Perceptual wind-up in the human oesophagus is enhanced by central sensitisation

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Background: Oesophageal acid infusion induces enhanced pain hypersensitivity in non-acid exposed upper oesophagus (secondary hyperalgesia) in patients with non-cardiac chest pain, thus suggesting central sensitisation contributes to visceral pain hypersensitivity in functional gut disorders (FGD). Perceptual wind-up (increased pain perception to constant intensity sensory stimuli at frequencies ≥ 0.3 Hz) is used as a proxy for central sensitisation to investigate pain syndromes where pain hypersensitivity is important (for example, fibromyalgia).

Aims: Wind-up in central sensitisation induced human visceral pain hypersensitivity has not been explored. We hypothesised that if wind-up is a proxy for central sensitisation induced human visceral pain hypersensitivity, then oesophageal wind-up should be enhanced by secondary hyperalgesia.

Methods: In eight healthy volunteers (seven males; mean age 32 years), perception at pain threshold to a train of 20 electrical stimuli applied to the hand and upper oesophagus (UO) at either 0.1 Hz (control) or 2 Hz was determined before and one hour after a 30 minute lower oesophageal acid infusion.

Results: Wind-up occurred only with the 2 Hz train in the UO and hand (both $p=0.01$). Following acid infusion, pain threshold decreased (17 (4)%; $p=0.01$) in the UO, suggesting the presence of secondary hyperalgesia. Wind-up to the 2 Hz train increased in the UO (wind-up ratio 1.4 (0.1) to 1.6 (0.1); $p=0.03$) but not in the hand (wind-up ratio 1.3 (0.1) and 1.3 (0.1); $p=0.3$).

Conclusion: Enhanced wind-up after secondary oesophageal hyperalgesia suggests that visceral pain hypersensitivity induced by central sensitisation results from increased central neuronal excitability. Wind-up may offer new opportunities to investigate the contribution of central neuronal changes to symptoms in FGD.

Functional gut disorders (FGD) such as non-cardiac chest pain, functional dyspepsia, and irritable bowel syndrome remain a significant management challenge to most gastroenterologists because, while they are extremely prevalent, treatment options are limited and often unsatisfactory. The main reason for this is because the aetiology of symptoms, including pain, in FGD is still not fully appreciated. However, visceral pain hypersensitivity, arising from an increase in responsiveness of their central nervous system (CNS) to normal visceral sensory, is thought to be important. This is because the most consistent feature found is that the stimulation of the intestinal organ, which is non-inflamed and thought to be the origin of symptoms in patients with FGD, elicits pain at intensities which are innocuous in healthy subjects.¹⁻³ Although numerous animal and human studies have been conducted in visceral pain hypersensitivity, the true mechanism, or mechanisms, still remains unclear.

Somatic pain hypersensitivity has been shown to be very important in contributing to the chronic debilitating pain suffered by patients with chronic somatic pain syndromes, such as rheumatoid arthritis^{4,5} and fibromyalgia.⁶⁻¹⁰ The mechanisms involved in this somatic pain hypersensitivity are relatively well established and have been shown to occur from an increased CNS responsiveness to sensory stimuli. One of the most important mechanisms involved is the increased excitability of spinal cord neurones from central sensitisation. The neurophysiological basis for central sensitisation comes from animal models of chronic somatic pain which have shown that following injury/inflammation there is heightened activity of the small diameter C fibre neurones which encode nociceptive stimuli and this induces activation of N-methyl-D-aspartate (NMDA) receptors expressed on dorsal horn spinal neurones to increase their excitability and

responsiveness.¹¹⁻¹³ Central sensitisation in humans manifests as either secondary allodynia (a previously non-painful stimulus becoming painful) and/or secondary hyperalgesia (an exaggerated pain response to a painful stimulus) which is the pain hypersensitivity in an area beyond the site of the injury/inflammation which provides the heightened C fibre activity.¹⁴⁻¹⁶ Many agents, including the NMDA receptor antagonist ketamine, have been shown to attenuate or reverse secondary hyperalgesia/allodynia in both the human pain models and in some chronic pain syndromes.¹⁷⁻²² Consequently, targeting central sensitisation has led to new opportunities in developing new therapeutic strategies to treat pain in many debilitated patients.²³

Wind-up is an experimental method of inducing NMDA receptor mediated neuronal plasticity that manifests as an increase in the excitability of dorsal horn spinal neurones (like central sensitisation).²⁴⁻²⁶ This occurs when a train of repetitive electrical stimulation of nociceptive fibres is delivered at a constant intensity at 0.3 Hz or greater, causing the spinal neuronal excitability to increase cumulatively with each successive stimulus because of amplification of the system.^{26,27} The correlate of wind-up in humans is thought to be perceptual wind-up, which is also commonly referred to as temporal summation. Perceptual wind-up is described as an increase in pain perception to a train of stimuli of the same intensity when delivered at 0.3 Hz or greater (that is, the same frequencies that induce cellular wind-up) which is again readily attenuated by NMDA receptor blockade.²⁸⁻³⁰

Abbreviations: NMDA, N-methyl-D-aspartate; FGD, functional gut disorders; ICC, intraclass correlation; CNS, central nervous system; VAS, visual analogue scale; UO, upper oesophagus; CEP, cortical evoked potential

Perceptual wind-up has been used as a proxy for central sensitisation to explore pathophysiological mechanisms in various chronic pain syndromes such as fibromyalgia.^{6, 31} The enhanced perceptual wind-up demonstrated by these patients has led authors to conclude that central sensitisation contributes to their pain and pain hypersensitivity. Furthermore, perceptual wind-up has been used to test proof of concept, and predict response of potentially new therapeutic strategies in these conditions.^{20–32} To date, there have been no studies examining perceptual wind-up in central sensitisation derived visceral pain hypersensitivity.

We have now developed a human model of central sensitisation in the viscera. In this model, acid exposure of the healthy lower oesophagus can induce pain hypersensitivity in the non-acid exposed upper oesophagus (secondary allodynia/hyperalgesia) which can be attenuated by pharmacological agents, including the NMDA receptor antagonist ketamine.^{3, 33–35} Furthermore, there seems to be a dose dependent relationship between oesophageal acid exposure and secondary hyperalgesia in this model, with a five minute exposure inducing a small transient effect and a 30 minute exposure inducing a greater and sustained effect. Interestingly, just five minutes of oesophageal acid exposure in patients with non-cardiac chest pain is sufficient to induces an enhanced and sustained secondary oesophageal hyperalgesia, thus suggesting that central sensitisation contributes to visceral pain hypersensitivity in FGD.³ However, if perceptual wind-up could be used as a proxy for central sensitisation in the human viscera, then it would be a relatively simple method of investigating the pathogenesis of symptoms and testing therapeutic options in patients with FGD where pain may result from central sensitisation derived pain hypersensitivity.

The aim of this study was to develop a model of perceptual wind-up in the human viscera that would allow us to investigate central sensitisation derived pain hypersensitivity. The hypothesis tested was that, in order to potentially use perceptual wind-up as a proxy for central sensitisation in the viscera, then perceptual wind-up should be enhanced following induction of secondary hyperalgesia in the oesophagus, thus indicating that central sensitisation results from increased central neuronal excitability.

MATERIALS AND METHODS

Subjects

Eight healthy volunteers (seven males; mean age 32.4 years (range 23–48)) were studied on two different occasions at least one week apart. There was no history of previous or current upper gastrointestinal symptoms and they were not taking any medication. All had normal oesophageal manometric function.

Visceral and somatic stimulation

Oesophageal stimulation

Electrical stimulation in the upper oesophagus (UO) was performed using a pair of silver-silver chloride bipolar ring electrodes (inter electrode distance 1 cm) sited 20 cm proximal to the tip of a 3 mm diameter catheter (Gaeltec, Dunvegan, Isle of Skye, UK). The electrode pair was connected to a constant current stimulator (model DS7; Digitimer Ltd, Welwyn Garden City, Herts, UK). A train of 20 stimuli of constant intensity was delivered at a frequency of either 0.1 Hz (control frequency) or 2 Hz (wind-up frequency) using square wave pulses of 500 μ s duration. The intensity of each train of stimuli could be varied between 0 and 100 mA. The stimulator was triggered automatically using a laboratory interface (CED 1401plus; Cambridge Electronic Design Ltd, Cambridge, UK) which had a count down clock from 20 to 0 that signalled stimulus delivery and

stopped triggering the stimulator automatically after delivery of the 20th (last) stimulus in the train. Inter electrode impedance was monitored throughout and a value below 10 K Ω was maintained to ensure good mucosal contact.

Hand stimulation

A pair of silver-silver chloride stimulating surface electrodes with an inter electrode distance of 1 cm was placed on the back of the subject's non-dominant hand (dermatome C7) (left hand in seven subjects). The electrode pair was connected to a stimulator and the equipment and parameters employed for stimulation were the same as those used for the oesophagus.

Acid/saline infusion

Hydrochloric acid (0.15 M concentration) or saline (sodium chloride) was infused into the lumen of the lower oesophagus, 3 cm above the lower oesophageal sphincter, through a 1 mm diameter catheter using a volumetric pump (IMED 960; Milton Trading Estate, Abingdon, Oxon, UK). The rate of the infusion was constant at 8 ml/min. These parameters for acid infusion have been used in our previous studies and are effective in inducing reproducible visceral pain hypersensitivity in the oesophagus.³

pH monitoring

The pH in the oesophagus adjacent to the stimulating electrode and the infusion site was monitored using two monocrystalline antimony pH probes (991-9011; Synectics Medical, Enfield, UK), connected to a pH recorder (Synectics Mark III, Digitrapper; Synectics Medical).

Assessment of visceral and somatic sensation

Visual analogue scale (VAS)

The VAS used had a range from 0 to 10 and was mounted on a card. The VAS was represented by a 10 cm horizontal line, marked at 1 cm intervals, each representing an increment on the scale. The VAS represented verbal descriptors of both non-painful and painful sensations previously validated to assess sensation induced by repetitive electrical stimulation within the oesophagus.³⁶ Non-painful sensations were scored on the VAS up to 4, with 1 representing vague perception and 4 moderately strong sensation. Painful sensations were scored from 5 to 10, with 5 representing mild pain and 10 the worst pain imaginable. The descriptor of 5 was used to define pain threshold.

Threshold determination and perceptual wind-up assessment

Pain threshold

Pain threshold was defined as the intensity (in mA) at which the subject rated 5 on the VAS to a single electrical stimulus and was determined on three occasions in the UO and the non-dominant hand, by increasing the intensity in increments of 2 mA in a stepwise fashion. The mean value of three readings was taken as the pain threshold.

Perceptual wind-up (temporal summation)

At pain threshold, trains consisting of 20 consecutive stimuli of the same intensity were delivered at a frequency of either 0.1 or 2 Hz. During the train, on two occasions, at the first and 20th stimulus, subjects were given a verbal queue to mark on the VAS the point on the scale that best represented the sensation experienced. Perceptual wind-up was deemed to have occurred if the stimulus became more painful during the train, as reflected by an incremental increase in the VAS score from the first to the 20th stimulus. The oesophagus and hand were tested in a random order with a 10 minute rest period between each assessment.

The two frequencies chosen in this study were representative of a wind-up frequency of 2 Hz (that is, >0.3 Hz) and one of a non-wind-up control frequency of 0.1 Hz (that is, <0.3 Hz). The large range between the two test frequencies was to minimise the ambiguity in the data set with the use of too many intermediate frequencies. In effect, if perceptual wind-up did exist then it would be easily demonstrated.

Experimental protocol

The study protocol was approved by the Salford Health Authority Research Ethics Committee and written informed consent was obtained from each subject before the study commenced. All subjects underwent two studies which were conducted at least a week apart.

As in our previous studies,^{3 33 34} in all experiments the catheter and pH probes were passed perorally into the oesophagus, without the aid of local anaesthetic, and their position adjusted manometrically until the infusion port was 3 cm above and the stimulating electrode pair 19 cm above the lower oesophageal sphincter. The pH probes were sited, one adjacent to the stimulating electrode and the other adjacent to the infusion port.

The subjects were seated upright in a comfortable chair throughout the study. Resting pain threshold measurements were determined from each electrode site situated in the UO and the hand in a random order.

At pain threshold, trains of 0.1 Hz and 2 Hz frequency stimuli were delivered to the oesophagus and hand with at least 10 minutes between each train. The sequence in which each train was delivered was randomised across subjects and scored on the VAS on two occasions. Then, depending on the randomised controlled study day, either acid or saline was infused into the lower oesophagus for 30 minutes. To assess the effect of either acid or saline, one hour following the infusions, pain threshold was determined and then 0.1 and 2 Hz trains were applied to the electrode sites at the preinfusion pain threshold intensities and scored by the subjects.

One hour post infusion was chosen to reassess sensation, as we have previously demonstrated that this period is adequate for oesophageal secondary hyperalgesia to manifest.³ Furthermore, during the infusions, subjects were asked not to disclose any sensation caused by the infusion to the investigator unless they wanted to stop the study. This was done to reduce bias and maintain the blindness of the investigator.

Data analysis

Perceptual wind-up/wind-up ratios

For each frequency, perceptual wind-up was assessed using the previously validated wind-up ratio,³⁰ as defined by: VAS score for the stimulus 20/VAS score for stimulus 1, within the train.

Perceptual wind-up and frequency dependency

To demonstrate that perceptual wind-up was a frequency related effect, data acquired in response to 0.1 Hz was used as a control. Subjects were divided into those that demonstrated perceptual wind-up and those who did not, and cross tabulated for frequency. The χ^2 test was performed and $p < 0.05$ was taken to show a difference between the two frequencies. To illustrate a further differential effect of the two frequencies, a Wilcoxon paired test was performed on the change in VAS score from the first to the 20th stimulus between the 0.1 and 2 Hz frequency (preinfusion).

Effect of hyperalgesia on perceptual wind-up

As in our previous studies,^{3 33 34} secondary hyperalgesia was defined by a reduction in UO pain threshold following acid

but not saline infusion. Comparisons between the pre and post infusion pain thresholds were made using the Wilcoxon paired test. The change in magnitude of perceptual wind-up in each region following induction of secondary oesophageal hyperalgesia was established by comparing the effect of acid with saline on the mean wind-up ratios. Comparisons of pain threshold and wind-up ratios in each region before and after each infusion were made using Friedman one way analysis.

Reproducibility of perceptual wind-up

Reproducibility of perceptual wind-up in each region was tested by calculating the intraclass correlation (ICC) (Shrout and Fleiss, model 2).³⁷ ICC was calculated for the change in VAS score for the two frequencies by comparing preinfusion values for acid and saline with the quality of the reproducibility being reflected by the closeness of the result to 1.

Values in the text are mean (SEM).

RESULTS

Symptoms and oesophageal pH induced by acid and saline infusions

Acid

As in our previous studies,³ heartburn was induced in the region of the lower chest at least 15 minutes after commencement of oesophageal acid infusion in all subjects, and it resolved within 30 minutes of stopping the infusion. In the lower oesophagus, pH fell to below 2 during acid infusion but remained above 5 in the UO.

Saline

In all subjects, saline evoked no symptoms and pH remained above 5 in both the upper and lower oesophagus during the studies.

Secondary oesophageal hyperalgesia

Oesophagus

There was a reduction in pain threshold from 83.4 (5.2) mA to 70.6 (7.2) mA (17 (4)%) following acid infusion ($p = 0.01$). There was no reduction in pain threshold following saline infusion (83.1 (7.3) to 87 (6.4) mA; $p = 0.14$) (fig 1).

Hand

There were no changes in pain threshold following either acid (22.1 (2.1) to 21.4 (2.5) mA; $p = 0.65$) or saline (20 (2.2) to 20.1 (2.7) mA; $p = 0.65$) infusion (fig 1).

Figure 1 Mean (SEM) changes in pain threshold (PT) in the upper oesophagus and in the hand in eight healthy volunteers following acid (A) or saline (B) infusion into the lower oesophagus. Secondary hyperalgesia was induced only in the oesophagus, as demonstrated by the reduction in PT in the upper oesophagus following acid infusion. * $p < 0.05$.

Figure 2 Individual visual analogue scale (VAS) scores in each subject to the first (VAS 1) and last (VAS 20) following delivery of stimuli at 0.1 and 2 Hz in the hand and oesophagus at pain threshold. Perceptual wind-up (or temporal summation) was demonstrated in both regions by the increase in VAS score to the 2 Hz train but not to the 0.1 Hz train. * $p < 0.05$. NS, non-significant.

Baseline frequency dependent perceptual wind-up Oesophagus

There was a clear difference in individual responses to the 2 Hz train compared with the 0.1 Hz train (χ^2 ; $p = 0.01$) (fig 2), with an increase in VAS score seen following the 2 Hz compared with the 0.1 Hz frequency (1.3 (0.2) and 0.2 (0.2), respectively; $p = 0.0002$), thus indicating perceptual wind-up only occurred to the 2 Hz frequency. This was also reflected by the wind-up ratios, with the 2 Hz ratio being substantially greater than the 0.1 Hz ratio (1.4 (0.1) and 1.0 (0.1), respectively; $p = 0.001$).

Hand

Similarly, there were differences in individual responses to the 2 Hz train when compared with the 0.1 Hz train (χ^2 ; $p = 0.01$) (fig 2) with an increase in VAS score after the 2 Hz when compared with the 0.1 Hz frequency (1.2 (0.2) and 0.1 (0.2), respectively; $p = 0.001$), thus indicating perceptual wind-up only occurred to the 2 Hz frequency. This was also reflected by the wind-up ratio for the 2 Hz train being substantially greater than the 0.1 Hz train (1.3 (0.1) and 1.1 (0.1), respectively; $p = 0.001$).

Perceptual wind-up following secondary hyperalgesia Upper oesophagus

2 Hz

Perceptual wind-up increased in magnitude following only acid infusion, as demonstrated by the increase in wind-up ratio from 1.4 (0.1) to 1.6 (0.1) ($p = 0.03$). For saline, the ratios were similar pre and post infusion (1.3 (0.1) and 1.3 (0.1), respectively; $p = 0.3$) (fig 3).

Figure 3 Changes in wind-up ratio as the mean (SEM) in eight healthy subjects in the upper oesophagus (UO) and hand (HA) with the 2 Hz train and the 0.1 Hz train, before and after acid (A) and saline (B) infusion. Perceptual wind-up in the oesophagus was enhanced by secondary visceral hyperalgesia, as suggested by the increase in wind-up ratio in the upper oesophagus to the 2 Hz frequency following acid infusion in the lower oesophagus only. * $p < 0.05$.

0.1 Hz

The wind-up ratios before and after acid (1.0 (0.1) and 1.1 (0.1), respectively; $p = 0.62$) and saline (1.1 (0.1) and 1.1 (0.1), respectively; $p = 0.5$) infusions were similar.

Hand

2 Hz

There was no increase in the magnitude of perceptual wind-up following either the acid (1.3 (0.1) to 1.3 (0.1); $p = 0.2$) or saline (1.2 (0.1) to 1.3 (0.1); $p = 0.3$) infusion (fig 3).

0.1 Hz

Wind-up ratios before and after infusions for acid (1.1 (0.1) and 1.1 (0.8), respectively; $p = 0.84$) and saline (1.0 (0.0) and 1.0 (0.2), respectively; $p = 0.75$) were similar.

Reproducibility

There was good reproducibility between studies for pain threshold (ICC for UO 0.8 and HA 0.7) and perceptual wind-up (ICC for UO 0.8 and HA 0.7) in all regions.

DISCUSSION

The results of our study suggests that perceptual wind-up (or temporal summation) in response to stimulation of the human oesophagus (viscera) not only has similar properties to that of the hand (somatic tissue) but also that it is enhanced by secondary oesophageal hyperalgesia.

In our study, a reproducible frequency at which the last stimulus in a train was more painful than the first, despite being at a constant intensity, was 2 Hz and not 0.1 Hz, in both the oesophagus and the hand. This suggests that perceptual wind-up occurs in both visceral and somatic tissue in humans with similar properties and hence are likely to occur via similar mechanisms. The argument that this frequency dependent perceptual wind-up is the correlate of electrophysiological wind-up is derived from human studies in somatic pain.^{24 29 38} Such studies show that pain produced by a stimulus such as heat to the skin has two components. These are: first pain, which is the initial sharp pain mediated by A δ nociceptors; and second pain, which is a slower onset duller pain mediated by C fibre nociceptors. Only the second pain undergoes perceptual wind-up when using a train of heat stimuli administered at a frequency of 0.3 Hz or above and this can be attenuated by NMDA receptor blockade.^{28 29}

Perceptual wind-up in human viscera has previously been described in the oesophagus, small intestine, and colon.^{36 39 40} In addition, perceptual wind-up using multiple stimulus modalities, including mechanical, electrical, and thermal

stimuli, has previously been studied in the human oesophagus.³⁶ These studies showed that perceptual wind-up with different stimulus modalities in human viscera occurred readily and that it increased not only pain intensity but also the area of pain referral. In addition, wind-up in response to feline visceral afferent stimulation has been studied and has shown similar characteristics to that of somatic afferents with attenuation by NMDA receptor blockade at the spinal cord.^{25 41}

Despite the similar characteristics of visceral and somatic perceptual wind-up in our study, there are fundamental differences in the afferent innervation and sensory processing between somatic and visceral tissues that need to be considered. These differences may possibly explain our observation of the fourfold differences in pain thresholds between the oesophagus and the hand, which is unlikely to solely reflect differences in stimulating electrodes, electrode contact, and stimulus delivery. In somatic tissues such as skin and muscle, low threshold large diameter afferents (A β fibres) convey non-nociceptive information, and high threshold small diameter afferents (A δ and C fibres) nociceptive information to the CNS.⁴² In contrast, afferent innervation of the viscera is more sparse and almost exclusively by small diameter afferents, with the majority being C fibres,^{43–45} thus possibly explaining the high activation thresholds for sensory perception in the viscera.

It is difficult to postulate which fibres are involved in mediating perceptual wind-up in our study. Wind-up in somatic pain studies has been demonstrated extensively and almost exclusively to repetitive C fibre stimulation.^{26 46} However, there is some evidence that A δ fibre stimulation can also induce wind-up.^{47 48} Furthermore, perceptual wind-up following electrical stimulation at 2 Hz frequency has been postulated to be mediated by A δ fibres in the somatosensory system.^{24 28} Our previous studies have suggested that the cortical evoked potential (CEP) induced by repetitive sub-pain threshold electrical stimuli delivered at 0.5 Hz to the oesophagus is mediated by A δ fibres.⁴⁹ This however merely reflects the fact that A δ fibres mediate the initial component of the CEP as this sensory signal arrives at the cortex first due to the faster conduction velocity of these fibres compared with C fibres. This does not mean that C fibres are not also activated by this experimental stimulus. Therefore, from this model, the exact nature of the fibres involved in mediating perceptual wind-up cannot be determined as electrical stimulation is likely to unselectively activate all visceral afferent fibre types simultaneously.⁴³ Interestingly, our previous CEP studies have also shown that the initial A δ fibre mediated CEP component to oesophageal stimulation is potentiated in the presence of secondary hyperalgesia, thus suggesting increased central pathway excitability following induction of central sensitisation.³⁴ In this scenario, there is little doubt that central sensitisation induced by oesophageal acid exposure (chemical stimulus) is predominantly mediated by heightened C fibre afferent activity.

The effect of secondary hyperalgesia on perceptual wind-up in the viscera has not been previously described. An important finding of our study was that perceptual wind-up is enhanced by the central sensitisation that produced the secondary hyperalgesia within the viscera, as suggested by the increased wind-up ratio in the UO following acidification restricted to the lower oesophagus. A plausible mechanism for this is that following induction of central sensitisation by oesophageal acid exposure, removal of voltage gated magnesium block and the altered channel kinetics induced by phosphorylation of the NMDA receptor, which mediates both central sensitisation and wind-up, would already have occurred in the innervating spinal neurones. Consequently, the facilitatory effects of wind-up of the dorsal horn would be

potentiated. Therefore, our demonstration of perceptual wind-up enhancement in an area of secondary hyperalgesia may represent central sensitisation and wind-up occurring via similar or converging mechanisms in human viscera. However, other mechanisms for perceptual wind-up in this study cannot be excluded such as recruitment of silent nociceptive afferents and increased central responsiveness as a result of alterations in either local spinal inhibitory or ascending and descending facilitatory-inhibitory supraspinal reflexes.^{40 50} Nevertheless, enhancement of perceptual wind-up to oesophageal stimulation in the presence of secondary hyperalgesia in our study does suggest that it is an effective method in detecting increased central excitability/responsiveness which is responsible for visceral pain hypersensitivity induced by central sensitisation. This finding therefore may potentially have an enormous clinical impact as an investigatory tool in the pathogenesis of FGD. Data from somatic pain studies are less clear and conflicting with regard to the interaction of perceptual wind-up and secondary hyperalgesia.^{21 22 30 51 52} Some studies have shown that secondary hyperalgesia enhances perceptual wind-up to some test stimuli but not others. Other studies have shown that although the threshold for perceptual wind-up to occur is lower following induction of secondary hyperalgesia, there is no change in the wind-up ratio.

In our study, lower oesophageal acidification did not induce somatic hyperalgesia or enhance perceptual wind-up in the hand. This is consistent with the findings of our previous study which showed that following lower oesophageal acidification, somatic hyperalgesia occurred in the upper chest wall within the referral area of the stimulated UO and not in the hand.³ For this reason, the same dermatome (C7) within the hand was used as a somatic control in this study. It is unclear why in both of these studies lower oesophageal acidification did not induce an increase in central responsiveness that could be detected within the hand even though spinal innervation of the oesophagus (C2 to L2) includes dermatomal convergence of the hand. A possible reason for this may be that the afferent input of the lower oesophagus, which only sparsely innervates the cervical spinal segments, was subthreshold to induce central sensitisation following oesophageal acidification within these spinal segments.

In conclusion, our study has demonstrated that perceptual wind-up in human viscera is enhanced by a pain hypersensitivity derived from central sensitisation. This suggests that the increased CNS excitability (responsiveness) which leads to secondary visceral hyperalgesia can now be reliably detected clinically using perceptual wind-up. These observations now offer a new opportunity to investigate the pathogenesis of FGD as the neurophysiological basis for symptom generation in these conditions is thought to involve altered responsiveness of the CNS to which central sensitisation may contribute. Using perceptual wind-up as a proxy for increased CNS excitability (responsiveness) may therefore help to identify subgroups of patients likely to respond to pharmacological agents that are known to abolish central sensitisation, such as NMDA antagonists, and thus stratify treatment in this difficult to manage patient population.

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REFERENCES

- Greenwood B, Rodriguez S, Deckert D, *et al*. Irritable bowel syndrome: a study to investigate the mechanism(s) of visceral hypersensitivity. *J Okla State Med Assoc* 1996;**89**:47–50.
- Mertz H, Fullerton S, Naliboff B, *et al*. Symptoms and visceral perception in severe functional and organic dyspepsia. *Gut* 1998;**42**:814–22.
- Sarkar S, Aziz Q, Woolf CJ, *et al*. Contribution of central sensitization to the development of non-cardiac chest pain. *Lancet* 2000;**356**:1154–9.
- Hogeweg JA, Kuis W, Huygen AC, *et al*. The pain threshold in juvenile chronic arthritis. *Br J Rheumatol* 1995;**34**:61–7.
- Morris VH, Cruwys SC, Kidd BL. Characterisation of capsaicin-induced mechanical hyperalgesia as a marker for altered nociceptive processing in patients with rheumatoid arthritis. *Pain* 1997;**71**:179–86.
- Staud R, Domingo M. Evidence for abnormal pain processing in fibromyalgia syndrome. *Pain Med* 2001;**2**:208–15.
- Staud R, Vierck CJ, Cannon RL, *et al*. Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. *Pain* 2001;**91**:165–75.
- Staud R, Smitherman ML. Peripheral and central sensitization in fibromyalgia: pathogenetic role. *Curr Pain Headache Rep* 2002;**6**:259–66.
- Staud R. Evidence of involvement of central neural mechanisms in generating fibromyalgia pain. *Curr Rheumatol Rep* 2002;**4**:299–305.
- Sorensen J, Graven Nielsen T, Henriksson KG, *et al*. Hyperexcitability in fibromyalgia. *J Rheumatol* 1998;**25**:152–5.
- Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain* 1991;**44**:293–9.
- Woolf CJ. Generation of acute pain: central mechanisms. *Br Med Bull* 1991;**47**:523–33.
- Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature* 1983;**306**:686–8.
- Treede RD, Meyer RA, Raja SN, *et al*. Peripheral and central mechanisms of cutaneous hyperalgesia. *Prog Neurobiol* 1992;**38**:397–421.
- Torebjork HE, Lundberg LE, LaMotte RH. Central changes in processing of mechanoreceptive input in capsaicin-induced secondary hyperalgesia in humans. *J Physiol Lond* 1992;**448**:765–80.
- Torebjork HE, LaMotte RH, Robinson CJ. Peripheral neural correlates of magnitude of cutaneous pain and hyperalgesia: simultaneous recordings in humans of sensory judgments of pain and evoked responses in nociceptors with C-fibers. *J Neurophysiol* 1984;**51**:325–39.
- Stubhaug A, Breivik H, Eide PK, *et al*. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. *Acta Anaesthesiol Scand* 1997;**41**:1124–32.
- Stubhaug A. A new method to evaluate central sensitization to pain following surgery. Effect of ketamine. *Acta Anaesthesiol Scand Suppl* 1997;**110**:154–5.
- Park KM, Max MB, Robinovitz E, *et al*. Effects of intravenous ketamine, alfentanil, or placebo on pain, pinprick hyperalgesia, and allodynia produced by intradermal capsaicin in human subjects. *Pain* 1995;**63**:163–72.
- Sorensen J, Bengtsson A, Backman E, *et al*. Pain analysis in patients with fibromyalgia. Effects of intravenous morphine, lidocaine, and ketamine. *Scand J Rheumatol* 1995;**24**:360–5.
- Pedersen JL, Andersen OK, Arendt Nielsen L, *et al*. Hyperalgesia and temporal summation of pain after heat injury in man. *Pain* 1998;**74**:189–97.
- Andersen OK, Felsby S, Nicolaisen L, *et al*. The effect of ketamine on stimulation of primary and secondary hyperalgesic areas induced by capsaicin—a double-blind, placebo-controlled, human experimental study (published erratum appears in *Pain* 1996;**68**:439). *Pain* 1996;**66**:51–62.
- Woolf CJ. A new strategy for the treatment of inflammatory pain. Prevention or elimination of central sensitization (discussion 46–7). *Drugs* 1994;**47**(suppl 5):1–9.
- Arendt Nielsen L, Petersen Felix S. Wind-up and neuroplasticity: is there a correlation to clinical pain? *Eur J Anaesthesiol Suppl* 1995;**10**:1–7.
- Alarcon G, Cervero F. The effects of electrical stimulation of A and C visceral afferent fibres on the excitability of viscerosomatic neurones in the thoracic spinal cord of the cat. *Brain Res* 1990;**509**:24–30.
- Woolf CJ. Windup and central sensitization are not equivalent (editorial). *Pain* 1996;**66**:105–8.
- Ji RR, Kohno T, Moore KA, *et al*. Central sensitization and LTP: do pain and memory share similar mechanisms? *Trends Neurosci* 2003;**26**:696–705.
- Arendt Nielsen L, Petersen Felix S, Fischer M, *et al*. The effect of N-methyl-D-aspartate antagonist (ketamine) on single and repeated nociceptive stimuli: a placebo-controlled experimental human study. *Anesth Analg* 1995;**81**:63–8.
- Price DD, Moa J, Frenk H, *et al*. The N-methyl-D-aspartate receptor antagonist dextromethorphan selectively reduces temporal summation of second pain in man. *Pain* 1994;**59**:165–74.
- Magerl W, Wilk SH, Treede RD. Secondary hyperalgesia and perceptual wind-up following intradermal injection of capsaicin in humans. *Pain* 1998;**74**:257–68.
- Staud R. New evidence for central sensitization in patients with fibromyalgia. *Curr Rheumatol Rep* 2004;**6**:259.
- Staud R. New pharmacologic therapies for fibromyalgia pain. *Curr Rheumatol Rep* 2005;**7**:337–8.
- Sarkar S, Hobson AR, Hughes A, *et al*. The prostaglandin E2 receptor-1 (EP-1) mediates acid-induced visceral pain hypersensitivity in humans. *Gastroenterology* 2003;**124**:18–25.
- Sarkar S, Hobson AR, Furlong PL, *et al*. Central neural mechanisms mediating human visceral hypersensitivity. *Am J Physiol Gastrointest Liver Physiol* 2001;**281**:G1196–202.
- Willert RP, Woolf CJ, Hobson AR, *et al*. The development and maintenance of human visceral pain hypersensitivity is dependent on the N-methyl-D-aspartate receptor. *Gastroenterology* 2004;**126**:683–92.
- Drewes AM, Schipper KP, Dimcevski G, *et al*. Multimodal assessment of pain in the esophagus: a new experimental model. *Am J Physiol Gastrointest Liver Physiol* 2002;**283**:G95–103.
- Shrout PE, Fleiss JL. Intraclass correlations: Uses in assessing rater reliability. *Psychol Bull* 1979;**86**:420–8.
- Arendt Nielsen L, Brennum J, Sindrup S, *et al*. Electrophysiological and psychophysical quantification of temporal summation in the human nociceptive system. *Eur J Appl Physiol* 1994;**68**:266–73.
- Arendt Nielsen L, Drewes AM, Hansen JB, *et al*. Gut pain reactions in man: An experimental investigation using short and long duration transmucosal electrical stimulation. *Pain* 1997;**69**:255–62.
- Ness TJ, Gebhart GF. Visceral pain: a review of experimental studies. *Pain* 1990;**41**:167–234.
- Laird JMA, de la Rubia PG, Cervero F. Excitability changes of somatic and viscero-somatic nociceptive reflexes in the decerebrate-spinal rabbit: role of NMDA receptors. *J Physiol Lond* 1995;**489**:545–55.
- McMahon SB. Are there fundamental differences in the peripheral mechanisms of visceral and somatic pain? *Behav Brain Sci* 1997;**20**:381–91.
- Sengupta JN, Gebhart GF. Gastrointestinal afferent fibres and sensation. In: Holte GE, eds. *Physiology of the gastrointestinal tract*. New York: Raven Press, 1992:483–519.
- Cervero F. Sensory innervation of the viscera: Peripheral basis of visceral pain. *Physiol Rev* 1994;**74**:95–138.
- Janig W. Neurobiology of visceral afferent neurons: neuroanatomy, functions, organ regulations and sensations. *Biol Psychol* 1996;**42**:29–51.
- Wall PD, Woolf CJ. The brief and the prolonged facilitatory effects of unmyelinated afferent input on the rat spinal cord are independently influenced by peripheral nerve section. *Neuroscience* 1986;**17**:1199–205.
- Herrero JF, Cervero F. Changes in nociceptive reflex facilitation during carrageenan-induced arthritis. *Brain Res* 1996;**717**:62–8.
- Jennings E, Fitzgerald M. Postnatal changes in responses of rat dorsal horn cells to afferent stimulation: a fibre-induced sensitization. *J Physiol* 1998;**509**:859–68.
- Hobson AR, Aziz Q, Furlong PL, *et al*. Identification of the optimal parameters for recording cortical evoked potentials to human oesophageal electrical stimulation. *Neurogastroenterol Motil* 1998;**10**:421–30.
- Cervero F. Visceral nociception: peripheral and central aspects of visceral nociceptive systems. *Philos Trans R Soc Lond B Biol Sci* 1985;**308**:325–37.
- Price DD, Long S, Huit C. Sensory testing of pathophysiological mechanisms of pain in patients with reflex sympathetic dystrophy (see comments). *Pain* 1992;**49**:163–73.
- Arendt Nielsen L, Andersen OK, Jensen TS. Brief, prolonged and repeated stimuli applied to hyperalgesic skin areas: a psychophysical study. *Brain Res* 1996;**712**:165–7.