

Increase and decrease of delayed cutaneous reactions obtained by hypnotic suggestions during sensitization

Studies on dinitrochlorobenzene and diphenylcyclopropenone

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Cutaneous reactivity to challenge with dinitrochlorobenzene (DNCB) and diphenylcyclopropenone (DCP) was studied in 16 volunteers following hypnotic suggestions to increase and decrease response during sensitization. The immunoreactivity to DNCB and DCP was modulated by direct suggestions and guided imagery under hypnosis. The volunteers were highly susceptible subjects selected by means of the Harvard Group Scale of Hypnotic Susceptibility, Form A. Measurement of skin reactions to the challenge 1 month after sensitization was performed double blindly. Results showed a significant ($P < 0.01$) difference in visually scored reactions to DCP and DNCB between the group instructed to increase reaction to DCP and decrease reaction to DNCB and the group given the opposite instructions. A non-significant difference ($P = 0.055$) in skin thickness measured by ultrasound was found between the two groups. The study supports previous reports of experimental modulation of immunoreactivity and indicates that the specific immunological processes involved in the development of allergic reactions may be susceptible to psychological factors.

Key words: allergy; dinitrochlorobenzene; diphenylcyclopropenone; hypnosis; imagery; immunity; psychoneuroimmunology; sensitization.

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It has been established that psychological factors may influence different aspects of the immune system (1, 27, 29), and it has been shown that psychosocial influences in the form of stress, bereavement, and emotional disorders (18) may alter the immune response and enhance disease susceptibility (7, 17). An increasing number of studies have described neural and endocrine pathways that may mediate such responses (30, 36). A number of disorders of the skin, such as eczema, psoriasis, and contact allergy, involve both humoral and cellular immune responses, and reviews of the literature (2, 19, 35) have indicated that psychological factors such as life stress, emotional distress and "personality" may play a role in the pathogenesis of these disorders.

Clinical investigations and case reports have shown psychological intervention in the form of relaxation therapy and hypnosis to be effective in the treatment of dermatological disorders such as psoriasis (32, 37), eczema (10, 35), allergic skin responses (8), and warts (13). Also, experimental investigations have shown that immunological and

inflammatory responses in humans can be modulated by psychological intervention techniques. In previous studies we have shown that delayed hypersensitivity response to tuberculin can be modulated by guided imagery under hypnosis (38), and that other immunological responses such as natural killer cell activity (39) and chemotaxis (41) can also be modulated by psychological intervention. Our investigations have further indicated that skin reactions, such as histamine flare reaction and induration, can be affected by hypnotic suggestions (38, 40).

It is, however, still unclear to what extent these reactions are due to general non-specific or more specific immunological processes. To further clarify this issue, we wished to investigate whether it would be possible to modulate aspects of the specific immunological response to an allergen. Though the response to the challenge by an antigen has been shown to be affected by psychological intervention, it has not yet, to the best of our knowledge, been investigated whether the sensitization to a specific allergen can be affected by psychological stimulation.

tion. In this study we therefore investigated the effect of psychological stimulation, in the form of hypnotic suggestions to decrease or increase the response to an allergen during sensitization, on the later response to the challenge.

Material and methods

A total of 120 undergraduate psychology students (81 women, 39 men) volunteered to have their hypnotic susceptibility measured with a Danish modification of the Harvard Group Scale of Hypnotic Susceptibility, Form A (25). The mean score for this group (on a scale from 0 to 12) was compared to the original mean score of 7.39 (26). Twenty highly susceptible subjects (6 men, 14 women; mean age 29.5; range: 20–44) (scoring from 10–12; mean score: 10.64) were selected for the study. The subjects all gave their informed consent according to the II Helsinki Declaration. The study was approved by the local ethics committee.

Sensitization

Since the individual response to an allergen may fall within a broad range, it is methodologically difficult to compare inter-individual responses. In this investigation we therefore chose to compare the simultaneous responses to two different experimental allergens, dinitrochlorobenzene (DNCB) and diphenylcyclopropanone (DCP), when subjects would receive suggestions to inhibit the response to one and enhance the response to the other during the primary sensitization phase.

For sensitization DNCB and DCP 2% in ethanol were applied under occlusion on the volar aspect of both forearms (11 mm Finn Chamber, Epitest, OY, Finland) for 48 h. The concentration of both sensitizers was 100 µg/cm². This concentration has previously been shown to induce 100% DNCB sensitization (22). All subjects developed an eczematous reaction on the areas of sensitization.

A double-blinded protocol was designed in which 10 subjects had DNCB placed on the right arm, and DCP on the left arm, and 10 subjects had DCP placed on the right arm and DNCB on the left. In both groups five subjects had their right arm marked with red and the left arm with blue, and five had their left arm marked with red and their right arm with blue. The red color indicated that the reaction should be increased, and the blue indicated that the reaction should be decreased. The protocol ensured that both the sensitizers and suggested increase and decrease were randomly assigned to the right and left forearms.

The subjects participated individually in 30-min sessions in which they had the allergens placed ac-

cording to the double-blinded protocol. The subjects were then given a 10-min standardized hypnotic induction. In the trance the subjects were then instructed that it is healthy to be able to both enhance and inhibit immunological reactions. The subjects were then given a standardized 10-min instruction to imagine that the reaction on the arm marked with red would increase and that the reaction on the arm marked with blue would only be small and insignificant. The subjects were also given instructions to perceive the target area on the arm marked with red becoming increasingly warm and itchy, and the target area marked with blue becoming cool and numb. The subjects were then instructed that they would be subconsciously aware of the target area marked with red and unaware of the target area marked with blue. They were then instructed to return to their active, awake condition, feeling refreshed and comfortable. The subjects were instructed to remove the occlusion chambers after 48 h. They were given a 20-min audiotape with the same hypnotic induction and imagery procedure used in the primary session. The subjects were instructed to follow the instructions given on the tape once a day in the following 5 days. The subjects were instructed to return 6 weeks later to test their reaction to DNCB and DCP.

Challenge

Six weeks later the subjects returned for allergen challenge, and had DNCB and DCP placed in 8-mm aluminum chambers (Finn Chambers, Epitest, OY, Finland) on the volar side of the left upper arm. The allergens were applied in two rows, using the following four doses: 1 µg, 6 µg, 30 µg, and 60 µg. The subjects were instructed to remove the antigens after 6 h (34), and to return after 48 h for quantification of the reactions. Four subjects did not complete the investigation, and hence the patch test reactions were monitored in 16 subjects.

Monitoring and measurement of reactions

The measurements and scoring of reactions were performed in a double-blind manner. The reactions were photographed and erythema was monitored and scored by the following scores: 0 = slight, patchy erythema or no reaction, 1 = target area partially erythematous, and 2 = vesicles or at least whole patch test area uniformly erythematous. Skin thickness (induration) of the target area as well as normal skin thickness (control) was measured by high-frequency pulsed ultrasound (Dermascan A, Cortex Technology, Denmark), and percent increase in induration compared to control was calculated.

Calculations and statistics

The difference between reaction to DCP and DNCB was calculated for visual scores and skin thickness for the group that received suggestions to increase reaction to DCP and decrease reaction to DNCB ($n = 7$) and the group which was given the opposite suggestions ($n = 9$). Differences were ranked and compared by the Mann-Whitney nonparametric test.

Results

Results of *visual observations* are shown in Tables 1 and 3. Due to negative results for DNCB in dilutions 2 and 1 and maximum score in 15 out of 16 subjects in dilution 4 for DCP, dilutions 4, 2, and 1 were considered unsuitable for comparison. When comparing the reaction to DCP and DNCB (dilution 3) of the two groups, a significant difference ($P < 0.01$) was found, as seen in Table 3.

Induration. On the same grounds as indicated for visual observations, dilution 3 was chosen for comparison. When comparing the difference in reaction

to DCP and DNCB (dilution 3) of the two groups, a nonsignificant difference ($P = 0.055$) was found. Results are shown in Tables 2 and 4.

Discussion

Previous investigations have shown that the *in vivo* cellular immune response related to allergic processes, such as delayed type hypersensitivity, can be altered by psychological stimulation in the form of conditioning (28) or hypnotic suggestions (38). It can be argued that such alterations may not necessarily be due to specific influence on the immune function, but may be caused by non-specific processes such as local vasodilatation. Several investigations have shown that "autonomic" physiological processes such as blood flow and peripheral skin temperature can be modified by hypnotic suggestions and guided imagery techniques (3, 6, 15, 21). The increased response in flare and induration following psychological intervention may therefore be the result of increased or decreased blood flow following indirectly or directly suggested increase or

Table 1. Visual observations of responses after challenge to dinitrochlorobenzene (DNCB) and diphenylcyclopropanone (DCP) in 16 subjects following hypnotically suggested increase and decrease of response during sensitization. Scorings of visual observations are shown for 4 doses: 1) 1 μ g, 2) 6 μ g, 3) 30 μ g, and 4) 60 μ g. Observations are based on the following scoring criteria: 0 = slight, patchy erythema or no reaction, 1 = target area partially erythematous, and 2 = vesicles or at least whole patch test area uniformly erythematous

Sugg.	increase	increase	increase	increase	decrease	decrease	decrease	decrease
Dil. Sub.	DNCB:4	DNCB:3	DNCB:2	DNCB:1	DCP:4	DCP:3	DCP:2	DCP:1
2	2	1	0	0	2	2	2	2
3	2	1	0	0	2	2	2	1
4	2	1	0	0	2	2	1	1
5	2	1	0	0	2	1	1	1
6	2	1	0	0	1	0	0	0
11	2	1	0	0	2	2	2	2
14	1	1	0	0	2	2	1	0
15	1	0	0	0	2	1	0	0
16	2	0	0	0	2	0	0	0
Dil.	DCP:4	DCP:3	DCP:2	DCP:1	DNCB:4	DNCB:3	DNCB:2	DNCB:1
1	2	2	1	1	1	0	0	0
7	2	2	1	1	0	0	0	0
8	2	2	2	2	1	0	0	0
9	2	2	2	2	2	1	0	0
10	2	2	2	2	1	0	0	0
12	2	1	1	1	1	0	0	1
13	2	1	0	1	1	0	0	0

Increase and decrease of delayed cutaneous reactions

Table 2. Percent increase in skin thickness (induration) compared to control after challenge to dinitrochlorobenzene (DNCB) and diphenylcyclopropenone (DCP) in 16 subjects following hypnotically suggested increase and decrease of response during sensitization. Results are shown for 4 doses: 1) 1 µg, 2) 6 µg, 3) 30 µg, and 4) 60 µg

Sugg:	increase	increase	increase	increase	decrease	decrease	decrease	decrease
Dil. Sub.	DNCB:4	DNCB:3	DNCB:2	DNCB:1	DCP:4	DCP:3	DCP:2	DCP:1
2	61.9	0	0	0	100	42.9	52.4	21.4
3	75.0	86.9	0	0	80.9	71.4	92.9	2.4
4	106.0	17.9	0	0	490.5	121.4	36.9	46.4
5	83.8	24.2	0	0	143.4	16.2	11.1	58.5
6	21.7	38.1	14.0	0	2.4	0	0	0
11	76.3	55.3	0	0	452.6	106.6	76.3	57.9
14	64.9	14.0	0	0	433.3	135.1	129.8	93.0
15	56.0	8.3	11.9	0	71.4	52.4	15.5	0
16	257.1	0	0	0	856.5	0	0	0
Dil.	DCP:4	DCP:3	DCP:2	DCP:1	DNCB:4	DNCB:3	DNCB:2	DNCB:1
1	736.0	35.5	39.1	4.5	10.9	0	0	0
7	73.1	64.1	47.4	24.4	14.1	0	0	0
8	198.9	207.4	156.4	173.4	47.9	0	0	0
9	223.6	179.8	130.3	136.0	118.0	109.0	0	0
10	192.9	192.9	108.3	175.0	88.1	0	0	0
12	55.3	40.8	10.5	130.3	0	2.6	0	22.4
13	366.2	100.0	50.0	80.9	10.3	0	0	0

Table 3. Difference between reaction (visual observations) to the challenge to diphenylcyclopropenone (DCP) and dinitrochlorobenzene (DNCB) following hypnotically suggested increase and decrease of response during sensitization for group 1) subjects instructed to increase reaction to DCP and decrease reaction to DNCB (n=7) and 2) subjects instructed to decrease reaction to DCP and increase reaction to DNCB (n=9) for dose: 30 µg (P<0.01)

Increase DCP decrease DNCB		Decrease DCP increase DNCB	
Subject No:	DCP-DNCB	Subjects No:	DCP-DNCB
1	2	2	1
7	2	3	1
8	2	4	1
10	2	11	1
9	1	14	1
12	1	15	1
13	1	5	0
		16	0
		6	-1
MEAN	1.57	MEAN	0.56

decrease of attention towards the specific challenge area (38).

In the present study no suggestions were given during the challenge, and since the challenge was performed double-blinded, any effect of psychological factors during the challenge itself can be excluded. Half of the subjects were instructed to increase the response to one of the antigens and the other half were instructed to increase the response to the other. In addition, half of the subjects had one antigen placed on the right arm and the other half had the same antigen placed on the left. Thus possible effects due to either lateralization or to one allergen inducing larger responses than the other were thought to be eliminated. It therefore seems reasonable to assume that the observed differences in the response to the challenge are due to the influence of psychological factors on the responsiveness of the immune system towards the allergen.

It is, however, still unclear which mechanisms may be responsible for the increased responsiveness of the immune system towards one specific allergen as compared to another. It may be that the same psy-

Table 4. Difference between reaction (induration) to challenge to diphenylcyclopropenone (DCP) and dinitrochlorobenzene (DNCB) following hypnotically suggested increase and decrease of response during sensitization for group 1) subjects instructed to increase reaction to DCP and decrease reaction to DNCB (n=7) and 2) subjects instructed to decrease reaction to DCP and increase reaction to DNCB (n=9) for dose: 30 µg (P=0.055)

Increase DCP decrease DNCB		Decrease DCP increase DNCB	
Subject No.	DCP- DNCB	Subjects No.	DCP-DNCB
8	207.4	14	121.1
10	192.9	4	103.5
13	100.0	11	51.3
9	70.8	2	49.9
7	64.1	15	44.1
12	38.2	16	0
1	35.5	5	-8.0
		3	-15.5
		6	-38.1
MEAN	101.3	MEAN	34.3

chophysiological processes thought to be responsible for the previously shown effects on the response to challenge, such as increased vasodilatation, also mediate the increased responsiveness due to hypnotic suggestions during sensitization. The subjects were given suggestions of increased activity and warmth in the arm where the response was to be increased, and imagery of warmth and increased attention have been shown to influence blood flow and peripheral skin temperature (3, 15, 21). Increased local vasodilatation may enhance the number of lymphocytes in contact with the antigen and thus increase the response to the challenge.

Even if this may be one of the psychophysiological processes responsible for our findings, it is not possible to determine whether the difference in sensitization is due to enhancement, inhibition or both. Our findings are further limited by the highly selected group of subjects used in our study. Research has indicated that highly hypnotically susceptible subjects and subjects capable of producing relevant sensory images show greater ability to modify autonomic physiological processes (3, 15, 16, 23).

The concept that a specific "learning" process of the immune response during sensitization may be altered by psychological processes may seem provocative. The idea, however, is not new (9), and it has been suggested that the central nervous system (CNS) and the specific immune system share a number of functional characteristics (12) related to "learning" processes, such as "memory" and "discrimination" (36). It has been suggested that

the immune system has the properties of a "sensory organ" (5) directed towards the cognition of non-self. Both neuroendocrine and immune systems seem to share a similar set of peptide information substances and receptors (4, 5, 33, 36), and it seems probable from research in so-called "state-dependent learning, memory and behavior" (9, 11, 31) that "learning" processes of both the CNS and the immune system are modulated at the cellular and molecular level (20).

In conclusion, the results of our investigation indicate that the responsiveness of the immune system towards a specific antigen may be modulated by influence on the sensitization process by psychological stimuli. This gives support to case histories indicating that psychological, emotional and learning processes may influence the development of eczematous and allergic reactions (14, 35), and that treatment of allergy and immunologically related disorders may benefit from the supplementary use of psychological techniques.

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