 mm uninsulated tip, inserted into m. TA, and separated by 1 cm were used to test the intramuscular (i.m.) sensibility to electrical stimulation. Two surface electrodes (13L20, Dantec, Skovlunde, Denmark) were used to test the cutaneous sensibility to electrical stimulation. A computer-controlled constant current stimulator (Aalborg University, Denmark) was used. Each stimulus consisted of a train of five 1-ms rectangular pulses repeated at 200 Hz. The PT to electrical stimulation was determined with a computer-controlled version of a modified staircase principle where the PT was defined as the mean of the five stimulation intensities evoking the sensations just exceeding the PT. The PTs to single and repeated (2 Hz) stimuli were determined. The summation PT was defined as the stimulus intensity causing the sensation to increase throughout the stimulus series and to induce pain at least at the 5th stimulus (Arendt-Nielsen et al., 1994, 1997b). The summation ratio was calculated: difference between the PT to single and repeated stimuli divided by the PT to single stimulus. The degree of temporal summation was reflected in the summation ratio as a low summation ratio indicated minor efficacy of temporal summation compared with a high value of the summation ratio.

2.3.3. Saline-induced muscle and referred pain

Infusion of hypertonic saline was accomplished with a computer-controlled syringe pump (IVAC, model 770) and a 10 ml plastic syringe. A tube (IVAC G30303, extension set with polyethylene inner line) was connected from the syringe to a disposable needle (27G, 20 mm) (Graven-Nielsen et al., 1997a). Infusion of sterile hypertonic saline (5.7%) into the right TA muscle was initiated with a bolus infusion of 0.5 ml over the first 20 s (rate: 90 ml/h), and 0.2 ml was then infused over the next 40 s (rate: 18 ml/h). In each session two infusions (before and after medication) separated by 2 cm were given.

The pain intensity of the saline-induced muscle pain was continuously scored on a 10 cm electronic visual analogue scale (VAS) where 0 cm indicated 'no pain' and 10 cm 'worse pain imaginable'. Pain intensities were sampled every 5th second by the computer and recorded for 20 min including the infusion time. The area under the VAS time curve (VAS area), maximal VAS (VAS peak), and the duration (VAS duration) of the saline-induced pain were determined from the VAS recordings. The subject drew the distribution of pain on an anatomical map before and after the experiments. The circumference was digitized (ACECAD D9000 + digitizer), and the area was calculated (Sigma-Scan) (Graven-Nielsen et al., 1997a). Pain around the injection site was defined as local pain. Referred pain was defined as pain that occurred outside and separated from the boundaries surrounding the local pain (Stohler and Lund, 1994).

2.4. Protocols

Two consecutive experiments were performed. The first experiment was used to find the ketamine-responders (Sörensen et al., 1997), who were included in experiment 2. This experiment was performed 1–6 months after experiment 1.

2.4.1. Experiment 1: screening for ketamine-responders

In two sessions separated by 1 week, the FMS patients received either placebo or ketamine given over 30 min. Before, 10, 20, 30, 40, 50, 60, 75, 90 and 150 min after infusion start, the patients gave VAS scores of their pain at rest.

2.4.2. Experiment 2: effect of ketamine on somatosensory sensibility and referred pain

In two sessions separated by 1 week, the FMS patients (ketamine-responders from experiment 1) received either

placebo or ketamine given over 30 min. The investigators were blinded as to infusion drug. Before, 10, 20, and 30 min after infusion start, the patients gave VAS scores of the ongoing pain. Somatosensory sensibility assessments (pressure algometry, cutaneous and i.m. electrical stimulation and saline-induced muscle pain) were performed before and after completed medication and took maximum 30 min (i.e. no assessment of somatosensory sensibility during infusion of ketamine or placebo). Reaction time and blood sampling were performed before and after medication and after the somatosensory sensibility assessment.

2.5. Statistical analysis

The non-parametric Friedmans test of variance was used on paired multiple data sets, and when it was found significant, it was followed by the non-parametric Student-Newman-Keuls (SNK) test in order to correct for multiple comparisons. The non-parametric Kruskal-Wallis test was used to test data between groups. In each session, the percentage difference in outcome variables between the pre- and post-drug treatment was calculated. The non-parametric Wilcoxon test was used to test if there was a significant difference between the active and placebo session. Spearman's correlation coefficient was used to describe correlation between ongoing pain and experimental parameters. Significance was accepted at $P < 0.05$ in all tests. NS denoted non-significant.

3. Results

3.1. Screening for ketamine-responders (experiment 1)

Seventeen out of 29 FMS patients fulfilled the definition of ketamine-responder. Seven were non-responders and five placebo responders. The age, duration of widespread pain and duration of FMS diagnosis did not differ significantly between the three groups of FMS patients (Table 1). The ketamine-responders gave VAS scores which were significantly reduced during ketamine infusion compared with before (Fig. 1A; Friedman: $P < 0.0001$; SNK: $P < 0.05$) in contrast to the placebo infusion. In general, non-responders and placebo responders showed minor decrease in VAS scores compared with ketamine responders (Fig. 1B).

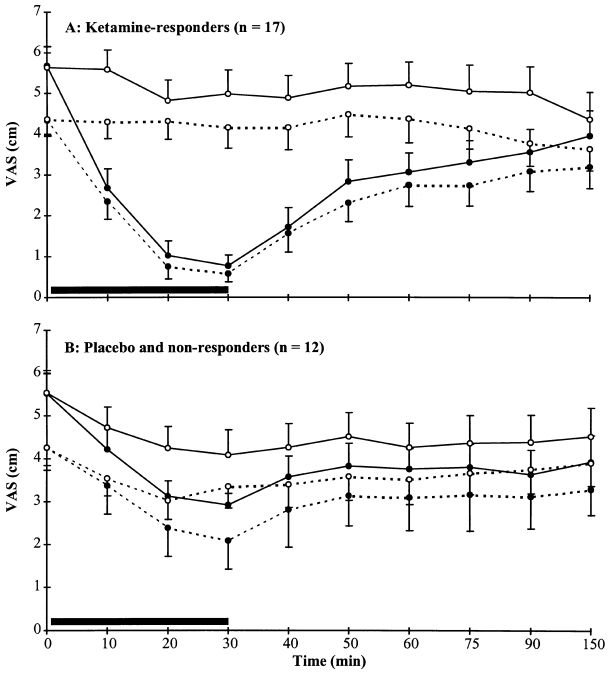

Fig. 1. Mean (±SE) VAS scores of the habitual pain in the FMS patients during i.v. infusion of ketamine (●) and placebo (○) in experiment 1. The VAS scores are related to the widespread pain intensity (dotted lines) and the pain intensity of the most painful part of the body (solid lines). The black bar indicates the time for drug infusion. (A) Seventeen FMS patients gave VAS scores of their habitual pain which were decreased (>50%) during infusion of ketamine and not during infusion of isotonic saline (ketamine-responders). (B) Twelve FMS patients gave VAS scores of their habitual pain which were decreased less than 50% during infusion of ketamine or isotonic saline (non-responders, $n = 7$) or decreased more than 50% during infusion of isotonic saline (placebo-responders, $n = 5$).

3.2. Effect of ketamine on somatosensory sensibility and referred pain (experiment 2)

Of the 17 patients included from experiment 1, one dropped out due to acute depression and one due to acute abdominal surgery. Fifteen FMS patients participated in experiment 2. VAS scores of the widespread pain were progressively reduced during the 30-min infusion of ketamine compared with the pre-infusion VAS-score (Fig. 2; Friedman: $P < 0.0001$; SNK: $P < 0.05$) in contrast to the placebo session (Friedman: NS).

The plasma concentration of ketamine was significantly decreased after the sensory testing compared with the one before (54.3 ± 7.3 vs. 124.7 ± 12.4 ng/ml, $P = 0.0015$) whereas the plasma concentration of norketamine was

Table 1
Description of responder groups after experiment 1 (mean years and range)

	Ketamine-responders ($n = 17$)	Non-responders ($n = 7$)	Placebo-responders ($n = 5$)
Age	44 (31–38)	48 (35–53)	46 (34–64)
Duration of widespread pain	7 (1–15)	4 (1–8)	6 (2–13)
Duration of FMS diagnosis	4 (1–15)	1 (1–1)	4 (1–13)

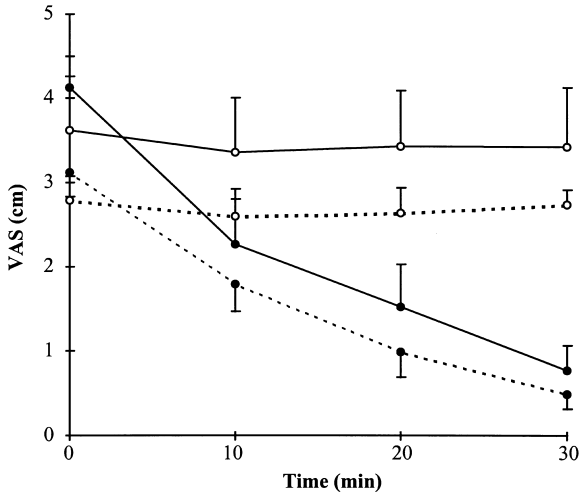

Fig. 2. Mean (±SE, $n = 15$) VAS scores of the habitual pain in the FMS patients during i.v. infusion of ketamine (●) and placebo (○) in experiment 2. The VAS scores are related to the widespread pain intensity (dotted lines) and the pain intensity of the most painful part of the body (solid lines).

increased (30.9 ± 4.9 vs. 19.9 ± 2.9 ng/ml, $P = 0.03$). In the ketamine session, the reaction time was increased by 102 ± 27 ms before the sensory testing compared with the pre-infusion reaction time (Table 2). Reaction time immediately after the sensory testing (maximal 30 min after drug infusion stop) was on average increased by 15 ± 12 ms compared with the pre-infusion reaction time after placebo infusion.

Mean pressure PTOL threshold from the three paired tenderpoints was significantly increased by ketamine compared with the placebo session in contrast to the pressure PT (Table 3). Pressure PT at the TA muscle was significantly increased after ketamine compared with the placebo session. The pre-drug pressure PT at tenderpoints was significantly lower than the pressure PT at the TA muscle (Table 3; $P = 0.002$) indicating that the main effect of ketamine was found at high intensity pressure stimulation.

Pain intensity (VAS area and VAS peak) after i.m. infusion of hypertonic saline was significantly reduced by ketamine compared with placebo (Table 4). Moreover, in the placebo session the saline-induced pain (VAS peak) was increased ($P = 0.03$) after the second infusion (post-drug) compared with the first infusion (pre-drug). The local and referred pain areas were reduced by ketamine compared with the placebo session (Table 4). Moreover, the saline-induced referred pain area was significantly ($P = 0.014$) increased after the second saline infusion compared with the first infusion (pre-drug).

There was no significant effect of ketamine on the PT to single electrical stimulus, but the summation ratio to intramuscular and cutaneous electrical stimuli was significantly decreased (i.e. inhibited temporal summation) by ketamine compared with the placebo session (Table 5).

The intensity of ongoing widespread pain (before and after medication) was significantly correlated to (1) the pressure PT at the TA muscle ($R = -0.33$, $P = 0.01$) and (2) saline-induced pain intensity (VAS area), and size of local and referred pain areas ($R > 0.31$, $P < 0.02$). No significant correlation was found between ongoing pain and the summation ratio to electrical stimulation. However, the summation ratio to intramuscular electrical stimulation was significantly correlated to the saline-induced muscle pain intensity (VAS area; $R = 0.28$, $P = 0.03$).

Table 2
Mean reaction time (ms ± SE; $n = 15$)[a]

	Pre-drug	Post-drug	After sensory test	*P*-value
Ketamine	269 ± 18	371 ± 32*	277 ± 12	0.00003
Placebo	265 ± 20	265 ± 13	280 ± 16*	0.03

[a] The *P*-value is from the Friedman test, and significantly (SNK: $P < 0.05$) increased reaction time compared with the pre-drug reaction times is indicated (*).

4. Discussion

Muscular hyperalgesia and muscle pain at rest were reduced by ketamine. The present study showed that the mechanisms of referred pain and temporal summation after intramuscular stimulation were attenuated by the NMDA-antagonist ketamine in a major sub-group of the fibromyalgia syndrome patients. This suggested a link between central hyperexcitability and the mechanisms for temporal summation and referred pain. The increased referred pain area and intensity for the second infusion in the placebo-session may indicate a potentiation of the central hyperexcitability.

4.1. Ketamine-responders

Seventeen of the 29 FMS patients could be categorized as ketamine responders after a placebo-controlled infusion. This is comparable with eight of 18 subjects in our previous study (Sörensen et al., 1998). The present plasma concentrations of ketamine and norketamine are higher than those obtained in a clinical study where a positive correlation between pain relief and plasma concentrations was found (Eide et al., 1995). The applied low-dose ketamine produced a significant effect on both experimental and clinical pain parameters. Recently, Schmid et al. (1999) reviewed the efficacy of low-dose ketamine in postoperative pain conditions and concluded that low-dose ketamine is a valuable way to improve pain management. It could further be expected that a combination of ketamine and low doses opioids may even further enhance the effect (Plesan et al., 1998).

4.2. Referred pain

The spread of referred pain has been found to be extended in FMS patients compared with controls (Sörensen et al.,

Table 3
Mean pressure pain threshold (PT) and tolerance (PTOL) threshold (±SE, $n = 15$) of the tenderpoints (average of the six tenderpoints) bilaterally located at the knee, at the epicondyle, and at the trapezius muscle[a]

	Drug	Pre-drug	Post-drug (% of pre-drug)	*P*-value
Pressure PT (kPa)	Ketamine	269.0 ± 28.7	24.0 ± 12.2	NS
	Placebo	216.6 ± 22.4	12.1 ± 6.2	
Pressure PTOL (kPa)	Ketamine	425.0 ± 42.9	21.1 ± 7.3	0.004
	Placebo	402.7 ± 39.8	−2.8 ± 4.6	
Pressure pain threshold of the TA muscle (±SE, n = 15)				
Pressure PT (kPa)	Ketamine	346.3 ± 33.3	42.0 ± 8.6	0.005
	Placebo	372.8 ± 44.3	4.7 ± 6.6	

[a] Post-drug values as percentage increase/decrease in pre-drug values. The *P*-value is from the Wilcoxon test between post-drug values in the ketamine and placebo session.

1998). Similar results are found in chronic whiplash associated disorder patients compared with control subjects (Johansen et al., 1999) and in patients with irritable bowel syndrome where referred pain to visceral balloon distension was increased compared with control subjects (Swarbrick et al., 1980; Munakata et al., 1997). Referred pain is probably a central mechanism because it is possible to induce referred pain to limbs with complete sensory loss due to spinal injury (Whitty and Willison, 1958) or a peripheral anaesthetic block (Feinstein et al., 1954; Laursen et al., 1997, 1998). Hypothetically, convergence of nociceptive afferents on dorsal horn neurones may mediate referred pain, but convergence between muscle and other deep tissues is an infrequent finding (Hoheisel and Mense, 1990). Other animal studies show enlargement of receptive fields by noxious muscle stimuli after a few minutes (Hoheisel and Mense, 1989; Hu et al., 1992; Hoheisel et al., 1993). Such expansion of receptive fields is probably due to increased efficacy of synaptic connections (central hyperexcitability). Recordings from a dorsal horn neurone with a receptive field located in biceps femoris muscle show new receptive fields in TA muscle and at the foot after i.m. injection of bradykinin into TA muscle (Hoheisel et al., 1993). In the context of referred pain, the unmasking of new receptive fields due to central hyperexcitability could mediate referred pain. Thus, enlarged referred pain areas in muscle pain patients compared with controls may indicate a state of central hyperexcitability. Moreover, in the present study the ongoing muscle pain intensity was significantly correlated to the intensity and area of experimentally induced local and referred pain indicating that the facilitated central processing is closely related to the ongoing muscle pain.

In the present study, the area of referred pain was reduced by ketamine. This might be explainable by a reduction in the effect of central hyperexcitability. Similar findings can be observed in humans receiving intradermal injection of capsaicin. Capsaicin causes a rapid development of the central hyperexcitability (seen as secondary cutaneous hyperalgesia) (LaMotte et al., 1992), and in this model, ketamine has significantly reduced the area of secondary cutaneous hyperalgesia to pin-prick (Warncke et al., 1997). Moreover, the area of mechanical hyperalgesia around surgical incision was reduced by ketamine compared with placebo (Stubhaug et al., 1997). In animals, myositis

Table 4
Assessment of saline-induced pain (±SE, $n = 15$)[a]

	Drug	Pre-drug	Post-drug (% of pre-drug)	*P*-value
VAS area (cm/s)	Ketamine	2563.0 ± 379.9	−19.3 ± 9.0	0.012
	Placebo	2255.6 ± 311.3	24.6 ± 16.8	
VAS peak (cm/s)	Ketamine	8.40 ± 0.51	−16.5 ± 7.3	0.0067
	Placebo	7.37 ± 0.72	27.4 ± 13.1	
VAS duration (s)	Ketamine	445.7 ± 46.8	−8.8 ± 8.0	NS
	Placebo	557.3 ± 92.1	6.1 ± 12.1	
Area of:				
Local pain (arbit. units)	Ketamine	2.43 ± 0.63	−25.2 ± 8.2	0.005
	Placebo	1.97 ± 0.52	113.2 ± 78.4	
Referred pain (arbit. units)	Ketamine	3.09 ± 0.85	−3.7 ± 13.4	0.012
	Placebo	4.85 ± 1.59	112.4 ± 53.1	

[a] Post-drug values as percentage increase/decrease in pre-drug values. The *P*-value is from the Wilcoxon test between post-drug values in the ketamine and placebo session.

Table 5
Mean electrical PT at the TA muscle and skin (±SE, $n = 15$)[a]

	Drug	Pre-drug	Post-drug (% of pre-drug)	*P*-value
Electrical i.m. [PT: single (mA)]	Ketamine	4.49 ± 1.06	−1.4 ± 16.4	NS
	Placebo	3.00 ± 0.53	−4.8 ± 11.3	
Electrical i.m. [summation ratio]	Ketamine	0.31 ± 0.04	−42.3 ± 15.0	0.03
	Placebo	0.26 ± 0.04	50.5 ± 49.2	
Electrical skin [PT: single (mA)]	Ketamine	3.76 ± 0.59	12.9 ± 11.6	NS
	Placebo	3.53 ± 0.87	8.2 ± 8.5	
Electrical skin [summation ratio]	Ketamine	0.34 ± 0.05	−41.9 ± 13.0	0.02
	Placebo	0.24 ± 0.04	29.8 ± 22.9	

[a] Post-drug values as percentage increase/decrease in pre-drug values. The *P*-value is from the Wilcoxon test between post-drug values in the ketamine and placebo session.

increases the number of synaptic connections on dorsal horn neurones, and this finding is reversed by an NMDA-antagonist (Hoheisel et al., 1997). The opening of latent synaptic connections caused by myositis may be related to the mechanism of referred pain, and the effects of the NMDA-antagonist fit with the present finding of decreased referred pain area and intensity caused by ketamine.

In the placebo session, the second infusion of hypertonic saline caused significantly increased pain intensity and referred pain areas compared with the first infusion. In healthy pain-free subjects, it has been shown that sequential infusions separated by 6 min give reproducible pain intensities and pain areas when given at 2 cm separated sites (Graven-Nielsen et al., 1997b) as also used in the present study. If sequential injections are given at the same site, progressive decreases in the pain intensity and pain areas (Zhang et al., 1993; Graven-Nielsen et al., 1997b) and the muscle afferent firing rate (Paintal, 1960) are observed. Thus, the peripheral effects of hypertonic saline in pain-free subjects do not result in an increased pain intensity or pain areas as found in the placebo session of present study on FMS patients. A possible explanation is a potentiation of the central hyperexcitability caused by the first infusion influencing the effect of the second infusion.

4.3. Temporal summation

In animals, wind-up, which is the increased neuronal firing of dorsal horn neurones to a train of stimuli, is decreased by an NMDA-antagonist (Dickenson and Sullivan, 1987). Temporal summation is probably the initial part of wind-up because repeated stimulation for at least 20 sec is causing central hyperexcitability (Wall and Woolf, 1984), which is not seen after a short duration of temporal summation (Arendt-Nielsen et al., 2000). The relation between temporal summation and wind-up is also indicated because both phenomena are inhibited by blocking the NMDA-receptor (Dickenson and Sullivan, 1987; Price et al., 1994; Arendt-Nielsen and Petersen-Felix, 1995; Andersen et al., 1996; Arendt-Nielsen et al., 1996). Previous studies have also shown an inhibition of temporal summation to repeated, but not single electrical painful skin stimuli by ketamine in healthy subjects (Arendt-Nielsen and Petersen-Felix, 1995; Arendt-Nielsen et al., 1996). From studies on capsaicin-induced cutaneous hyperalgesia, the summation pain threshold for electrical stimuli in the secondary hyperalgesic area has been shown to decrease compared with baseline measurements, and the decrease was reversed by application of ketamine, whereas single stimulation is affected by neither secondary hyperalgesia (Arendt-Nielsen et al., 1996) nor ketamine (Andersen et al., 1996). Thus, central hyperexcitability is likely to augment temporal summation, and ketamine probably reduces central hyperexcitability. Previously, temporal summation of painful muscle stimuli was found to be more pronounced in FMS patients compared with controls (Sörensen et al., 1998) suggesting the involvement of central hyperexcitability in these patients. Moreover, in the present study temporal summation of muscle pain was reduced by ketamine.

Sequential infusions of hypertonic saline (0.1 ml) show that saline-induced muscle pain intensity and area are influenced by temporal summation (Graven-Nielsen et al., 1997b) in line with the present study where the summation ratio and saline-induced pain intensity was correlated. Interestingly, a larger number of subjects developed referred pain during the sequential infusions given at 90-s compared with 360-s interstimulus interval (Graven-Nielsen et al., 1997b). The size of the referred pain area tended to increase in a similar way during sequential infusions given at 90-s interstimulus interval. This is also found during sequential colon distension (Ness et al., 1990), bladder fillings (Ness et al., 1998) or continuous electrical gut stimulation (Arendt-Nielsen et al., 1997a) where an increase in the size of the referred pain area is observed together with increased evoked pain. A similar finding was made during intraneural stimulation of muscle nociceptive afferents in which the pain area increases with maintained stimulation (Marchettini et al., 1996). Thus, the mechanisms for temporal summation and referred pain are probably associated and together with the present results also related to central hyperexcitability.

4.4. Muscular hyperalgesia

In the present study, muscular hyperalgesia was assessed by pressure at points, which are tender according to the diagnostic criterion (Wolfe et al., 1990) and at the TA muscle, which is only occasionally tender. The sensibility to pressure stimulation at both tender and non-tender assessment sites was reduced by ketamine compared with placebo. In FMS patients hyperalgesia to pressure stimulation has previously been determined in muscles without ongoing pain (Lautenbacher et al., 1994; Sörensen et al., 1998). Moreover, Kosek et al. (1996) showed a relation between the increase in pressure sensibility and the ongoing pain intensity at the pressure site in FMS patients. A similar finding was seen in the present study where the decrease in ongoing pain due to ketamine was correlated to the increase in pressure pain threshold. The pressure pain threshold may possibly have been increased as a result of the increased reaction time. An increased reaction time of approximately 100 ms would, however, only explain an increase in pressure pain thresholds of 5 kPa (50 kPa/s 0.1 s), and we observed a significant increase in pressure pain thresholds of 90 kPa (Table 3).

Previously, hyperalgesia and allodynia has been reduced by an NMDA-antagonist in neurogenic pain patients (Kristensen et al., 1992; Eide et al., 1995; Felsby et al., 1996; Nikolajsen et al., 1996). The effects of ketamine in the present study indicate that muscular hyperalgesia in a major sub-group of FMS patients is mediated by a central mechanism involving NMDA receptors. This is in line with an animal study where the proportion of dorsal horn neurones responding to a peripheral electrical stimulation at C-fibres strength was increased by myositis (central hyperexcitability) and normalized with an NMDA-antagonist (Hoheisel et al., 1997). Nevertheless, peripheral sensitisation may be involved in hyperalgesia of tenderpoints and thus contribute to induction of central hyperexcitability (Henriksson, 1999). Moreover, increased intramuscular serotonin concentrations in FMS patients compared to controls have been suggested as a possible explanation for peripheral sensitisation (Ernberg et al., 1999). In whiplash patients, assessment of structures outside a possible traumatized area (i.e. no peripheral sensitisation) is showing facilitated muscular sensibility and extended spread of referred pain (Johansen et al., 1999) in line with the FMS patients (Sörensen et al., 1998). At present it is not known, however, if similar findings can be seen in patients with another trauma history, and thus it is not specific to whiplash or FMS.

4.5. Conclusion

The parallel inhibitory effect of ketamine on pain at rest, temporal summation, referred pain and muscular hyperalgesia suggests that the NMDA antagonist is targeting a common, facilitated central mechanism in a major sub-group of fibromyalgia syndrome patients. This suggests a link between central hyperexcitability and the mechanisms for referred pain, temporal summation, and muscular hyperalgesia in these patients. Whether this is specific for FMS patients or a general phenomenon in painful musculoskeletal disorders is not known.

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