Clinical Observations

Psychologic Modulation of the Human Immune Response to Varicella Zoster

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- Psychoneuroimmunology, the interrelationship between the brain/mind/psyche and the immune system, is now an established area of scientific research. Based on prior investigations we hypothesized that an experienced mediator could affect her delayed hypersensitivity reaction by a psychological process. A single-case study design was employed in which the subject was skin tested weekly with varicella zoster skin test reagent. After baseline immunologic studies, she was able, as hypothesized, to significantly reduce both the induration of her delayed hypersensitivity skin test reaction and in vitro lymphocyte stimulation to varicella zoster. Then, as predicted, she was able to allow her reaction to return to baseline. As a confirmation of what is to our knowledge this previously undescribed phenomenon, she was able to reproduce the entire sequence nine months later. It appears that this subject can intentionally modulate her immune response by a psychologic mechanism.

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For centuries physicians have theorized about the possible role of the mind and/or psyche as a mediator between health and disease. There have been countless postulated mechanisms for this modulation. In recent years, attention has turned to the immune system as one possible system whereby the mind may affect, either negatively or positively, the transition from health to disease and at times back to health. This report will present data demonstrating an apparent voluntary, direct, psychologically mediated effect on the human immune system. Specifically, in a carefully designed single-case protocol, a woman mediator intentionally suppressed her cell-mediated immune response to varicella zoster viral antigen as measured in vivo by delayed hypersensitivity skin test reactions and in vitro by lymphocyte stimulation.

Direct evidence has been accumulating for several decades linking the mind and the immune system.1 There is a growing body of evidence demonstrating a direct link between psychological or behavioral processes and the immune system. Both animal and human data now provide sound evidence that a psychic event may alter some aspects of immune function.

In a series of studies attempting to modulate the immune system, Black and associates2 successfully modified a clinical measure of cell-mediated immunity. Using four highly selected tuberculin-positive male subjects, they demonstrated an inhibition of delayed hypersensitivity reaction to tuberculin (Mantoux reaction) via hypnosis. After an extensive training period they forcefully sug-gested to the hypnotized subjects that they not react to further injections of tuberculin. When retested, all subjects inhibited the Mantoux reaction.

In 1983 Smith and McDaniel3 reported another direct psychologically mediated effect on the tuberculin reaction in seven tuberculin-positive subjects. The subjects were exposed to a behavioral conditioning paradigm in which they expected the reaction on one arm to be positive and on the other arm to be negative. When unknown to them the tuberculin, or unconditioned stimulus, was switched to the opposite arm, they had a significantly reduced response to tuberculin. Their clinical reaction, measured by induration, was reduced from a mean of 15 mm to a mean of 4 mm when they expected their reaction to be negative.

In light of the above findings, we hypothesized that a highly selected subject could use meditation or self-hypnosis to modulate her immune response. The paradigm was a simple, single-case design in which the subject was her own control. She was given a skin test weekly for nine weeks. During the first three weeks (phase 1) she was told to react normally. The second three weeks (phase 2) she was asked to try to inhibit her reaction using any psychologic practice or technique she chose. Finally, for the final three weeks (phase 3) she was again asked to react normally. We hypothesized that the immune response during the second phase would be decreased compared with the first and third phases.

METHODS

The subject, an experienced mediator, was known to have a positive reaction to the varicella zoster (VZ) viral antigen. After obtaining informed consent, we applied 0.1 mL of antigen to the volar aspect of the right forearm. For three weeks of phase 1, she was instructed to respond in a normal or unmodulated fashion. Her skin tests were read at 24 and 48 hours. The skin tests were read independently by two readers, one of whom was “blind” to the protocol condition. After the 48-hour reading, blood was obtained for in vitro assay of lymphocyte stimulation by VZ antigen. The phase 2, three-week period served as the intervention period in which the subject was asked to use whatever mechanism she thought would be helpful to modulate or reduce her skin test response. She was asked not to take medicines during this time, some of which are steroids, and was asked to inform us if she became ill in any way. Her skin tests were read and blood samples were obtained on a weekly basis just as during the baseline study. Phase 3 served as a return to baseline, in which she was instructed to allow her skin test to react in an unmodulated fashion for each of three weeks.

Nine months after the first study period, the subject was studied again with the same protocol. All skin tests used the Mantoux technique with tuberculin syringes and 25-gauge needles. Tests were read using the ballpoint pen technique described by Sokal.4 All readings were in millimeters.

Varicella zoster virus antigen was prepared from the Scott strain of VZ and human diploid cells as reported by Steele and associates.5 The skin test antigen consisted of the necessary protocols for an investigative new drug and has been assigned number BB-IND 1568.

Antigen-induced lymphocyte stimulation was performed on lymphocytes separated from peripheral whole blood obtained after the 48-hour readings. Lymphocytes were separated from whole blood by centrifugation on a Ficoll-Hypaque gradient. Using a micro-pipette, 0.1 mL of the lymphocyte suspension (2 × 10^6 lymphocytes) was added to an equal volume of various concentrations of VZ antigen each in triplicate, in a sterile microtitrator plate. The cultures were incubated for five days using a 24-hour tritiated thymidine pulse. A harvesting apparatus, as previously described, was employed for separation of the stimulated lymphocytes on glass filters for washing of these cells and for recovery of tritiated thymidine uptake.4 Variation among triplicate samples with this antigen has averaged 26%. Data were analyzed by absolute counts per minute (cpm) in cultures that contained VZ antigen and by

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calculation of a blastogenic index: cpm of tritiated thymidine uptake for lymphocytes incubated with VZ divided by cpm after incubation with medium alone. These determinations were made for each of three concentrations of VZ antigen.

The subject is a 39-year-old woman who has followed an Eastern religious practice for the last nine years. During most of this time, as part of her religious practice, she would usually meditate once or twice daily for about 30 minutes. For the last three years, she has followed a specific tantric generation meditation practice whereby “higher energies” are visualized and she seeks to transform herself into those energies.

During the phase 2 periods of the original and repeat experiment, she would usually reserve about five minutes of her daily meditation for attention to the study. First she would dedicate her intention concerning the study for universal good instead of self-advancement. She would also tell her body not to violate its wisdom concerning her defense against infection. Finally she would visualize the area of erythema and induration getting smaller and smaller. Soon after each phase 2 injection, she would pass her hand over her arm, sending “healing energy” to the injection site.

RESULTS

The subject remained healthy throughout both study periods. There was high interrater reliability between the two skin-test readers (Pearson’s correlation coefficient = .86). Figure 1 represents the induration measured at 48 hours for each phase. The solid line represents the first study period, the broken line is the second study period, and the heavy line is the mean.

For lymphocyte stimulation assays, control cultures (medium alone) averaged 2,641 ± 798 cpm and had no significant influence on calculation of the blastogenic index. Changes for the optimal concentration of antigen in all cases were representative of changes seen with other VZ antigen concentrations in the dose-response curve. Therefore, for simplicity, data are presented using the mean blastogenic index with optimal VZ antigen concentrations for the study periods. Figure 2 represents the mean blastogenic index. The likelihood of changes in induration or blastogenic index happening as predicted by chance alone is P < .001 (binomial expansion).

COMMENT

The data confirmed the hypothesis, that this subject could voluntarily modulate her immune responses by a psychic mechanism. Both a clinical measure, delayed hypersensitivity, and an in vitro measure, lymphocyte stimulation of immune response, were affected. In other words, it appears that the subject, acting with intention, was able to affect not only her skin test response but also the response of her lymphocytes studied in the laboratory.

These data are entirely consistent with the growing body of evidence that uncontrollable psychological events are associated with immune changes.16 Adler and Cohen16 have provided important data linking psychic events, in this case learning or behavioral conditioning, with modulation of the immune response in animals. Their carefully controlled and designed studies have demonstrated decreased antibody production, decreased graft-vs-host response, and prolonged survival in an immunologically mediated disease.10,11 They used a Pavlovian (learning) paradigm in which they paired saccharin, the conditioned stimulus, with cyclophosphamide, the unconditioned stimulus, and obtained reproducible immunosuppression when the conditioned animals were reexposed to saccharin alone. In effect, animals “learned” that when they were given saccharin they suppressed their immune response. Their work has been reproduced in two independent laboratories.11,14

Studies of human subjects have been less rigorously controlled, yet several intriguing reports have been published linking unavoidable life events with suppressed immune response.10,17

To our knowledge these are the first published data of an intentional direct psychologic modulation of the human immune system. The results from this study certainly cannot be generalized to all humans; however, perhaps other people have the ability to modulate their immune response or to develop the capacity to do so. Certainly, these data, along with the previously cited results, should allow for many new carefully designed studies to be undertaken.

If it proves to be the case that humans can significantly modulate their immune response, then two important outcomes may occur. The mechanism of infectious or neoplastic disease onset associated with various psychologic processes such as hopelessness or depression can possibly be better understood. Perhaps, also, intentional modulation can be used therapeutically to increase or decrease immune response, depending on the particular disease state.

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References

Sarcoidosis and Reactive Pulmonary Hypertension

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- Despite diffuse disease of the lungs (often with widespread inflammation or obliteration of blood vessels) in sarcoidosis, pulmonary hypertension is uncommon, occurring in 1% of patients. We report a case of sarcoidosis and severe pulmonary hypertension that, in striking contrast to other reports, occurred in the absence of obliterative pulmonary vascular disease. We therefore examined the possibility of whether an abnormality in pulmonary vascular tone might be a cause of the pulmonary hypertension. In pharmacologic studies, we demonstrated pulmonary vasodilatation and, in response to increased pulmonary blood flow, the elaboration of the pulmonary vasoconstricting eicosanoid, thromboxane. (Arch Intern Med 1985;145:2112-2114)

Sarcoidosis is a multisystem disease characterized pathologically by the presence of noncaseating granulomas in affected tissues. At least 90% of patients have pulmonary manifestations due to alveolitis, noncaseating granulomas, and varying degrees of fibrosis or parenchymal alteration.1

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Despite the frequent occurrence of significant parenchymal destruction, pulmonary hypertension is uncommon, occurring in 1% to 4% of cases.1 It has been suggested that the pulmonary hypertension results from severe fibrosis and destruction of the pulmonary vascular bed.2

We report a case of sarcoidosis and severe pulmonary hypertension that, in striking contrast to other reports, occurred in the absence of obliterative pulmonary vascular disease. Because obliterative vascular disease was not seen, we examined the possibility of whether an abnormality in pulmonary vascular tone caused the pulmonary hypertension. In pharmacologic studies of the pulmonary vascular bed, we demonstrated pulmonary vasoreactivity (the bed could be dilated) and, in response to increased pulmonary blood flow, the elaboration of a pulmonary vasoconstricting eicosanoid.

REPORT OF A CASE

A 23-year-old woman was admitted to the hospital for evaluation of exertional chest pain and syncope of one month's duration. Her health and family history were unremarkable and she took no regular medication. On examination she had a right ventricular heave and a loud pulmonary component of the second heart sound. A chest roentgenogram revealed clear lung fields with a prominent pulmonary artery silhouette. The electrocardiogram and echocardiogram were consistent with right ventricular enlargement and pulmonary hypertension. On cardiac catheterization the pulmonary arterial pressure was 108/52 mm Hg (normal, 15 to 30/5 to 12 mm Hg) and there was no evidence of an intracardiac shunt. Cardiac index was 1.9 L/min/sq m (normal, 2.5 to 4.2 L/min/sq m). The hemoglobin level was 15.5 g/dL. The alkaline phosphatase level was 462 units/L (normal, <100 units/L) and gamma-glutamyl transpeptidase was 216 units/L (normal, <55 units/L).

Repeated chest roentgenograms revealed hilar adenopathy and parenchymal infiltrates. A liver biopsy specimen showed multiple noncaseating granulomas. A Kveim test was interpreted as positive based on the criteria established by Steigledger and co-workers; the patient was tested with the antigen prepared according to Nelson.3 Arterial oxygen tension was 78 mm Hg, arterial carbon dioxide tension was 32 mm Hg, and pH was 7.42 breathing room air. An open lung biopsy was performed (Figure). The parenchyma was studded with small to medium-sized noncaseating granulomas that did not involve blood vessels. Medial hypertrophy, slight mural fibrosis, and fibromuscular proliferation were present in the pulmonary arteries. Pulmonary hypertensive lesions were focal and grade 1 to 3 on the Heath-Edward scale. There was no evidence of fibrosis, vasculitis, thrombosis, or embolism. Microorganisms were not detected.

The stable breakdown products of prostacyclin (6-keto-PGF\(_1\alpha\)) and thromboxane A\(_2\) (TXB\(_2\)) were measured by radioimmunoassay using commercially available kits. The patient's peripheral venous plasma TXB\(_2\) was 60 pg/mL (laboratory normal, <80 pg/mL) and 6-keto-PGF\(_1\alpha\) was 130 pg/mL (laboratory normal, <80 pg/mL). A detailed study of pulmonary vasoreactivity and vasoactive mediators was performed during repeated cardiac catheterization. Administration of epoprostenol (prostacyclin), nitroglycerin, and nifedipine demonstrated that vasodilatation of the pulmonary vascular bed could be induced (Table). An increase in the concentration of TXB\(_2\) was detected from the pulmonary artery to the aorta, concomitant with the increase in flow seen with administration of epoprostenol, nitroglycerin, and nifedipine, suggestive of pulmonary production of thromboxane A\(_2\) (TXA\(_2\)). No transpulmonary gradient of 6-keto-PGF\(_1\alpha\) was detected during administration of nitroglycerin or nifedipine.

Despite treatment with prednisone (1 mg/kg/day) for two months, the patient developed progressive right ventricular failure. In an attempt to reverse her rapidly deteriorating condition, nifedipine and cyclophosphamide were added; she died two weeks later.

COMMENT

Pulmonary hypertension is an unusual but well-recognized complication of sarcoidosis. Rizzuto and co-workers'...