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The effect of hypnotically induced analgesia on flare reaction of the cutaneous histamine prick test

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Summary. The effect of psychological pain reduction on the cutaneous inflammatory process was investigated by studying the effect of hypnotically induced analgesia on the flare reaction of cutaneous histamine prick tests. Ten highly hypnotically susceptible volunteers had their cutaneous reactivity against histamine prick tests on both arms measured before hypnosis. Their pain-related brain potentials were measured on the basis of eight argon laser stimulations. These measurements were repeated in the hypnotic condition, where subjects were given repeated suggestions of analgesia in one arm. Final measurements were performed in the post-hypnotic condition. Subjectively felt pain was measured on a visual analogue scale. Results showed a mean reduction in subjectively felt pain of 71.7% compared to the baseline condition. A significant ($P<0.01$) mean reduction of the evoked potentials was found in the hypnotic analgesic condition compared to both the pre-hypnotic (49.9%) and the post-hypnotic condition (36.9%). A significant difference was measured in the histamine flare area between the pre-hypnotic and the hypnotic analgesic condition ($P=0.01$–0.02) and between the hypnotic analgesic and the post-hypnotic condition when compared with the control arm. The mean ratio of flare area between the analgesic arm and the control arm was 1.04 (SD, 0.16) in the pre-hypnotic condition, 0.78 (SD, 0.22) in the hypnotic analgesic condition, and 1.37 (SD, 0.49) in the post-hypnotic condition. The results support the hypothesis that higher cortical processes can be involved in the interaction of inflammatory and pain processes.

Key words: Hypnotic analgesia – Histamine prick test – Brain potentials

The body's response to external threatening or damaging stimuli can be viewed as mediated by highly integrated mechanisms involving both the central and peripheral nervous systems which interact to produce the adaptive cardiovascular, endocrine, metabolic, immunological and somatosensory responses necessary to maintain the adequate physiological and psychological function of the organism when confronted with external stressors. Both pain signalling mechanisms and mechanisms that produce and inhibit inflammatory responses are of fundamental interest for the understanding of the body's adaptive responses. The involvement of higher cortical and psychological mechanisms in these responses seem likely. However, little is known about how the different systems collectively respond and coordinate their responses [10, 42].

In recent years it has become increasingly clear that both pain perception and the inflammatory response is mediated by the central nervous system, and can be modulated by psychological intervention [3, 4]. Hypnosis has been shown to be an effective psychological pain intervention method in both clinical and experimental pain [18], and there is little doubt that hypnotic suggestions of analgesia can produce subjective responses indicating analgesia [2, 18]. However, it was not until recently that methodological problems of measuring physiological correlates of hypnotic analgesia and of securing reliable experimental pain stimuli were overcome [2, 41]. Also, inflammatory responses can be modulated by psychological intervention. It has been reported in several case studies that inflammatory and immunological responses can be modulated by hypnotic suggestions [6, 15, 27]. These reports have recently been confirmed in a controlled study, where hypnotic inhibition of the flare reaction to the histamine prick test was demonstrated [40].

In this investigation we wished to investigate further the possible centrally mediated links between the inflammatory response, as measured by the flare reaction to the cutaneous histamine prick test, and hypnotic analgesia, as determined by the reduction of the related brain response to painful argon laser stimuli.

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Materials and methods

Subjects

A group of 96 undergraduate psychology students (64 female and 32 male) volunteered to have their hypnotic susceptibility measured using a modified version of the Harvard Group Scale of Hypnotic Susceptibility, Form A [35]. The mean score for this group was 7.85 (on a scale of 0–12) compared with the original mean score of 7.39 [34]. Ten high-scoring individuals (5 female, 5 male; aged 21 to 35) scording from 9 to 12 (mean score, 10.4) were selected for this study. The subjects were informed regarding the purpose of the investigation, and all gave their informed consent according to the Declaration of Helsinki.

Experimental procedure

The selected subjects participated individually in a 90-minute session. First, the subjects had their cutaneous reactivity against the histamine skin prick measured. Then the subjects had their pain thresholds measured in the waking state and following this procedure, they had their pain-related brain potentials measured on the basis of eight laser stimulations. Histamine skin prick induced weal and flare, and pain-related brain potential measurements, were repeated in the hypnotic state during suggested analgesia of one arm, and after hypnosis in the normal waking state.

The pre-hypnotic condition

Histamine skin pricks. Standard histamine skin prick tests were performed for elicitation of a Type I inflammatory reaction. A sterile lancet covered with lyophilized histamine (Phazet, Pharmacia, Sweden) equal to a solution of 10 mg/ml was used, and a skin prick was made in the upper dermal layer on the ventral side of both forearms before, during and after the hypnotic induction and suggested analgesia procedure. The test and control area were chosen symmetrically on the forearms with at least a 6-cm space between subsequent tests, moving from wrist to elbow to ensure that the flare areas did not overlap.

Monitoring of skin reactions. The monitoring of the histamine skin reaction was performed blindly. After 7 min the cutaneous weal and flare areas were traced on a plastic film and measured by computerized planimetry (Videoplan, Kontron, Munich, FRG).

Laser stimulation. The output from an argon laser (Spectra Physics, 168) was transmitted to the skin C_7 dermatome on the dorsum of the hands via a quartz fibre. Output power could be adjusted from 0.05 to 3.5 W. The argon laser wavelengths were 488 nm (blue) and 515 nm (green). An external laser power meter (Ophir, Israel) was used to measure the dissipated output power. A continuous, low energy beam (50 mW) from the argon laser was used to visualize the stimulation site. The laser stimulus was applied to a target of 1×3 cm area on the dorsal part of the hand. Repeated stimulations at identical points within the area were avoided.

Determination of pain thresholds to laser stimuli. The laser stimulus had a duration of 200 ms, and the laser beam diameter was kept constant at 3 mm (0.07 cm^2). The pain threshold was defined as a distinct sharp pinprick without any burning after-sensation. Initially the thresholds were determined five times.

Recording of pain-related brain potentials. Laser stimuli with an output equal to 1.5 times the output necessary to reach the subjective pain threshold were used. The brain potentials were recorded with a platinum needle electrode (Disa 25C04) inserted over vertex with reference to a linked ear lobe. The EEG was filtered by a second order filter (0.5–12 Hz) amplified 200000 times (Disa 5C01), and sampled at 64 Hz by a computer. A total of eight single potentials were averaged. The summated peak-to-peak amplitude of the major pain related complex (0.3–0.7 s) was used for monitoring. During the experiments the volunteers rested comfortably and wore protective goggles. To avoid any acoustic interference at the time of the stimulus, white noise was administered through earphones.

Recording of subjective pain levels. For the recording of the subjective pain experience visual analogue scales (VAS) were constructed. Single lines, of length 10 cm and with indications of minimum and maximum felt pain, were used for the monitoring of subjective felt pain during the pre-hypnotic and post-hypnotic condition. A 20-cm line, with the mid point indicating the pain felt in the pre-hypnotic condition, was used to monitor the subjective changes in pain felt during the hypnotic analgesic situation relative to the pain felt in the pre-hypnotic condition. The results were transformed into percentages.

Statistics. For statistical analysis, the Wilcoxon Signed Ranks Test was used.

Hypnotic inductions and suggestions

After measurements in the normal pre-hypnotic state the subjects were given a standardized hypnotic induction procedure lasting 15 min with instructions to go into a deep relaxed trance. The subjects were instructed that in the trance state it would be possible to alter perceptions of different stimuli such as pain.

Suggestions of analgesia. The subjects, while in the hypnotic state, were given the following suggestions of analgesia in the right hand and arm. They were instructed to recall the feeling of anaesthesia experienced following the injection of a local anaesthetic at the dentist, and then instructed that they would be able to experience the same sensations in the right arm. The subjects were instructed to give a signal when they were certain that the whole of the arm up to the shoulder was anaesthetized. They were then given repeated suggestions to experience that sensation in the arm. A series of eight laser stimuli of the same magnitude as used in the pre-hypnotic state was given, and brain potentials were measured. Histamine skin prick tests were given symmetrically on both forearms, as in the pre-hypnotic condition, and measured after 7 min. The subjects were then instructed to return to their normal, waking state, feeling relaxed and refreshed.

The post-hypnotic condition

In the post-hypnotic condition the subjective reduction in pain was recorded using the VAS described above. Histamine skin reactions and pain-related brain potentials were measured using the same procedure as in the pre-hypnotic and the hypnotic analgesic condition. Subjective pain levels were again recorded as described above.

Results

Subjective pain

In the pre-hypnotic condition subjects reported a mean subjectively experienced pain on a scale from minimum to maximum felt pain of 44.2% (SD, 19.5), with 100% representing the worst pain imaginable from a laser stimulus. During the hypnotically suggested analgesia the subjects reported a mean reduction in subjectively felt pain of 71.7% (SD, 12.5). The mean pain reported in the post-hypnotic condition was 49.3 (SD, 24.3).

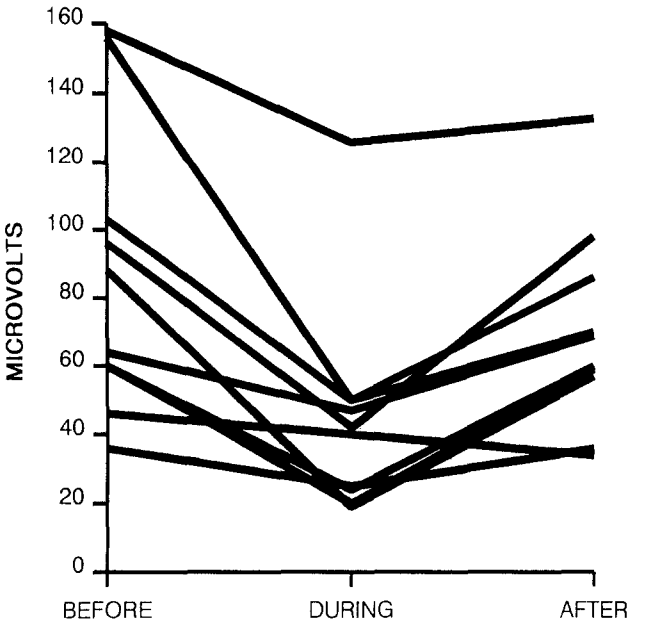

Fig. 1. Pain-related brain potentials in ten subjects in the pre-hypnotic, hypnotic analgesic, and post-hypnotic condition. ($P < 0.001$)

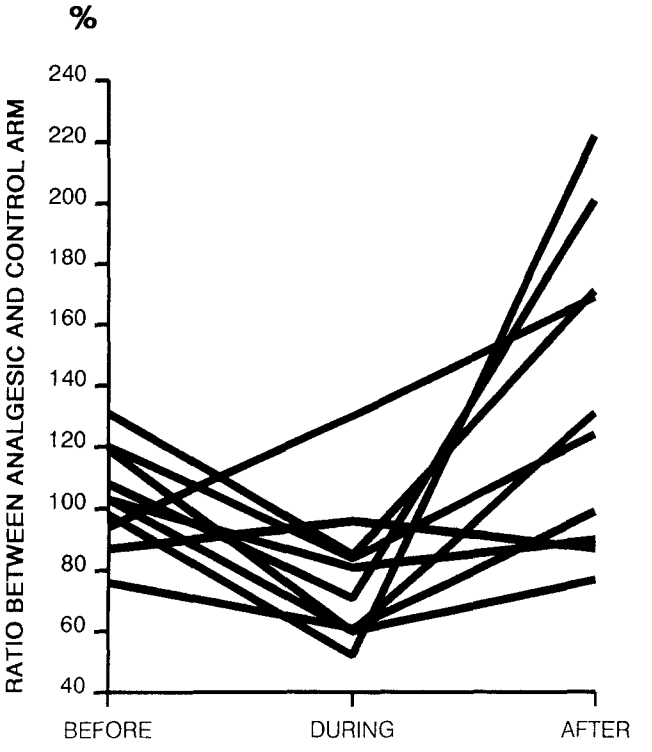

Fig. 2. The ratio between histamine flare reaction in the analgesic and the control arm in the pre-hypnotic, hypnotic analgesic, and post-hypnotic condition. A significant reduction in ratio in the hypnotic analgesic condition compared with the pre-hypnotic ($P = 0.01$–0.02) and the post-hypnotic condition ($P < 0.01$) can be observed

Pain-related brain potentials

As shown in Fig. 1, there was a significant ($p < 0.01$) reduction of the laser-induced brain potentials in the hypnotic analgesic condition compared with both pre- and the post-hypnotic conditions. The mean voltages were 86.70 μV (SD, 40.51 μV) in the pre-hypnotic condition, 44.30 μV (SD, 29.64 μV) in the hypnotic analgesic condition, and 70.20 μV (SD, 28.02 μV) in the post-hypnotic condition.

Histamine skin prick reaction

As the histamine prick reaction decreases for repeated measurements in the same area, new symmetrical sites were chosen for each subsequent measurement. It is also well known that a standardized histamine prick reaction changes from wrist to elbow. Therefore, absolute flare area measurements are not comparable. Thus, the ratio of the flare area of the anesthetized and the control arm was calculated. A significant difference was measured in the histamine flare reaction between the pre-hypnotic and the hypnotic analgesic condition ($p = 0.01$ -0.02) and between the hypnotic analgesic and the post-hypnotic condition ($p < 0.01$). As shown in Fig. 2, the histamine flare reaction measured in the hypnotic analgesic condition was significantly reduced compared with both the pre- and post-hypnotic condition.

Correlations

The correlation between the analgesic/pre-hypnotic ratio of pain-related brain potentials and the analgesic/control ratio of the histamine flare reaction was +0.43 (not significant). No correlation ($r = 0.10$) could be found between the analgesic/pre-hypnotic ratio of pain-related brain potentials and the analgesic/pre-hypnotic ratio of the subjectively felt pain, nor between the analgesic/pre-hypnotic ratio of the VAS scores and the analgesic/control ratio of the histamine flare reaction ($r = 0.16$).

Discussion

The results of this study confirm earlier findings that the subjective response to experimentally induced pain can be reduced by hypnotic suggestions of analgesia [2, 18, 36], and also confirm recent findings that this pain reduction can be quantitated as a reduction in pain-related brain potentials [2, 41]. The results also show that an early inflammatory process, as expressed by the flare response to histamine prick tests, could be modulated by the psychologically induced inhibition of cutaneous pain in the form of hypnotic analgesia. This gives support to a hypothesis that central nervous system mechanisms are involved in the interactive processes of inflammatory and pain-regulatory systems [10, 20, 25, 42]. The results also indicate that higher cortical processes may be involved. This may also have a bearing on the type I immune reaction, in which histamine is an important mediator. There is no available method to indicate whether the decrease of the flare ratio in the hypnotic analgesic condition is a result of a decrease of the flare reaction in the analgesic arm or an increase

in the control arm, since different skin areas must be used for subsequent histamine skin pricks.

The results show that the prick test response ratio is increased in favour of the tested arm in the post-hypnotic condition compared with the pre-hypnotic baseline condition. In the pre-hypnotic condition no suggestions regarding differences in sensation were given. In the hypnotic analgesic condition suggestions that one arm was analgesic were given, and that normal sensation would be experienced in the control arm. In the post-hypnotic condition the subjects were instructed that the analgesic arm was *no longer* analgesic, which may have increased or changed attention to sensations in this arm, as indicated by the increase in mean subjectively felt pain. This may be the mechanism behind the increased reaction. Due to the intervention, the 'before' and the 'after' condition cannot be regarded as similar in psychophysiological terms.

The study gives no clear answer as to which neural and neurochemical mechanisms may be involved in this interactive process. Several mechanisms may be of importance. That inflammation is associated with the nervous system was suggested as early as the beginning of this century [25]. It was found that the flare reaction around small skin injuries depended on intact peripheral sensory innervation, and more recently it has been shown that the sensory fibres of the skin are able to produce increased microvascular permeability by liberation of neuropeptides [20]. Also a large number of the substances released during the inflammatory response, including acetylcholine, bradykinin, prostaglandins and histamine, have been shown to produce pain, as well as some of the vascular responses characteristic of inflammation [9].

There may be at least two different views of acute tissue reactions to injury [25]. One favours a peripheral mechanism, where the stimulus acts directly on local immunocompetent cells and blood vessels to produce inflammation, and the other favours a neurogenic mechanism, where a stimulus excites sensory nerve fibres which signal to the central nervous system, which activates local vascular mechanisms. Painful stimuli are modulated by the central nervous system by a gate control system [8, 28] at the dorsal horn of the spinal cord, which is activated by descending neutral pathways [14]. Numerous transmitter substances in the central nervous system, and other neuromodulators, may be responsible for directly or indirectly mediating both the nociceptive and inflammatory responses [7, 19, 21, 23, 24, 26, 29, 30, 38, 39].

Substance P is of special interest because of its importance for Aδ and C fibre afferents. Local release of substance P induces many inflammatory reactions: it produces vasodilation and flare, it excites afferent units in low doses, and it potentiates other inflammatory mediators [9]. The possible role of this neurotransmitter as a link between pain and inflammatory processes is indicated by findings that release of this intraneuronal substance contributes to the severity of experimental arthritis [22]. The substances that mediate hypnotic analgesia, however, are still largely unknown [37]. They are probably of a non-opioid nature, since studies have shown hypnotic analgesia to be insensitive to the opioid antagonist naloxone [16].

Pain related to peripheral inflammatory reactions can only fully be understood when investigated in conscious man, and experiments must of course be of a limited nature. Therefore, many studies on nociception have been performed on animals in which it is difficult to find reliable and appropriate responses to the stimuli [9]. In the present investigation, and other recent studies [2, 41], this problem has been overcome by the use of brief and well-defined argon laser pulses to elicit pain, and the pain response on the cortical level determined by pain-related brain potentials. The effectiveness of pleasant imagery, hypnotic analgesia, and other psychological intervention techniques, has been proposed to be due to the consumption of a finite reservoir of attention [1, 11, 17, 33]. The finding that the effect of hypnotic analgesia on experimental acute pain is positively correlated with hypnotic susceptibility has been hypothesized to be related to the ability of highly hypnotically susceptible subjects to absorb themselves in distracting imagery [5, 12, 18, 31, 36]. In this study the analgesic suggestions, on the contrary, focused attention on the analgesic arm, so that distraction was not responsible for the analgesic effect as shown by the reduction of brain potentials. Studies showing the possibility of control of skin temperature [32], blood flow [13], and histamine flare reaction [40] indicate that our results may be due to the ability of subjects in hypnosis to control specific peripheral responses by focused attention on the particular part of the body, probably by modulating the vascular component of these responses through selective autonomic nervous system control at a higher cortical level. This might explain the reduction of vasodilation (flare) after histamine skin pricks in the hypnotic analgesic condition.

In conclusion, our results support other findings that indicate the role of a neurogenic component in inflammatory processes [10, 20, 25, 42], and further indicate that the interactions between pain and inflammatory mechanisms can be modulated by higher cortical processes. In a clinical perspective, this points toward the necessity for greater attention toward patients' subjective reports of pain and discomfort. Also, our results suggest that psychological intervention, in some cases, could supplement traditional treatment procedures, not only in the management of pain, but also in patients with inflammatory states.

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