

Modulation of Type I immediate and Type IV delayed immunoreactivity using direct suggestion and guided imagery during hypnosis

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Cutaneous reactivity against histamine skin prick test (Type I) and purified tuberculin protein derivative (Mantoux reaction, Type IV) was studied in eight volunteers under hypnosis. Types I and IV immunoreactivity were modulated by direct suggestion (Type I) and guided imagery (Type IV). The volunteers were highly susceptible subjects, selected by means of the Harvard Group Scale of Hypnotic Susceptibility, Form A. When the volunteers underwent hypnotic suggestion to decrease the cutaneous reaction to histamine prick test, a significant ($P < 0.02$) reduction of the flare reaction (area of erythema) was observed compared with control histamine skin prick tests. The wheal reaction did not respond to hypnotic suggestion. Neither wheal nor flare reaction could be increased in size by hypnotic suggestion compared with control histamine skin prick tests. A hypnotic suggestion of increasing the Type IV reaction on one arm and decreasing the reaction on the other revealed a significant difference in both erythema size ($P < 0.02$) and palpable induration ($P < 0.01$). In two cases the reactions were monitored by laser doppler blood flowmetry and skin thickness measurement by ultrasound. The difference between the suggested increased and decreased reaction was 19 % for the laser doppler bloodflow (in favor of the augmented side), and 44 % for the dermal infiltrate thickness. This study objectively supports the numerous uncontrolled case reports of modulation of immunoreactivity in allergic diseases involving both Type I and Type IV skin reactions following hypnotic suggestions.

Key words: allergy; histamine; hypnosis; immune responses; imagery: Mantoux; suggestion.

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Many dermatological disorders are related to an altered immune response, and several of these, e.g. atopic dermatitis, are known to be altered by emotional factors in which inflammatory mediators, such as histamine and C5a release are thought to be important in initiating the clinical manifestations. Psychic stress may probably provoke psoriasis, in which an inflammatory response most likely initiates the disease (6, 32). The reaction is microscopically seen as mast cell activation and capillary dila-

tation (19, 24). The effect of emotional stress in skin disease was reviewed by Medansky et al. (18), and it was concluded that in treating the dermatological patient, both the psyche and the soma should be considered. A possible connection between the central nervous system and the immune system may be mediated by the local antidromic secretion of substance P, acting on the T-lymphocyte receptors for neurotransmitters (20, 22).

In the present study, the effect of direct suggestion and guided imagery during hypnosis on experimentally induced cutaneous immune reactions of Types I and IV was investigated.

MATERIAL AND METHODS

In this study, 43 undergraduate psychology students volunteered to have their hypnotic capacity measured by means of a group test. The volunteers were tested using a modified Danish version of the Harvard Group Scale of Hypnotic Susceptibility, Form A (25). In this test, the score range is 0 to 12. The mean score for this group was 7.55 compared with the original mean score of 7.39 (26). The test was performed in three groups of 12, 15, and 16 persons. The eight most susceptible individuals (5 men and 3 women) who scored from 10 to 11 were selected for the study. The subjects were informed of the purpose of the investigation and gave their informed consent. The study was approved by the local ethics committee.

A normal control group, consisting of 10 undergraduate students (8 men and 2 women), who did not receive suggestion was included. The control group was selected from a normal population of students and matched for sex and age. This group was not tested for hypnotic susceptibility, so that they should not differ from the normal population.

Skin prick test injections

Histamine skin prick tests were performed for elicitation of a Type I reaction. A sterile lancet covered with a lyophilised histamine solution (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 and during the hypnotic suggestion session. The tests were carried out blindly as the person who performed the tests did not know on which arm the hypnotizer would suggest the reaction increased and on which arm the suggestion would be to decrease the reaction.

For the Type IV reaction, 0.1 ml containing 10 units purified protein derivative (PPD) for

Mantoux reactions (Statens Serum Institut, Denmark) was injected symmetrically in the dorsal aspect of both forearms just before hypnotic suggestion. The injection area was marked on the arms with a water resistant pen, so that the subjects would be aware of the locations of the tested areas during the time needed for development of the PPD reaction. The tests were carried out blindly.

Monitoring of skin reactions

For Type I reaction monitoring was performed blindly, and after 7 min the cutaneous wheal and flare areas were traced on a plastic film and measured on a computerized digitizer (Videoplan, Kontron, FRG). Areas of the Type 4 reactions were measured after 72 h for both erythema and induration. The volunteers were instructed not to reveal which side was suggested to increase or decrease, and the readings of the results were therefore conducted blindly. The measured areas were transferred to a plastic film for calculations. In two cases, the depth of the dermal infiltration was measured by high frequency ultrasound (Smith and Kline, USA), and the degree of erythema was quantitated by quadruple measurements by laser doppler flowmetry (Periflux, Perimed, Sweden).

Hypnotic induction and suggestion during hypnosis

The experiments were performed individually. After an initial Type 1 test on each forearm (ventral aspect) the subjects were given a hypnotic induction, using a combination of direct and indirect suggestion to go into deep relaxation. It was also suggested that it would be possible in the deep relaxed state to alter and control different bodily functions, e.g. skin responses. In the deep hypnotic state the subjects were given a second histamine prick test on both arms, separate from the former injections, and were then given suggestions to alter their skin response. It was suggested, that the reaction on the right arm would be less than prior to the hypnotic induction and that the size of the reaction on the left arm would increase.

Suggestions included instructions to 1) imagine that an ice cube was placed on the target area on the right arm and 2) imagine that the target area on the left arm would soon be hot, itching and reddened. After 7 min the wheal and flare reactions were traced by a marking pen and the areas transferred to plastic sheets for planimetry.

The subjects were then instructed to imagine themselves taking a "guided tour inside their own bodies". They were instructed to imagine themselves travelling to the site of the Mantoux test area in the skin of their left arm. They were informed that the cutaneous injection would activate white blood cells, which would travel to the site and react to the antigen. They were told that this would be a normal and healthy reaction and that it would serve as a "training-mission" for the attacking cells. The volunteers were instructed to imagine more and more lymphocytes travelling to the target area in the left arm making that part of the skin swollen, infiltrated and reddened. It was also suggested that the swelling would be a normal and healthy reaction, indicating that the blood cells were active and highly responsive.

Following this, they were instructed to "travel" in the blood stream to their right arm, and it was suggested that they would here encounter only the normal amount of white blood cells. Knowing that the injected material only contained harmless proteins from dead bacteria, the cells in the right arm would perhaps check the site of the injection but not react much further. The subjects were also told that they could imagine ice cubes on the skin or whatever

they felt would best reduce the process. The subjects were then given an audio tape containing hypnotic induction and guided imagery instructions repeating the above mentioned suggestions. They were instructed to use the tape twice daily for about 20 min during the following 72 h. They should then return for measurement of the skin reactions.

Statistical method

Wilcoxon's test was used for statistical evaluations. Significance level: 0.05 %.

RESULTS

Type I reactions

The volunteers who during hypnosis suggestion were to decrease the cutaneous reaction had a mean reduction of 41 % of erythema (flare) after histamine prick test compared with the initial reaction ($P < 0.02$). No changes were found for the wheal reaction (Fig. 1). Hypnotic suggestions of increasing the reaction only increased the flare reaction by 1.6 % (mean score). The wheal was reduced by 0.02 cm², and both changes were non-significant. In the control group, no significant differences between the initial and final reactions of wheal and flare were observed.

Type IV reactions

A suggestion of increasing the immune reaction on one side and decreasing the reaction on the

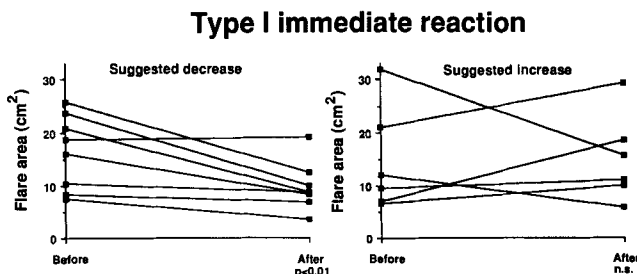


Fig. 1. Type I immediate reaction with hypno-suggested decreased response. Significant reduction ($P < 0.01$). Type I immediate reaction with hypno-suggested increased response. No significant change (data for 6 volunteers only).

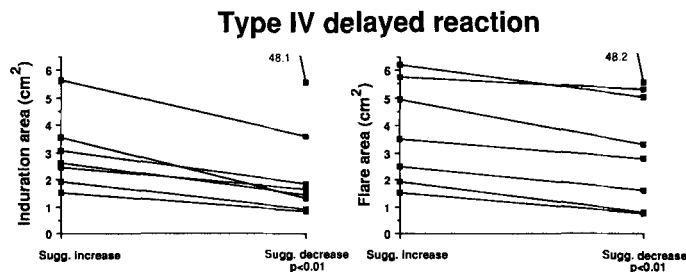


Fig. 2. Type IV (Mantoux) reaction (flare) with hypno-suggested increased/decreased response on either arm. A significant difference is demonstrated ($P = 0.01$). Type IV (Mantoux reaction (induration) with hypno-suggested increased/decreased response on either arm. A significant difference is demonstrated ($P = 0.01$).

other resulted in a mean relative difference in erythema area for the suggested larger reaction of 35%, and an even larger difference for the palpated induration of 84%. This difference was significant for both erythema size and induration ($P = 0.01$) (Fig. 2). For the volunteers, who besides visual and palpable determinations had their reactions monitored by laser doppler blood flowmetry and ultrasound skin thickness measurements, the difference in blood flow (arbitrary units) was 19%, and the dermal infiltrate was increased by 44%. No significant difference in erythema and induration was observed in the control group.

DISCUSSION

Type I reaction

A number of clinical cases have been presented, in which Type I-mediated immune reactivity (asthma and hay fever) to egg, dog, cat, etc.

has been inhibited by hypnotic suggestion (11, 16, 17, 21, 27). Other case stories have indicated the possible modulation of Type I skin reactivity (1, 8, 31, 32).

In 1959, Chapman et al. (55) demonstrated that the erythema (flare) from a noxious thermal stimulus could be inhibited by hypnotic suggestion. In the present study, a quantitative measure of the degree of inhibition of the flare reaction was obtained, and the effect is shown to be restricted to an inhibition of flare. Augmentation of the flare was not possible. This may be explained by the already maximal capillary dilation in the flare area.

Previously, Black (2) showed that a control group, receiving no suggestion did not exhibit reduced response of Type I reactions, and in the present study, no significant difference was found in the control group between the size of wheal and flare on the arms.

The possible mode of action may be a centrally modulated contraction of the affected capillaries, presumably mediated by thin unmyel-

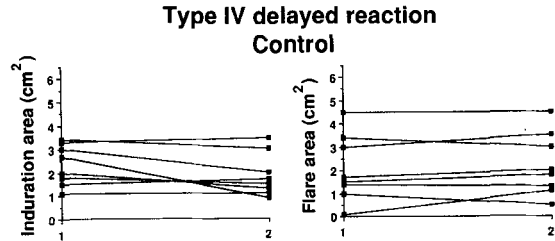


Fig. 3. Type IV (Mantoux) reaction (flare) on each arm with no suggestion to in- or decrease the reaction (controls). No significant change. Type IV (Mantoux) reaction (induration) on each arm with no suggestion to in- or decrease the reaction (controls). No significant change.

inated C-fibres in which substance P is a intracutaneous neurotransmitter. This is supported by the known inhibitory effect of capsaicin (a substance P depletor) on the histamine-induced flare reaction (10). The fact that hypnotic suggestions did not have any effect on the wheal reactions supports the theory that the nervous system plays a specific rôle in flare inhibition. The central neural and psychological processes remain obscure.

Type IV reaction

The reaction to skin prick test and PPD of tuberculin (Mantoux reaction) in previously vaccinated persons is a well-established method for monitoring the Type IV reaction (30). Black et al. (3) demonstrated that the Mantoux reaction may be inhibited by suggestions given during a 12-day hypnosis course. However, this test was preceded by a control injection of PPD. Later, Thestrup-Pedersen (30) showed that this procedure may induce a state of hyposensibilisation and that a subsequent PPD injection would elicit a decreased cutaneous inflammatory reaction. In the study of Black (3), three of four volunteers had no inflammatory response measured by palpable infiltration after hypnosis, and one volunteer was able to inhibit the erythema completely. In the present study, where the pre-hypnotic PPD injection was omitted, large doses of the PPD were injected in order to obtain a quantitative response even after hypnosis, and the injections were performed at the same time, just before hypnosis. By this method, the maximal effect of suggestion may be evaluated. In spite of methodological differences, the present results are in accordance with those obtained by Black et al. who found stronger inhibition of the induration than of the erythema of the Mantoux reaction.

In the present study, the volunteers represented a highly selected population. Fry et al. (7) reported that the degree of inhibition of Type I responses was much more readily obtained in highly hypnosis susceptible persons.

It is suggested that the observed effects are due to an ability to influence vascular innerv-

ation and thus the capillary leakiness for both osmotically active proteins and inflammatory cells to a measurable, functionally significant degree. This theory may find support from the fact that both hypnosis and mental imagery seem to influence the vascular response. Maslach et al. (15) found that subjects trained in hypnosis were able to change the peripheral skin temperature of their hands in opposite directions. Kunzendorf (12) found that the ability to achieve such temperature control was related to mental imagery capacity. Both capillary innervation and modulation of the secretion of neuroinflammatory substances have pronounced effects on the efferent limb of the immune response. It is not possible to evaluate whether augmentation or inhibition of the Type IV reaction by hypnotic suggestion is the most prominent factor.

The effect of suggestion during hypnosis on the immune reactivity may be initiated by a central neural response, peripherally transmitted by antidromic activity of the afferent sensory system. In this system, increased activity results in increased secretion of neurotransmitters into the skin (4, 20). These transmitters, predominantly substance P, are among the most potent chemotactic substances and potent releasers of histamine (9, 13).

Stein et al., (28) found that hypothalamic influence may be a possible mediating factor in the hypnotically suggested inhibition of Type I and IV reactions. Investigations show that hypothalamic lesions can cause inhibition of experimentally induced anaphylactic shock in animals (14, 23, 29). This focuses on the possibility of hypothalamic modification of immune processes. However, an extensive network of endocrine interactions resulting in elevated plasma cortisols and other autonomic and biologic mechanisms may be involved.

REFERENCES

1. Ader, R.: A histological account of conditioned immunobiologic response. In: Ader, R. (ed.): *Psychoneuroimmunology*, pp. 521-541. Academic Press, New York, 1981.
2. Black, S.: Inhibition of immediate type hypersensitivity response by direct suggestion under hypnosis. *Br. Med. J.* 6, 925-929, 1963.

3. Black, S., Humphrey, J. H. & Niven, J. S.: Inhibition of Mantoux reaction by direct suggestion under hypnosis. *Br. Med. J.* 6, 1649-1652, 1963.
4. Carpenter, S. E. & Lynn, B.: Vascular and sensory responses of human skin to mild injury after topical treatment with capsaicin. *Br. J. Pharmacol.* 73, 755-758, 1981.
5. Chapman, L. F., Goodell, H. E. & Wolff, H. G.: Changes in tissue vulnerability induced during hypnotic suggestion. *J. Psychosom. Res.* 4, 99, 1959.
6. Farber, E. M., Nall, L. & Charuwnon, A.: Proceedings of the XXI International Congress of Dermatology, Tokyo, 1982, pp. 81-85. Tokyo University Press, Tokyo, 1982.
7. Fry, L., Mason, A. A. & Pearson, B.: Effects of hypnosis on allergic skin responses in asthma and hay-fever. *Br. Med. J.* 1145-1148, 1961.
8. Hall, H. R.: Hypnosis and the immune system: A review with implication for cancer and the psychology of healing. *Am. J. Clin. Hypn.* 25, 2-3, 92-103, 1983.
9. Hall, N. R. & Goldstein, A. L.: Neurotransmitters and the immune system. In Ader, R. (ed.): *Psychoneuroimmunology*, pp. 521-541. Academic Press, New York, 1981.
10. Jancsó, G., Høkfelt, T., Lundberg, J. M., et al.: Immunohistochemical studies on the effect of capsaicin on peptide and monoamine neurons using antisera to substance P, gastrin/CCK, somatostatin, VIP, enkephalin, neurotensin and 5-hydroxytryptamine. *J. Neurocytology* 10, 963-980, 1981.
11. Kroger, W. S.: Current state of hypnosis in allergy. *Ann. Allergy* 22, 123-129, 1964.
12. Kunzendorf, R. G.: Individual differences in imagery and autonomic control. *J. Ment. Imag.* 5, 47-60, 1981.
13. Lembeck, F.: Mediators of vasodilation on the skin. *Br. J. Dermatol.* 109, Suppl. 25, 1-9, 1983.
14. Luparello, T. J., Stein, M. & Park, C. D.: Effect of hypothalamic lesions on rat anaphylaxis. *Am. J. Physiol.* 207, 911-914, 1964.
15. Maslach, C., Marshall, G. & Zimbardo, P. G.: Hypnotic control of peripheral skin temperature: A case report. *Psychophysiology* 9, 600-605, 1972.
16. Mason, A. A.: Hypnosis and allergy, *Br. Med. J.* 1, 1675-1676, 1963.
17. Mason, A. A. & Black, S.: Allergic skin responses abolished under treatment of asthma and hay fever by hypnosis. *Lancet* 2, 877-880, 1958.
18. Medansky, R. S.: Dermatopsychosomatics: An overview. *Psychosomatics* 21, 195-200, 1980.
19. Parwaresch, M. R., Horny, H.-P. & Lennart, K.: Tissue mast cells in health and disease. *Pathol. Res. Pract.* 179, 439-461, 1985.
20. Payan, D. G., Levine, J. D. & Goetzl, E. J.: Modulation of immunity and hypersensitivity by sensory neuropeptides. *J. Immunol.* 132, 1601-1604, 1984.
21. Perloff, M. M. & Spiegelman, J.: Hypnosis in the treatment of a child's allergy to dogs. *Am. J. Clin. Hypn.* 15, 269-272, 1973.
22. Piotrowski, W., Devoy, M. A. B., Jordan, C. C. & Forman, J. C.: The substance P receptor on rat mast cells and in human skin. *Agents Actions* 14, 420-423, 1984.
23. Schiavi, R. C., Macris, N. T., Camerino, M. S. & Stein, N.: Effect of hypothalamic lesions on immediate hypersensitivity. *Am. J. Physiol.* 228, 596-601, 1975.
24. Schröder, J.-M. & Christophers, E.: Transient absence of C5a-specific neutrophil function in inflammatory disorders of the skin. *J. Invest. Dermatol.* 85, 194-198, 1985.
25. Shor, R. E. & Orne, E. C.: Harvard Group Scale of Hypnotic Susceptibility, Form A. Consult. Psychol. Press, Palo Alto, 1963.
26. Shor, R. E. & Orne, E. C.: Norms on the Harvard Group Scale of Hypnotic Susceptibility, Form A. *Int. J. Clin. Exp. Hypn.* 11, 39-47, 1963.
27. Smith, R. G., Mackenzie, J. M., Marmer, D. J. & Steele, R. W.: Psychologic modulation of the human immune response to varicella zoster. *Arch. Intern. Med.* 145, 1985.
28. Stein, M., Schleifer, S. J. & Keller, S. E.: Hypothalamic influences on immune responses. In Ader, R. (ed.): *Psychoneuroimmunology*. Academic Press, New York, 1981.
29. Szentivanyi, A. & Filipp, G.: Anaphylaxis and the nervous system, Part II. *Ann. Allergy* 16, 389-392, 1985.
30. Thestrup-Pedersen, K.: Suppression of tuberculin skin reactivity by prior tuberculin skin testing. *Immunology* 28, 342-348, 1975.
31. Teshima, H., Kubo, C., Kihara, H., Nagata, S., Ago, Y. & Ikemi, Y.: Psychosomatic aspects of skin diseases from the standpoint of immunology. *Psychother. Psychosom.* 37, 1982.
32. Whitlock, F. A.: Psychophysiological aspects of skin disease. W. B. Saunders, London, 1976.

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