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Exploring the neurophysiological basis of chest wall allodynia induced by experimental oesophageal acidification – evidence of central sensitization[1]

R. P. WILLERT,* C. DELANEY,* K. KELLY,* A. SHARMA,* Q. AZIZ* & A. R. HOBSON†

*GI Sciences Department, University of Manchester, Hope Hospital, Salford, Lancs, UK
†Neurology & GI CEDD, Clinical Pharmacology and Discovery Medicine, GSK R&D Ltd, Harlow, Essex, UK

Abstract *In somatic models of central sensitisation (CS) allodynia develops following changes to somatic A-β fibres, allowing these afferents which normally only process innocuous sensations to encode pain. The aim of this study was to determine whether somatic allodynia induced by visceral sensitisation occurs via N-Methyl-D-Aspartate (NMDA) receptor mediated changes to the neurophysiological characteristics of somatic A-β fibres. Twelve healthy subjects had oesophageal, chest wall and foot pain thresholds (PT) to electrical stimulation measured, and chest wall evoked potentials (CEP) recorded before and 30 minutes after distal oesophageal acidification on 2 separate visits. Intravenous ketamine (an NMDA receptor antagonist) or saline was given 30 minutes post acid with repeated oesophageal and chest wall PT measurements and CEP recordings. Distal oesophageal acidification reduced PT to electrical stimulation on the anterior chest wall (37 ± 10mA v 29 ± 7mA p = 0.01) and proximal oesophagus (46 ± 10mA v 33 ± 11mA p = 0.001) but not the foot (37 ± 25mA v 39 ± 23mA p = 0.12). The induction of chest wall somatic allodynia was accompanied by a reduction in the latency of the P1 (36 ± 3ms to 30 ± 4ms p = 0.016) and P2 (87 ± 7 ms to v 76 ± 7ms p = 0.049) components of the CEP. NMDA receptor antagonism reversed both visceral and somatic pain hypersensitivity but did not affect CEP latencies. These data provide objective neurophysiological evidence that CS contributes to the development of somatic allodynia following visceral sensitisation.*

Keywords *central sensitization: chest wall-evoked potentials, N-methyl-D-aspartate receptor, visceral hypersensitivity.*

INTRODUCTION

Pain associated either with peripheral tissue damage and inflammation or with lesions to the nervous system (neuropathic pain), is characterized by persistent pain hypersensitivity. Postinjury pain hypersensitivity is initially mediated by peripheral sensitization of primary afferent nerves, but this itself leads to an enhanced synaptic efficacy at the dorsal horn, which can outlast the duration of the injurious stimulus. This is known as central sensitization (CS) and is characterized by a reduction of activation threshold and increase in the responsiveness of dorsal horn neurones to a given sensory input, and by enlargement of their receptive fields.[1]

One consequence of peripheral and CS is that previously innocuous sensory input can evoke pain from both injured tissue (primary allodynia) and from the surrounding uninjured tissue (secondary allodynia). In animal somatic pain models primary allodynia occurs because of phenotypic changes to somatic A-β fibre afferents. Inflammatory mediators such as substance P and prostaglandins activate intracellular signalling pathways via G-protein-coupled receptors, or tyrosine kinase receptors, expressed on nociceptor terminals which then phosphorylate receptors and ion channels in the nociceptor terminal and so change their threshold and kinetics, allowing these afferents which normally encode innocuous sensations to encode pain.[2]

Address for correspondence
Professor Qasim Aziz, GI Sciences Department, University of Manchester, Hope Hospital, Salford, Lancs M6 8HD, UK.
Tel: +44 161 206 4362; fax: +44 161 206 1495; e-mail: qasim.aziz@manchester.ac.uk
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In human studies, evidence that CS contributes to somatic pain hypersensitivity has been provided by several experimental models.[3–5] In addition, it has been demonstrated that antagonism of the *N*-methyl-D-aspartate (NMDA) receptor, a receptor proven to play a pivotal role in the development of CS, can reduce or prevent somatic secondary allodynia as demonstrated by a concurrent reduction in pain sensitivity.[6–8]

In the viscera, animal studies involving direct electrophysiological recordings of spinal neurones suggest that CS is important in mediating visceral pain hypersensitivity.[9,10] Although direct recordings from spinal neurones are not possible in man, except during invasive spinal surgery, another method which non-invasively measures somatic and visceral afferent pathway sensitivity is the technique of cortical-evoked potentials (CEP).[11] Cortical-evoked potential is a well-established neurophysiological technique which represents the measurement of the sequence of voltage changes generated in the brain in response to a sensory stimulus. The recorded CEP waveform consists of both positive and negative deflections with each corresponding to specific steps in the central processing of sensory information. Cortical-evoked potentials have been acquired in response to stimulation of various somatic nerves and visceral organs including the oesophagus[12–14] and rectum.[12] Visceral CEP are thought to be mediated predominantly by spinal A-δ afferents which convey visceral afferent information to a wide array of cortical and subcortical regions.[15] Cortical-evoked potential can therefore provide an objective neurophysiological correlate of subjective pain threshold (PT) reporting, overcoming the inherent response bias often encountered in studies of pain.[16]

In a validated model of human visceral pain hypersensitivity,[17,18] the development of secondary allodynia in the proximal oesophagus, following a distal oesophageal acid infusion, corresponds to a reduction in latency of the CEP response obtained by stimulation of this proximal site.[19] This reflects enhanced sensitivity of the central visceral afferent pathway and supports the hypothesis that oesophageal secondary allodynia, in this experimental model, results from CS. Further evidence to support the role of CS as the likely mechanism responsible for the development of oesophageal secondary allodynia, in response to acid infusion, is provided by a study which demonstrated that NMDA receptor antagonism can block and reverse this phenomenon.[18]

Recent studies have shown that a distal oesophageal acid infusion also induces a reduction of PT in the area of viscerosomatic referral on the anterior chest wall.[20] As chest wall afferents project to dermatomal regions within the spinal cord which are convergent with oesophageal afferents[21] oesophageal acidification is likely to increase chest wall pain sensitivity by increasing the sensitivity of spinal dorsal horn neurones. However, subjective pain ratings following oesophageal acid infusion do not change in somatic control regions (i.e. the foot or hand),[17,18,20] which suggests that heightened somatic sensitivity only occurs in those regions that have convergent spinal input from the sensitized oesophageal afferents.

The aim of this study was to provide objective evidence that chest wall allodynia is associated with a change in the stimulus response characteristics of somatic A-β fibre afferents using CEP. A decrease in the latency of chest wall CEP would indicate increased sensitivity of the central afferent system and support the notion that CS is the primary mechanism by which secondary allodynia develops in this model. A secondary objective was to determine whether this response may be reversed by NMDA receptor antagonism.

MATERIAL AND METHODS

Subjects

Twelve healthy adult volunteers, eight female, age range 23–56 (mean age 32 years) were studied on two different occasions at least 2 weeks apart. All had normal medical assessments and none was taking any medication. Oesophageal manometry was performed and analysed using specialized software (Polygram for Windows 1995, Synectics Medical, Enfield, Middlesex, UK) and was normal in all subjects. The study was given full ethical approval from the regional ethics committee.

Electrical stimulation

Electrical stimulation was used to determine PTs in the proximal oesophagus. Oesophageal electrical stimulation was delivered via a pair of platinum ring electrodes (inter-electrode distance 1 cm) sited proximal to the tip of a 3 mm diameter catheter (Gaeltec, Dunvegan, Isle of Skye, Scotland). These electrodes were positioned 19 cm above the lower oesophageal sphincter. Electrical stimulation of the chest wall and foot was performed using a pair of disposable surface silver electrodes (Oxford Instruments, Medical Systems Division, Woking, Surrey, England) which were placed 1 cm apart on the dorsum of the right foot and on the anterior chest wall in the midline at the level of the sixth intercostal space after cleaning the skin with preparation paste.

The chest wall electrodes were positioned over the area to which the sensation evoked by the oesophageal electrical stimulus was referred. All electrodes were connected to an electrical stimulator (Model DS7, Digitimer Ltd, Welwyn Garden City, Herts, UK) and stimuli were delivered at a frequency of 0.5 Hz, using square wave pulses (500 μs duration), at intensities varying between 0 and 100 mA.

Cortical-evoked potentials

Cortical-evoked potentials were recorded using a silver–silver chloride surface electrode that was applied to the scalp using electrode paste (Ten20 Conductive, D.O.Weaver and Co, Aurora, CO, USA). The electrode was positioned at the vertex of the scalp (Cz), using the international 10–20 system of EEG electrode placement. Cz was chosen, as previous topographic mapping studies have shown this to be the site where all components of CEP are adequately recorded.[22] A reference electrode was positioned on the right ear lobe and an additional ground electrode was placed on the right side of the neck. All recordings were made in a quiet room with the subject semi-recumbent, awake with eyes open and as still as possible.

A CED 1902 programmable signal conditioner (Cambridge Electronics Design Ltd, Cambridge, UK), with a 50/60 Hz humbug noise eliminator unit (Digitimer Ltd) to minimize background interference, was used for data acquisition. SIGAVG program version 6.04 (Cambridge Electronics Design Ltd) was used to display and analyse the data. The amplifier gain was set at 3000 and the recording sensitivity was 25 μV. The sampling rate was 4000 Hz with a recording epoch of 400 ms duration. Scalp electrode impedance was measured before each recording using an impedance tester (XI-1, Oxford Medical Systems, Abingdon, UK) to ensure it was below 5 kΩ. Individual CEP recordings and the total averaged traces were saved with the averaged CEP waveform being viewed during the data acquisition to ensure quality CEP traces were being obtained.

Acid/saline infusion and pH monitoring

Using an infusion pump (KDS Scientific 100, Linton Instrumentation, Pulgrave, Norfolk, UK) 0.15 mol L^{-1} hydrochloric acid was infused into the lower oesophagus, at a constant rate of 8 mL min^{-1} for 30 min, through an infusion port incorporated in a 1 mm diameter pH catheter (Synectics Medical). The infusion port was positioned 3 cm above the lower oesophageal sphincter.

Assessment of oesophageal and chest wall sensation

Perception scores Chest wall sensation was scored using the following scale: 1, unaware; 2, slight sensation; 3, definite sensation; 4, slight discomfort; 5, uncomfortable; 6, painful. This scale has previously been used to assess the intensity of oesophageal sensation and has been correlated with the oesophageal CEP response.[13] It has been shown that as perception scores increase there is a concurrent increase of the amplitude and decrease of the latency of the oesophageal CEP response.[19]

Threshold determination Pain thresholds to electrical stimulation were determined at the proximal oesophagus, chest wall and foot on three occasions 1 min apart, in a stepwise fashion by increasing the intensity of the stimulus in 2 mA increments. Pain threshold was defined as the lowest intensity in mA at which the subject reported pain. The mean of the three readings at each site was used as the PT. Sensory thresholds (ST) on the chest wall were determined, as above, with ST being defined as the lowest intensity in mA at which the subject first reported the perception of the electrical stimulation using 1 mA increments.

Unlike the oesophagus where several studies have assessed the optimal parameters for recording oesophageal CEP[13] there were no data on the optimal parameters to be used for recording CEP from the chest wall. A pilot study was therefore conducted in eight subjects to assess the parameters required to record reproducible chest wall CEP data. Stimulation intensity was increased incrementally in steps of 2× ST, 3× ST, 4× ST and 5× ST to determine which intensity would give the best quality CEP response using two runs of 100 stimuli 15 min apart (see Results section – Pilot study of chest wall CEP).

Intravenous ketamine infusion

Racaemic ketamine (2-*o*-chlorophenyl-2-methlyamino cyclohexanone, Ketalar®, Parke Davis and Co. Ltd, NJ, USA), a non-competitive antagonist to the phencyclidine site of the NMDA receptor, was diluted in 0.9% saline to a concentration of 1 mg mL^{-1} and administered via an indwelling i.v. cannula (22GA Becton Dickinson Ltd, Oxford, UK) inserted into the left antecubital vein. An initial loading dose of i.v. ketamine (0.075 mg kg^{-1}) over 10 min was followed by a maintenance dose infusion (0.005 mg kg^{-1} min^{-1}) for 20 min via an infusion pump (Graseby 3100, Graseby

Medical Ltd, Watford, Herts, UK). Saline (0.9%) was used as the control infusion. All infusions were prepared, coded in identical syringes and their order of delivery for each subject randomized, by the Hope Hospital pharmacy. The choice of ketamine dose was based on the efficacy of similar doses used in previous studies[18] and on published pharmacokinetic data.[23–25]

Assessment of attention level

Given that NMDA receptor antagonists can have CNS side effects, which include cognitive impairment, the neuropsychological paced auditory serial attention test PASAT[26] was undertaken at baseline, 30 min postacid, directly post-i.v. infusion and at 30 min post-i.v. infusion in each subject.

Experimental protocol

Following intubation and in randomized order, baseline PTs to electrical stimulation were recorded in the proximal oesophagus and foot together with chest wall sensory and PTs. In each subject, chest wall CEP were recorded following stimulation at 3× ST (a level derived from pilot studies). An average of 200 chest wall stimuli acquired in two runs of 100 stimuli, 15 min apart, to establish baseline latency and amplitude measures.

Acid was then infused into the lower oesophagus for 30 min and PTs at each site were recorded 30 min following cessation of the infusion. A further two runs (100 stimuli each) of chest wall CEP were then acquired at the 3× baseline ST level. Intravenous saline or ketamine was then administered (randomized double blind crossover protocol) for 30 min following which PTs at each site were recorded directly after the i.v. infusion and then 30 min after cessation of the infusion. Following this a final two runs (100 stimuli each) of chest wall CEP were then acquired at the 3× baseline sensory level (Fig. 1). After each run of CEP recordings the subjects were asked to score the sensation experienced during the run using the perception score on a level of 1–6.

Data analysis

The effect of i.v. ketamine and saline on chest wall perception scores after oesophageal acid for each subject was assessed using the mean scores taken after each CEP run before and after the i.v. infusions, using the Wilcoxon paired sample test. As with our previous studies[17,18,20,27] a method of summary measures was used to make comparisons of the change in PTs from baseline over numerous time points preacid and postacid, using the calculated trapezoid area under the curve (*AUC*) at each time point, for PT measurements at each site. Comparisons between the two studies (ketamine and saline) were made using a Friedman analysis of variance with repeated measures (ANOVA). Paired data were analysed using the Wilcoxon paired sample test.

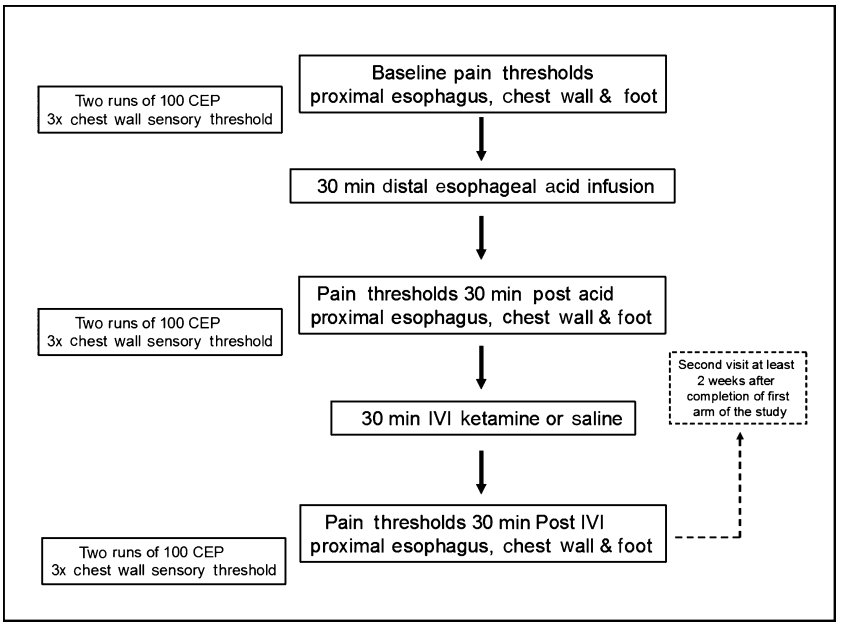

Figure 1 The protocol for assessing the chest wall cortical-evoked potentials (CEP) and pain thresholds in the proximal oesophagus, chest wall and foot following a distal oesophageal intraluminal acid infusion was shown in this figure. Intravenous ketamine or saline was given in a randomized double blind placebo-controlled crossover study design. A minimum of 2 weeks occurred between the two visits.

To compare the effect of acid on chest wall CEP, the average CEP of the 200 stimuli acquired before and after the infusion of acid was given a code. These data were then analysed by a blinded independent operator experienced in neurophysiological analysis. In order to assess the change in CEP following acid, comparisons of the latencies were made before and after the oesophageal infusion, using the Wilcoxon paired sample test.

To compare the effect of i.v. ketamine and saline on chest wall CEP postacid the same independent operator blindly analysed the average CEP of the 200 stimuli acquired after the acid infusion and after the i.v. infusion of ketamine or saline. Comparisons of the CEP latency (the interval in milliseconds between the onset of the stimulus and the peak of each potential) and amplitude (the potential difference in microvolts, between the maximal positive and negative deflection) were made using the Wilcoxon paired sample test. Statistical evaluations were performed using a standard software package (SPSS 10.1.0, SPSS Inc., Chicago, IL, USA).

RESULTS

Pilot study of chest wall CEP

At 5× ST the CEP waveform was maximal and despite increasing stimulus intensity above this no changes in CEP latency or amplitude could be achieved (Fig. 2). At 2×, 3× and 4× ST the CEP waveform demonstrated a progressive reduction in latency consistent with increasing central afferent neuronal input but saturation occurred between 5× and 6× ST (Table 1 and Fig. 3). However, at 2× ST the signal to noise ratio of the CEP waveforms resulted in poor quality tracings which improved sufficiently to discern a reproducible response at 3× ST, and this was the level at which we acquired CEP throughout the study.

Oesophageal acid infusion

All subjects completed the crossover study. During the acid infusion the pH fell below 2 in the distal oesophagus as expected, but remained above 5 in the proximal oesophagus in all subjects.

Effect of acid on pain thresholds

A reduction in PTs in the proximal oesophagus (46 ± 10 mA *vs* 33 ± 11 mA, $P = 0.001$) and chest wall (37 ± 10 mA *vs* 29 ± 7 mA, $P = 0.01$) occurred following the distal oesophageal acid infusion. Foot PTs remained unchanged following distal oesophageal acid (37 ± 25 mA *vs* 39 ± 23 mA, $P = 0.12$).

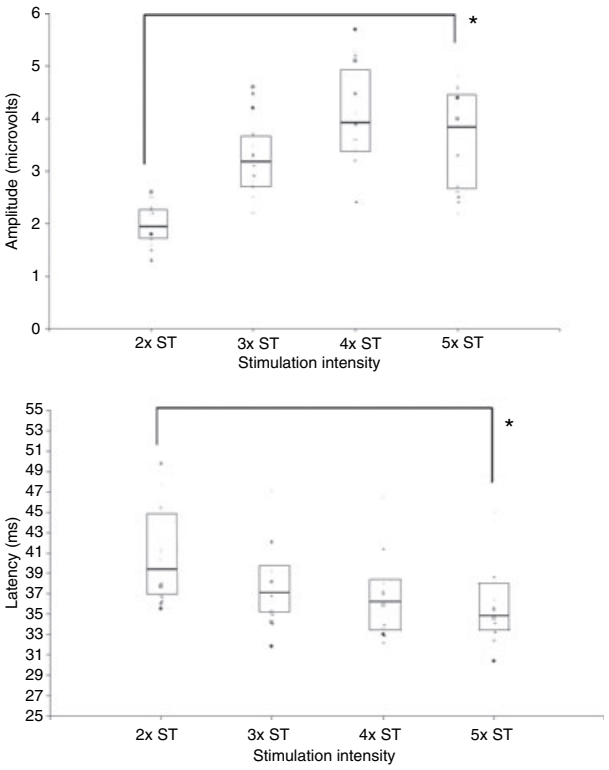

Figure 2 The increase in amplitude (A) and reduction in latency (B) of the chest wall cortical-evoked potential response as the stimulation intensity (ST) increases from 2 to 5× (*$P < 0.05$) was demonstrated. Data shown are individual scatter plots with box charts of the median and interquartile range ($n = 8$).

Effect of ketamine on pain thresholds

Pain thresholds following i.v. ketamine were significantly increased compared with PTs postsaline both in the proximal oesophagus (*AUC* −335 ± 133 *vs* −125 ± 168, $P = 0.01$) and chest wall (*AUC* −191 ± 70 *vs* −67 ± 89, $P = 0.007$). Foot PTs were unchanged (*AUC* 56 ± 66 *vs* 84.6 ± 48, $P = 0.35$).

Perception scores

After the oesophageal acid infusion, but prior to the i.v. saline/ketamine infusion, there was an increase in the chest wall perception scores compared with the baseline sensation scores (2.3 ± 0.5 to 3.8 ± 0.5, $P = 0.001$ i.v. saline visit and 2.5 ± 0.5 to 4 ± 0.5, $P = 0.001$ i.v. ketamine visit), indicating that the perception of the 3× ST stimulus had increased in severity after acid (Fig. 4). Increased perception scores persisted after i.v.

Table 1 Table shows values for the latency and amplitude (median and interquartile range) for the P1 component taken from the pilot phase of the project

Component	2× ST	3× ST	4× ST	5× ST
P1 latency (ms)	39.3 (36.7–45)	37.0 (35–39.9)	36.4 (33.4–38.8)	34.9 (33.3–38.3)
P1 amplitude (μV)	1.9 (1.7–2.2)	3.15 (2.8–3.8)	3.9 (3.4–4.9)	3.8 (2.7–4.4)

There was a significant difference between the 2× and 5× P1 latency ($P = 0.01$). In addition, there were significant differences between the 2× P1 amplitude when compared with 3× ($P = 0.01$), 4× ($P = 0.05$) and 5× P1 amplitudes ($P = 0.05$).

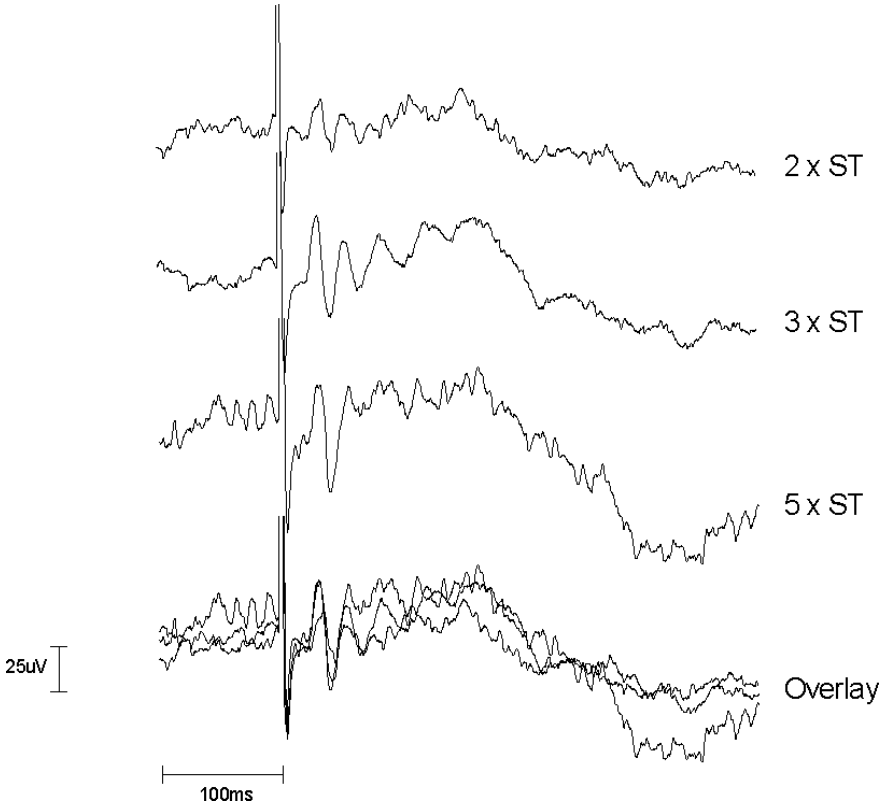

Figure 3 The chest wall cortical-evoked potential response as the stimulation intensity (ST) increases from 2 to 3× with a corresponding reduction in latency with saturation at 5× ST as seen on the overlay was demonstrated.

saline (3.8 ± 0.5 to 4.1 ± 0.5, $P = 0.2$); however, perception scores were reduced by i.v. ketamine (4 ± 0.5 to 2.8 ± 0.3, $P = 0.002$) returning to preacid baseline levels (2.5 ± 0.5 to 2.8 ± 0.3, $P = 0.3$, Fig. 4).

Effect of acid on CEP latency

On both study visits, when compared with preacid baseline CEP, there was a reduction of the P1 latency following acid infusion (36 ± 3 ms to 30 ± 4 ms saline visit, $P = 0.016$ and 41 ± 4 ms to 34 ± 3 ms ketamine visit, $P = 0.003$). The P2 latency was reduced post-acid on the saline visit (87 ± 7 ms *vs* 76 ± 7 ms, $P = 0.049$) but did not reach statistical significance on the ketamine visit (81 ± 8 ms to 73 ± 8 ms, $P = 0.055$).

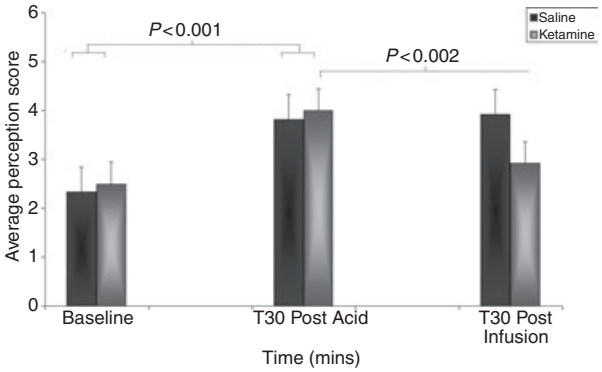

Figure 4 Following a distal oesophageal acid infusion the perception scores increased in the chest wall on both visits ($P = 0.001$). Following i.v. ketamine the perception scores were reduced compared with saline ($P = 0.002$). Data shown are group mean ± SEM ($n = 12$).

Effect of acid on CEP amplitude

No change in amplitude of any CEP component occurred following acid on either the saline (4.4 ± 0.4 μV to 5.5 ± 1.0 μV, $P = 0.2$) or ketamine visit (3.3 ± 2 μV to 4.9 ± 0.8 μV, $P = 0.14$).

Effect of ketamine on latency

There was no effect of i.v. ketamine or saline on the P1 latency 30 min after cessation of the infusion (ketamine −30 ± 4 ms to 30 ± 3 ms, $P = 0.9$ and saline −34 ± 3 ms to 33 ± 4 ms, $P = 0.6$). The P2 latency component was also unaffected by ketamine (73 ± 8 ms to 81 ± 8 ms, $P = 0.09$) or saline (76 ± 7 ms to 77 ± 6 ms, $P = 0.9$).

Effect of ketamine on amplitude

Following ketamine the amplitude of the CEP was reduced from 4.9 ± 0.8 μV to 3.5 ± 0.5 μV ($P = 0.04$). This reduction in amplitude was not seen with saline (5.5 ± 1.1 μV to 5.5 ± 0.4 μV, $P = 0.95$).

Attention scores

On completion of the ketamine infusion there was a reduction in attention score (ketamine 45 ± 5 *vs* saline 57 ± 3, $P < 0.001$ Wilcoxon). However, this effect had ceased by 30 min postinfusion (ketamine 57 ± 1 *vs* saline 56 ± 2, $P = 0.53$ Wilcoxon) and remained unchanged for the remainder of the study.

DISCUSSION

This study provides objective neurophysiological evidence to support the role of CS in the development of visceral and somatic pain hypersensitivity which develops following experimental oesophageal acidification. We have demonstrated that the development of secondary allodynia on the chest wall following acid is associated with a potentiation of the A-β fibre-mediated CEP response. This novel finding indicates increased afferent recruitment due to enhanced excitability of spinal dorsal horn neurones and provides further evidence to support the role of CS in this model of visceral pain hypersensitivity.

Following distal oesophageal acid infusion the CEP latency was reduced on both visits prior to i.v. saline or ketamine. The explanation for this finding can be extrapolated from observations made from studies of evoked potentials recorded in other modalities. These studies have shown that a reduction in latency occurs due to either an increase in sensitivity of the afferent pathway or via a recruitment of novel afferents.[28–30] This would support the hypothesis that the chest wall secondary allodynia observed in this study results from CS, as by definition CS is an increase in the excitability of the dorsal horn neurones, which gives rise to allodynia by recruitment of non-nociceptive primary afferents.

Furthermore, the fact that the acid infusion was delivered to the distal oesophagus but changes in PT were demonstrated on the chest wall means that primary afferent peripheral neuronal sensitization of chest wall afferents cannot account for the secondary allodynia which developed. However, whilst an increase in excitability at the spinal cord level is the most likely mechanism to account for the reduction in CEP latency, modulation of neuronal excitability of supra-spinal regions may also contribute to this observation via central descending pathways.[31–35] The balance between the descending facilitatory and inhibitory systems from supra-spinal regions appears to produce a net facilitatory effect following tissue injury, perhaps as an evolutionary defence mechanism to enable protection of the injured site. Therefore, one could speculate that the distal oesophageal acidification could induce a net facilitatory effect on primary afferent input to the spinal cord that would also result in a reduction of the chest wall CEP latency.

Another explanation for the reduction in chest wall CEP latency seen after oesophageal acidification is due to a change in the subject's vigilance to the stimulus, as it has previously been shown that changes in latency of the CEP components can occur with alteration in attention to the stimulus.[30] However, the lack of change in PT in the foot during the experiment together with normal attention scores at the time of CEP recording suggests that a shift in attention to repeated stimuli over time did not occur. Furthermore, no change in CEP amplitude was seen and it is the amplitude, not latency, which is most susceptible to changes in the level of a subject's attention.[30] Whilst a reduction in the P1 latency following acid was a robust finding, the results were less clear for the P2 component, which remained unchanged following acid in the ketamine arm of the study. This finding may represents a type II error due to the small number of subjects studied.

Despite a reduction in latency of the chest wall CEP and an increase in the sensation score following acid, secondary allodynia did not correspond with a change in CEP amplitude. This finding is consistent with previous evoked potential studies[19,30] where it has been demonstrated that the reduction in latency is far

more sensitive than an increase in amplitude for demonstrating afferent neuronal recruitment. This is probably because CEP amplitude is far more affected by variables such as subject habituation, attention and the signal to noise quality of the CEP recordings. Furthermore, once the maximal receptor threshold is reached further increases in stimulation intensity do not increase evoked potential amplitude despite an increase in perception of the stimulus. This is because the increased perception of the stimulus results from an increase in the frequency of receptor firing rather than an increase in magnitude of receptor response.[36] This is reflected by the reduction in CEP latency without a concomitant increase in amplitude, as demonstrated in this study.

Ketamine had no effect on the chest wall CEP latency following oesophageal acidification despite normalizing pain scores. This may be due to limitations of the methodology used to elicit A-β fibre activity and record CEP in this study. A-β fibres have very low activation thresholds when compared with A-δ and C-fibres, therefore using increments of 1 mA to measure chest wall STs may have been too indiscriminate to provide sufficient definition to detect the small changes in chest wall CEP. Another possible explanation is that descending spinal facilitatory pathways mediated via nitric oxide, substance P or cholecystokinin, may be of greater importance than NMDA receptor activation in determining CEP latency in CS.[37] Whilst selective spinal CEP recording in humans is not currently possible, future chest wall CEP studies will improve threshold discrimination by increasing the stimulus intensity in smaller (0.1 mA) increments. A multimodal approach to studying chest wall sensitivity, incorporating heat cold and tactile stimuli, will also provide more selective information about the neurological mechanisms of chest wall allodynia.

In conclusion, this experiment has demonstrated that the subjective development of secondary allodynia in the proximal oesophagus and chest wall following distal oesophageal acidification is accompanied by an objective reduction in the latency of the primary component of the chest wall CEP response. This finding suggests that the mechanism responsible for the development of secondary allodynia in this model is an increase in the sensitivity of central pain primary afferent pathway (CS).

The presence of somatic allodynia is commonly observed in clinical practice and frequently occurs in functional gastrointestinal disorders such as irritable bowel syndrome[38] and non-cardiac chest pain.[17] Neurophysiological assessment of somatic allodynia in patients with functional gastrointestinal disorders may therefore provide us with a non-invasive and objective biological marker of CS in patients with visceral pain.

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