Does acute intraoral pain alter cutaneous sensibility?

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SUMMARY Cutaneous sensibility was tested in eight patients suffering from acute postoperative intraoral pain. Tactile-, cold-, warm-, and heat-pain thresholds as well as reaction time to cold pulses were unaffected by the presence of pain. However, reaction time to warm pulses was increased in the painful area on the day of pain compared to a non-painful state. The findings are discussed in relation to (1) functional convergence of different sensory fibres on central neurons (2) the phenomenon of diffuse noxious inhibitory controls and (3) secondary hyperalgesia. The observed effect of clinical pain on the warm pathway could be explained as an intrasegmental noxious inhibitory effect.

In the last two decades an impressive amount of knowledge has emerged from animal experiments concerning functional convergence of different sensory fibres on central neurons.¹⁻⁴ From these studies one might suggest that the activation of central neurons by nociceptive afferents in clinical pain conditions could result in lowered thresholds to various stimuli applied in the same area. On the other hand it has been shown⁵ that activity set up by noxious stimulation increased the threshold of central neurons (that is, neurons having convergent input from large myelinated and small unmyelinated fibres, wide dynamic range neurons) that received input from the same or a remote area. The basis for this effect is the activation of descending inhibitory systems by the noxious input,^{5,6} that is, diffuse noxious inhibitory controls (DNIC). Results from human experimental studies argue in favour of the existence of systems similar to those proposed by Le Bars *et al.*,⁵ since heterotopic nociceptive stimuli have been shown to modulate experimental pain^{7,8} but, to our knowledge, findings like these have not been demonstrated in clinical studies. However, human experimental⁷ and clinical⁹ studies on acute pain have failed to demonstrate pain induced changes in thresholds to tactile,⁷ thermal^{7,9} and painful⁹ stimulation. The discrepancy between results from animal and human studies might be due to the possibility that: (1) modulation of a small neuron pool, as seen in recordings from a

restricted number of neurons in the animal, does not necessarily correlate with the global sensory performance in humans, (2) the contribution to sensory perception by neurons having convergent input from different sensory afferents could perhaps only be detected by tests that more selectively investigate the temporal and spatial summation function of a sensory pathway. Perhaps earlier studies have used too crude techniques to be able to study this, (3) neurons having convergent input might not be essential for general sensory perception.

In the present study we have tried to extend earlier observations by studying a selective clinical pain model, using patients with a well defined localised pain in the trigeminal innervated area, and by studying the reaction time to thermal stimulation in order to stress the temporal and spatial summation function of the cold- and warm pathways.

Methods

Eight patients (6 females, 2 males, aged 18-38 years, mean 27.5) who underwent elective surgical removal of impacted third molars were referred from two surgical dental clinics. Referral criteria were: (1) presence of pain after cessation of the local analgesic effect, (2) not taking any medication, (3) Swedish speaking. The patients were informed that the study was performed to investigate their ability to detect different sensory stimuli and was not intended to have any therapeutic significance. Seven patients had a mandibular tooth removed and one had a maxillary tooth extracted. In all cases a mucoperiosteal flap dissection was made and bone surrounding the tooth was removed using a drill.

Each patient was tested in a painful condition less than 18 hours (mean 8.4 h, range 5-18) after surgery and in a pain-free condition about a week later. Before sensory

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testing a questionnaire was administered to the patients. The essence of it was: (1) rating of subjective pain intensity on a VAS (10 cm in length, endpoints meaning no pain and worst pain ever), (2) rating of subjective pain intensity on a numerical scale; 0–100 (0 meant no pain and 100 worst pain ever), (3) the patients were asked to report if they experienced any decrease in sensibility in the facial area. This was done to detect whether any subjective effect of the local analgesia was present or if any surgical damage to sensory nerves was present, (4) all patients made a drawing of their pain localisation.

The sensory testing was performed in the cutaneous territory of the trigeminal branch innervating the area of surgery. The contralateral branch and the volar side of the wrist ipsilateral to the pain were also tested. In half of the patients the order of the testing for each sensory modality was; wrist area, painful area of the face and contralateral area of the face. The order for the other half was; wrist area, non painful area of the face and painful area of the face. The wrist area was studied to be able to observe possible sensory changes in an area extrasegmental to the pain.

The sensory testing was performed using: (1) von Frey hairs to test the low threshold mechanoreceptive function, (2) a modified Marstock-technique¹⁰ to test perception thresholds for cold, warm and painful heat (fig), (3) warm and cold pulses to test reaction time¹¹ to cold and warm (fig). Reaction time was tested only in the face. Von Frey hairs were applied in a descending order of magnitude to assess the threshold at which the sensation disappeared (3 times), and in an ascending order to assess the threshold at which the sensation appeared (3 times). The mean of the six values was calculated. The thermal thresholds were tested by applying a Peltier element of 3.6 cm² delivering, in consecutive order, five cold and five warm stimuli. All measurements started from skin temperature (range of skin temperature: on the operated side of the face at the day of pain and day of no pain 29.5–33.5 °C and 29.5–32.5 °C; face area contralaterally 29.5–33.5 °C and 29.5–32.5 °C; wrist area 29.5–33.5 °C and 29.5–32.5 °C). The mean of five values was calculated. The heat pain threshold was tested twice with the same stimulator and the mean of the two values was calculated. The heat pain threshold was tested in an area separated from other tests to avoid sensitization effects.

The reaction time to cold and warm was tested by applying a thermode (see technical note) delivering 10 cold and 10 warm stimuli (stimulus interval was one minute). All measurements started from an adapting skin temperature of 30 °C. The mean of the 10 values was calculated. Thermal thresholds were tested using commercially available equipment (Thermotester, Smedic AB, Stockholm, Sweden). The thermal pulse stimulator used was a custom made equipment, adapted from the thermal stimulator described by Fruhstorfer and Detering.¹¹

Statistical analyses

Comparison of means was accomplished using a two-tailed Student's *t* test.

Technical note concerning reaction time measurements

The stimulator is a water operated thermode. The surface in contact with the patient is circular and 35 mm in diameter. The thermode has a chamber with two valves. One valve

Fig 1 Rise time curves for the thermode stimuli. On the abscissa is the time and on the ordinate the temperature, decreasing or increasing from the baseline of 30 °C. Hatched line: Thermotester. Full line: Thermode pulse stimulator. As shown, the thermode pulse stimulator transmits temperature faster in the first 2000 ms, both in the cold and warm direction. Both methods have a better performance in the warm than in the cold direction. The curves have been calculated with thermal load (wrist area of human skin).

controls the circulation of water set at a reference temperature (30 °C). This water is constantly circulating through the chamber. The other valve controls the flow of test water which can be either cold or warm. At the opening of the test valve the other valve closes. When the patient presses the switch, indicating time of perception (reaction time), the test water flow is arrested and the reference water flow restarts. The opening and closing of the valves is controlled by hydraulic pressure produced by electrically operated pumps. The flow of water of reference temperature, cold water and warm water are controlled by three different pumps. When one pump is turned on by the same switch which controls the starting of a clock, measuring reaction time, the other pumps

are automatically turned off. Accessory pumps control the back flow from the thermode.

The delay time for activation of a test pump and opening of the test valve is 600 ms, which is deducted from the final reaction time. The thermal stimulus delivered by the thermode is not a square pulse but rather has the shape of a curve (see fig). The rise time of the curve, which is the time needed for changes in temperature to be transmitted from the water to the surface of the thermode is dependent on several variables: (1) the size of the thermode, that is, the larger the size the longer the rise time. In our study we used a larger thermode than the one reported by Fruhstorfer and Detering¹¹ (35 mm instead of 18 mm), (2) the thermode material. Fruhstorfer and Detering¹¹ used bronze and our thermode is made of silver, (3) difference in temperature between test and reference water. In our study we used 46–48 °C for the warm and 12–14 °C for the cold water, the difference from the reference (30 °C) being 16–18 °C in both directions.

Results

No patients reported numbness or paraesthesia at the time of sensory testing. Six out of the seven patients operated in the lower jaw reported pain localised to the mandibular branch. The seventh patient and the one operated in the maxilla reported pain from widespread areas of the ipsilateral side of the head and neck. The mean subjective pain ratings using the VAS was 29 (SD = 15.2, range 16–66 mm). Mean recording

using the numerical scale was 29 (SD = 15.1, range 10–65 mm). The overall results from the sensibility testings are presented in tables 1 and 2. No significant changes in sensory thresholds could be demonstrated comparing sides at the time of pain or comparing the same area under painful and painfree conditions as well as comparing sides at the day of no pain. However, reaction time to warm was significantly longer ($p < 0.05$) in the painful area at the time of pain as compared to the painfree state. The reaction time to cold was unaffected.

Reaction time to cold was in the range of 211–397 ms and to warm in the range of 328–790 ms. This difference was significant ($p < 0.01$) (measurements made at the painfree day contralateral to the operated side). This difference in reaction time between perception of warm and cold was significant ($p < 0.01$) in both face areas at the day of pain as well as in the painfree state.

Discussion

The difference in reaction time to cold and warm indicates that thermal information is conveyed in two different types of nerve fibres in the periphery, in keeping with results in the human¹² and in the monkey.¹³ However, it was shown by Dubner and Sumino¹³ that warm fibres in the face were both in the A-delta- and C-fibre range. This might explain the overlap in reaction time between warm and cold perception found in the present study.

The results from animal experiments showing convergence of peripheral fibres conveying information of different sensory modalities on to central neurons, lead us to hypothesise that ongoing clinical pain could lower the perception threshold of different sensory modalities, including pain. The results of the study do not support such an hypothesis, since we did not find any decrease in sensory thresholds or decreased reaction time. Since the animal data on convergent input is indeed convincing,^{1 2 4} including convergence from intraoral and extraoral tissues,⁴ the outcome of the present study could be explained by the possibility that neurons receiving convergent input are not of any major importance for threshold perception or that our techniques were too crude to detect eventual changes.

We also considered a different observation reported by Le Bars *et al.*⁵ They found that painful stimulation of nearby and remote areas increased the excitation threshold of neurons having convergent input from both high and low threshold afferents (that is, diffuse noxious inhibitory controls, DNIC). If this effect was present in our clinical pain model we were only able to detect it in terms of a prolonged reaction time to warm stimuli in the painful area on the day of pain compared to the non-painful state. All other sensory

Table 1 Means of thresholds and reaction times for different sensory modalities in a painful compared to a painfree state.

	Painful state	Painfree state	
<i>Mechanoreceptive Thresholds (g)</i>			
Wrist	0.093	0.046	NS
Face: operated side	0.014	0.010	NS
Face: contralateral side	0.010	0.012	NS
<i>Thermal Thresholds (°C)</i>			
WARM			
Wrist	37.2	36.4	NS
Face: operated side	36.1	35.7	NS
Face: contralateral side	35.7	34.8	NS
COLD			
Wrist	30.2	29.9	NS
Face: operated side	30.2	29.4	NS
Face: contralateral side	30.2	29.4	NS
HEAT PAIN			
Wrist	43.3	43.7	NS
Face: operated side	44.1	45.1	NS
Face: contralateral side	44.6	45.0	NS
<i>Reaction Time (ms)</i>			
COLD			
Face: operated side	270	258	NS
Face: contralateral side	264	246	NS
WARM			
Face: operated side	593	488	$p < 0.05$
Face: contralateral side	523	486	NS

NS = non significant difference.

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Table 2 Means of threshold values and reaction times in the operated and contralateral side at the time of pain and at a painfree state.

	Operated side	Contralateral side	
<i>Painful state</i>			
Mechanoreceptive Threshold (g)	0.014	0.010	NS
<i>Thermal Thresholds (°C)</i>			
Cold	30.2	30.2	NS
Warm	36.1	35.7	NS
Heat pain	44.1	44.6	NS
<i>Reaction Time (ms)</i>			
Cold	270	264	NS
Warm	593	523	NS
<i>Painfree state</i>			
Mechanoreceptive Threshold (g)	0.010	0.012	NS
<i>Thermal Thresholds (°C)</i>			
Cold	29.4	29.4	NS
Warm	35.7	34.8	NS
Heat pain	45.1	45.0	NS
<i>Reaction Time (ms)</i>			
Cold	258	246	NS
Warm	488	486	NS

NS = non significant difference.

functions, including warm thresholds measured with a different technique, were normal. The two techniques used to study warm perception differed in stimulus rise time (fig) and stimulus area (see *Methods*), resulting in differences in temporal and spatial summation centrally. Since we in the present study only detected reaction time changes for the perception of warm and not to cold, we do not consider the difference in thermode area a major cause for our significant finding. Also, to our knowledge, no data exist on convergence of non-nociceptive cold afferents and nociceptive afferents onto central neurons.

It is also plausible that the ongoing pain in our patients was of a too low intensity (see *Results*) to induce clear noxious inhibitory effects detectable with our techniques. A previous study in the rat¹⁴ has clearly shown a positive correlation between conditioning pain input and the magnitude of pain inhibition. Furthermore, DNIC-related effects could be phenomena that do not play any significant role in clinical pain conditions since only neurons having convergent input are inhibited by noxious input. These neurons do perhaps not play a significant role for the perception of pain. Also, suprathreshold pain stimulation and subjective magnitude assessments would perhaps have been a more refined way to detect eventual changes in sensibility.

In previous human studies^{7,8} it has been demonstrated that experimentally induced pain in one part of the body significantly elevated the pain threshold in

remote parts of the body. In a previous study by two of us⁹ we could not detect any extrasegmental pain inhibitory effect of acute clinical trigeminal pain, when measuring heat pain thresholds on the dorsal aspect of the hand, ipsilateral to the painful side. Our present findings confirm the absence of extrasegmental pain inhibitory effects as measured by the pain threshold. Since the subjective pain intensity of the subjects tested in the study by Pertovaara *et al.*⁷ on average reported a more intense pain experience than the patients in the present study, as rated on the VAS (58.8 compared with 29), this might explain the discrepancy of the results. In the same study they did not find any effect of ischaemic pain on mechanoreceptive or thermal thresholds. Our findings, using a clinical model, are in agreement with those observations.

After surgical removal of impacted third molars, patients usually have intraoral hyperalgesia in the operated area. Recently, Sessle *et al.*⁴ have shown that nerves innervating extraoral and intraoral tissues converge on central neurons. This could be a basis for possible pain referral and secondary hyperalgesia in the cutaneous area of the face following intraoral surgery since, to our knowledge, no report has described branching of primary afferents to both intraoral and extraoral tissues. Although all of our patients subjectively experienced hyperalgesia intraorally we could not, by the performed sensory tests, detect the secondary type in the cutaneous area tested.

In conclusion, the present study supports the notion that acute postoperative intraoral pain does not affect, in any major way, cutaneous sensory perception performance. The only significant finding was an increased reaction time to warm stimuli intra-segmentally to the pain at the time of pain compared with a non-painful state, supporting a segmental noxious inhibitory effect. No secondary hyperalgesia could be detected in the cutaneous area being tested.

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