Testing the gate-control theory of pain in man

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SYNOPSIS According to the gate-control theory of pain, the electrical stimulation of large nerve fibres should stop the pain induced when only C fibres are active. This kind of pain was induced by pressure, repeated pinprick, cold and heat in the ischaemic limb. The peripheral nerves were electrically stimulated in the same way as is done by patients treating their chronic pain by electrical stimulation. There was no change in the quantity nor the quality of the C fibre pain. In other experiments, electrical stimulation of the peripheral nerves induced no change in pain threshold to a heat stimulus when only C fibres were conducting, nor when the whole spectrum of fibres were conducting. Although many experiments have been reported that are consistent with the gate-control theory, the experiments reported here, and others mentioned, are inconsistent with the theory.

In 1965 Melzack and Wall put forward a theory of pain, which they called the gate-control theory. They based this theory upon work previously done by Mendell and Wall (1964), in which it was shown that stimulation of small afferent nerve fibres resulted in a positive dorsal root potential, whereas stimulation of large afferent fibres caused a negative dorsal root potential. These observations were interpreted as evidence of presynaptic facilitation and presynaptic inhibition of the cutaneous input. According to the gate-control theory, the output of a group of first central transmission (T) cells in the posterior horn depends upon the balance of large and small afferent fibre activity of the posterior roots. If this balance is such that the small fibre activity predominates, there will be presynaptic facilitation and a large increase in T cell activity; this results in pain phenomena (gate open). The converse applies if large fibre activity predominates (gate closed). This is a quantitative theory of pain; the number of impulses in a given time reaching the relevant parts of the brain determines the occurrence of pain. The implication of the theory, as Melzack and Wall pointed out, is that exciting the large afferent fibres will cause a reduction of the local input to the spinal cord and thus pain will be reduced or stopped.

Cases have been published by Wall and Sweet (1967) and Sweet and Wepsic (1968) in which chronic pain was abolished during the period of electrical stimulation of the large nerve fibres. Since that time, the technique of stimulating large fibres has been developed for the treatment of many painful conditions.

Although the theory has led to the successful treatment of chronic pain, this does not necessarily mean that it is correct. Certain implications of the theory can be examined in normal subjects. According to the theory, the excitation of large peripheral nerve fibres should be particularly effective in stopping or greatly reducing the pain induced when only the non-myelinated or C fibres are active. It should also be effective in raising the pain threshold to every form of noxious stimulus. The aim of the investigation reported here was to test these aspects of the theory. The experiments were designed to find out if stimulation of large nerve fibres of peripheral nerves of the upper limb with the apparatus used by patients causes any changes in the perception of induced pain or in the pain threshold.

MATERIAL

Seven males between the ages of 28 and 60 years were the subjects of these experiments.
METHODS

In most experiments, pain was induced by heating the dorsal surface of the blackened terminal phalanx of a finger by means of radiant heat; the source was a mounted motor-car cigar lighter. The distance between the heater and the skin was adjusted so that the pain occurred when the terminal phalanx had been heated for five to 12 seconds. This distance was kept constant throughout the experiment. The pain threshold was measured as the length of time of heating. The subject was given a stopwatch and told to start it when the stimulus was swivelled into position over the blackened digit. He was not allowed to look at the digit being heated, or the stopwatch. When the subject felt pain, he stopped the watch and the stimulus was moved away. The pain stimulus was applied at one minute intervals. At first we expected that there would be two end-points, a pain perception threshold when warmth became pain, and a pain tolerance threshold, when the pain became so severe that the subject involuntarily withdrew his hand. But in fact these thresholds turned out to be very close.

In some experiments, the stimulus to cause pain was squeezing the terminal phalanges, spraying them with ethyl chloride, and single and repeated pinpricks. In most series of experiments, pain was induced in the upper limb with the circulation occluded. The circulation to the distal part of the limb was blocked by a sphygmomanometer cuff at a pressure of 220 mmHg, placed on the lower arm.

PRELIMINARY TRIALS ON PAIN THRESHOLD TO RADIANT HEAT  As our method of inducing pain was by heating a small area of skin, a preliminary series of experiments was carried out to examine the relation between the initial skin temperature of the area and the pain threshold. The time taken to reach pain threshold was recorded at various skin temperatures; this was done both with and without occlusion of the circulation. The temperature of the blackened skin was taken by a thermocouple immediately before each application of the heat stimulus. It was found that the initial temperature of the skin of the terminal phalanx affected the pain threshold if the skin temperature was below 29–30°C.

In the experiments with the circulation to the limb occluded, the skin temperature always fell below this figure when the cuff had been on the limb for about 30 minutes. The application of the stimulus once a minute always raised the skin temperature. An example is shown in Fig. 1. With the circulation to the limb intact, the temperature of the skin remained constant around 32°C. There was no consistent change in the pain threshold. With the circulation occluded, the temperature of the skin rose progressively with repeated application of the heat stimulus. It rose from 25°C to 32°C with the first four applications of the heat stimulus, and then remained constant. For the first three applications of the stimulus, the pain threshold fell; after this, there was no consistent change. For this reason, no electrical stimulation was performed until the skin temperature had reached a constant plateau and two consecutive threshold readings were similar.

![Diagram showing relationship between skin temperature of terminal phalanx and pain threshold with a radiant heat stimulus. On the left, the circulation to the limb is unimpeded; on the right, the circulation to the limb has been occluded for 20 minutes. Temperature °C (●) indicated on vertical axis on left; pain threshold in seconds (○) indicated on vertical axis on right. Horizontal scale, time in minutes.](http://jnnp.bmj.com/ on July 6, 2017 - Published by group.bmj.com)
METHOD OF ELECTRICAL STIMULATION

Electrical stimulation of the peripheral nerves was carried out with a Stimtech EPC Stimulator; this is the portable stimulator issued to patients with chronic pain. This stimulator is designed to give a constant current output of 0–50 mA for an electrode impedance into 0 to 5,000 Ω. It delivered modified rectangular pulses, the duration of which could be varied between 50 and 500 microseconds at a frequency between 15 and 180 pulses/second. An analysis of the output showed that it was linear over the range used in these experiments. The electrodes used were those supplied with the apparatus. They were two discs 4.5 cm diameter; the surface was Gelfoam and the backing was stainless steel, mounted in a plastic framework. The dampened electrodes were placed firmly on the skin of the upper arm so that they stimulated the median or the ulnar nerve. They were proximal to the phymomanoimeter cuff in experiments in which the circulation was occluded. Voltage and pulse frequency were adjusted so that the subject felt definite but not painful paraesthesiae in the little finger in the case of the ulnar nerve, and in the middle or index fingers in the case of the median nerve. Both the electrodes and the stimulation parameters were adjusted so that they did not cause local pain beneath the electrodes. It was emphasized to the subjects that these paraesthesiae were not to be painful, but should be the same as patients would be likely to experience when they treated themselves by transcutaneous electrical stimulation. In some experiments, the voltage was increased so that the electrical stimulation was painful. The electrodes were fixed firmly by strapping and a crepe bandage. Throughout an experiment, care was taken to see that the amount of paraesthesiae due to electrical stimulation was the same as it had been during the control period. Minor adjustments of voltage, usually a decrease, were sometimes needed to obtain this.

PROCEDURE

The electrodes were placed on the subject’s arm and the parameters needed for both non-painful and painful paraesthesiae were noted. The pain threshold without electrical stimulation of the nerves was then determined at intervals of one minute; 10 observations were made. After this, the effect of electrical stimulation on the pain threshold was determined. The procedure consisted of giving the heat stimulus alternately with and without electrical stimulation. This procedure was followed throughout, in order to eliminate any possible drift of threshold. The electrical stimulation of the nerves was applied just before the heat stimulus, and removed after the pain threshold had been obtained.

RESULTS

FIRST SERIES

In the first series of experiments, the effect of electrical stimulation of large nerve fibres on the kind of pain experienced when only C fibres are conducting was examined. For the sake of convenience this will be referred to as C fibre pain. After the cuff had been on the upper limb for 20 to 25 minutes, the sensibility of the ends of the fingers was examined to find out if C fibre pain was present. When this point had been reached, this pain was induced by squeezing, repeated pinpricks, radiant heat, and ethyl chloride spray. In all five subjects, electrical stimulation of the relevant nerves in the arm, at a strength that caused non-painful paraesthesiae, had no effect on C fibre pain.

As the amount of inhibition said to occur from excitation of the large afferent fibres might be insufficient to have an effect on the perception of the pain, this stimulation was increased so that it became painful. The result differed among the subjects. In two subjects, the induced pain was abolished; in one, the pain was lessened; in two, it had no effect.

As an increase in the intensity of electrical stimulation above that used by patients appeared to have an effect on C fibre pain in some subjects, it did appear that the relationship between electrical stimulation and the pain might well be quantitative. It was therefore necessary to have a measure of the amount of pain. In all subsequent series of experiments, pain was induced by the radiant heat stimulus, and the effect of electrical stimulation on the pain threshold was studied.

SECOND SERIES

As electrical stimulation is effective in preventing pain in patients, many of whom have nerve fibres of all groups conducting, a series of experiments was performed without a cuff blocking the circulation to the limb. In this series, pain was induced by the radiant heat stimulus, the duration of heating being a function of pain threshold.

In none of the five subjects did an electrical stimulation that caused non-painful paraesthesiae have any effect on the threshold of pain induced by radiant heat. When the intensity of electrical stimulation was increased to a painful degree, in three subjects there was again no change in the pain threshold. In the other two
subjects, there was a significant increase in the threshold.

THIRD SERIES As the gate theory would predict that the electrical stimulation of large nerve fibres would reduce C fibre pain, and as this was not found in the first series of experiments, it was important to find out if stimulation nevertheless changes its threshold. In this series of experiments, pain was induced by the radiant heat stimulus in the ischaemic limb.

Electrical stimulation both at non-painful and painful intensities had no effect on the pain threshold in all five subjects. The results of a typical experiment are shown in Fig. 2. Figure 2, A, shows the results with non-painful electrical stimulation of the nerve, and Fig. 2, B—to the right of the arrow—shows those with painful electrical stimulation. The black columns show pain threshold during electrical stimulation and the white columns show threshold without stimulation. It is clear that the thresholds are similar with and without stimulation. It will also be seen in this example how the first pain thresholds are slightly longer than all subsequent ones. As was mentioned in the Methods sections, this is due to the fingers having a lower temperature before any heat has been applied. But as the pain thresholds were always determined in alternating pairs with and without electrical stimulation, any changes that occurred in the background temperature of the skin would not have obscured possible effects of electrical stimulation.

In no experiments did electrical stimulation of the opposite limb have any effect on pain measured in the other limb.

An incidental finding in all series of experiments was that the voltage of stimulation might have to be reduced for the subject to feel the same amount of paraesthesiae later in the experiment as he had done at the start of the experiment; the voltage never had to be raised.

DISCUSSION

The gate-control theory of pain supposes that the effect of any cutaneous input to the spinal cord is determined by the preceding balance of the activity of large afferent nerve fibres on the one hand and small afferent fibres on the other. The theory has been used by Melzack et al. (1963), by Sullivan (1968), by Higgins et al. (1971), and by Satran and Goldstein (1973) to account for the results they obtained on the perception of pain when it was associated with various forms of concurrent or preceding

FIG. 2. Pain threshold in limb with circulation occluded, with and without electrical stimulation. In A, to left of the arrow, intensity of electrical stimulation caused comfortable paraesthesiae. In B, to right of arrow, electrical stimulation was painful. Black columns, with electrical stimulation; white columns, no electrical stimulation. Vertical axis, pain threshold in seconds; horizontal axis, duration of occlusion of circulation in minutes. No observation was made at 30·5 minutes.
stimulation. The theory has also been used to explain the pain and hyperaesthesia of many forms of neuropathy, in which there may be selective damage to the large afferent fibres. Electrical stimulation of the large afferent fibre is now used for treating many painful conditions; this is one of the results of the gate-control theory of pain. But although this form of treatment is helpful in a minority of patients with chronic pain, this theory is not the only possible explanation of its effectiveness.

According to the theory, the electrical stimulation of large afferent fibres carried out just as patients do for relieving their pain should have abolished or diminished the pain produced by a variety of stimuli in the ischaemic limb, when only the small nerve fibres are conducting. It did not do so. Nor did it reduce the pain when all nerve fibres were conducting. It might be considered that the pain caused by the radiant heat stimulus was so intense that any small change in threshold would not be detected. This explanation is unlikely to be correct for two reasons. First, it was sometimes seen that if a subject turned his attention away from the stimulation of his finger, the threshold for pain went up considerably; yet it never went up with electrical stimulation of the nerves. Secondly, electrical stimulation had no effect on the quantity and quality of C fibre pain induced by stimuli other than radiant heat. We conclude that electrical stimulation as used by patients has no effect on cutaneous pain induced in normal subjects.

The question one is asking is not whether inputs arriving in afferent fibres of various sizes converge at some place in the central nervous system; it is whether the diminution or obliteration of pain caused by electrical stimulation of large afferent fibres is due to the mechanism occurring at the entrance to the spinal cord proposed by Melzack and Wall (1965).

To disprove the gate theory, it is necessary to demonstrate facts that are inconsistent with it. The facts presented here—that large fibre stimulation did not alter the quantity or quality of radiant heat skin pain—are inconsistent with the theory. If the gate theory merely proposed that there is an interaction between the effects of arriving impulses, all will accept it. There is a convergence of afferent nerve impulses at many places in the central nervous system; perhaps the first place is in lamina v, as has been shown by Wall and many other physiologists. There are many facts that fit this conception better than the gate hypothesis. For instance, one of the authors (P.W.N.) found that electrical stimulation in patients with post-herpetic neuralgia raised the threshold to the tactile sensation caused by von Frey hairs; and the threshold remained raised for minutes after stopping electrical stimulation. This is not accounted for by the gate theory; it is a different phenomenon from the kind of interaction proposed in that theory. There are the experiments reported by Satran and Goldstein (1973). In these experiments the increase in pain tolerance lasted for 20 minutes after stopping electrical stimulation; this is surely not the kind of presynaptic inhibition envisaged in the gate theory. Contralateral electrical stimulation was also effective in raising the threshold; this was also not envisaged by the gate theory.

It is our opinion that deep pain is different from the rapidly rising, severe pain we induced in the digits. Because the word pain is used for the aching pain induced by certain stimuli to the fascia, tendons, and muscles, for the burning pain induced in the skin, for referred pain and for various pains due to lesions of neural structures, one is tempted to believe that they all have the same mechanism and make use of the same neurones and neural pathways. We prefer not to assume this. Indeed we do find that the same electrical stimulation as we have used here reduces and tends to obliterate the pain induced by strong squeezing of the tendo Achillis.

Other explanations of the effects of non-painful stimulation of large afferent fibres on the treatment of painful states in patients might be based on the phenomena of attention and distraction. In our experiments, when the electrical stimulation itself was painful, subjects agreed that what they felt was related to attention. On introspection, one has the feeling that one can direct attention either to the primary painful stimulus or to the painful electrical stimulation. If the electrical stimulation is on one upper limb and the painful stimulus is on the other, we found that it is easy to direct ones attention to either the one or the other. It is more difficult, but not impossible, to concentrate on either the painful stimulus or the peripheral electrical stimulus.
when they are both in the same nerve territory. Similarly, as has been mentioned, if a subject had his attention distracted, the threshold was raised. This shows that attention is important in the set-up of these experiments and also that it had more effect on pain threshold than had the electrical stimulation.

These experiments have shown that what the gate-control theory forecast was wrong; and that the successful treatment of pain by electrical stimulation does not work on account of the premises of the gate-control theory, although these premises were the instigation and the rationale of this form of therapy. Furthermore, the experiments are one more example of how laboratory pain and pain in clinical medicine are two different things. It is the merit of the gate-control theory that it has once more awoken interest in the interplay of two or more inputs to the central nervous system and in phenomena such as counter-stimulation and referred pain.

The gate-control theory gives a special role to the ongoing activity of some afferent nerve fibres. It requires that certain afferent fibres are continuously active and that their activity keeps the ‘T-cells’ adequately facilitated and ready to send massive volleys of impulses to the brain. These volleys are believed to cause pain and the reactions associated with pain. Some clinical evidence that this ongoing activity exists was recently put forward by Nathan et al. (1973). They had electrodes on peripheral nerves, proximal to a cuff obliterating the circulation, in a set-up similar to that reported in the present work. They showed that it was necessary to increase the strength of the electrical stimulation gradually to obtain a constant amount of paraesthesiae during the production of the ischaemic block. From this, they concluded that the ongoing activity in the peripheral nerves had been removed by the ischaemia, and that this was the reason that the amount of electrical stimulation had to be increased. In the present series of experiments, this was not found; indeed, there was a tendency for the strength to require reduction. This difference can be explained by the larger electrodes (45 mm) used in these experiments compared with the small (7.5 mm) ones used before. With large electrodes, the current applied to the nerves is less dependent on the position of the electrodes than with small ones.

Since in the previous work the small electrodes were placed in the optimum position for paraesthesiae, any change in position induced by the cuff would have resulted in an increase in the current needed to obtain the same amount of paraesthesiae. In the present experiments with large electrodes, such movements were of less importance; and in these experiments no changes in the voltage were needed. If the explanation is correct it appears that the previous evidence of Nathan et al. (1973) is invalid and was an artefact of the method. The same method of stimulating a large peripheral nerve proximal to an occluding cuff was used in the present experiments; no change was needed in the intensity of electrical stimulation to maintain a constant amount of paraesthesiae; and so no evidence for the occurrence of ongoing activity has been obtained.

The gate-control theory has resulted in the treatment of many chronic painful conditions by continuous electrical stimulation of large afferent fibres and in about one-third of cases this form of treatment of chronic pain is successful. In many patients in whom it is successful, the pain is less for an hour or more after stimulation of the peripheral nerves has stopped; and in some patients, the whole course of the painful condition is greatly improved. These beneficial results are not readily explained on the gate-control theory. It also appears from the experiments reported here on normal subjects that certain essential parts of the theory are wrong. Needless to say, that in no way lessens the value of electrical stimulation of large nerve fibres for the treatment of chronic pain.

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