Can an Immune Response Be Conditioned?

Recent reports that classical conditioning may be useful as a form of immunotherapy for various diseases – including cancer – have immunologists, behavioral psychologists, and clinicians arguing the validity of these claims.

The debate is far from settled.

Russian physiologist Ivan Pavlov described classical conditioning as occurring when a previously neutral stimulus (bell sound) is paired with a natural stimulus (food shown to a hungry dog) that can elicit a specific response (salivation).

Eventually, the association between the neutral stimulus (also known as a conditioned stimulus) and the response becomes strong enough to become a substitute for the natural stimulus (also known as an unconditioned stimulus). Exposure to the conditioned stimulus alone will then produce the desired behavior.

Modulate Response

Researchers who support the concept of psychoneuroimmunology, the ability of the brain and immune system to communicate with each other (see News, *J Natl Cancer Inst*, May 2, 1990), have looked to such conditioning as a means of modulating immune response.

"Conditioning is a rather dramatic illustration of the functional relationship between the immune and central nervous systems," said Robert Ader, M.D., professor of psychiatry, psychology, and medicine at the University of Rochester Medical Center.

Ader said that his group's initial study of immune system conditioning in 1975 was greeted with skepticism by a scientific community hesitant to accept the link.

"Since that time, there have been about 50 studies on conditioning that say we didn't make a mistake," Ader said. "There are an increasing number of scientists who recognize this as a bona fide area of study."

Donald L. Morton, M.D., director of the John Wayne Cancer Clinic of the Jonsson Comprehensive Cancer Center at UCLA, said, "The data certainly appear firm that immune system changes do occur with conditioning. The question remains, are these changes of significant magnitude to impact disease, especially tumor growth."

Suppression Observed

The earliest immune conditioning experiments, conducted by Ader's team and a group of Canadian researchers led by immunologist Reginald M. Gorczynski, M.D., Ph.D., determined that conditioned stimuli could have biological significance.

"Our animal studies, as well as those by Gorczynski, paired injections of the immunosuppressive drug, cyclophosphamide, with the novel taste of saccharin and then looked to see if there was a lowering of immune function when the saccharin was given alone and the immune system was challenged," Ader said.

While Ader demonstrated a suppression of antibody titer, Gorczynski challenged his mice with a plasmacytoma tumor, Ader said. "Elevated tumor growth and mortality were only seen in the mice re-exposed to saccharin, indicating that the stimulus alone could produce the same results as the immunosuppressive drug."

These results, and similar evidence from suppression studies of autoimmune diseases, Ader said, strongly support the validity of immune system modulation through classical conditioning.

"The question now becomes, can you achieve the opposite effect – increased immune response?" he said.

Enhancement?

Recently, researchers at the University of Alabama at Birmingham Comprehensive Cancer Center reported that a conditioned stimulus in mice had evoked a "protective immunological effect" against a transplanted lymphoma.

"One can immunize against the tumor we used, YC8 lymphoma, with the alloantigen present on the spleen cells of DBA/2 mice," said Vithal K. Ghanta, Ph.D., leader of the UAB scientific team. "Knowing that, we wanted to see if we could condition this specific immune response with a neutral stimulus."

Dr. Robert Ader

CONDITIONAL IMMUNE RESPONSE

A potentially important application of Pavlovian conditioning involves the body's *immune system*. Like other body systems, it can be activated or suppressed through classical conditioning. This has exciting implications. If learning can stimulate immune system activity, people should be able to arrange conditions to improve health or healing. Perhaps humans have already been doing this for thousands of years. Classical conditioning may shed a light on healing rituals and trances practiced by pre-modern cultures.

An early experiment reported by Schmeck (1985) involved a team of researchers at the University of Alabama medical school. They studied effects of classical conditioning on activity of *natural killer cells* (NK cells) that destroy germs and other invaders in the body. In the experiment, mice were exposed for three hours at a time to a powerful odor (camphor). Exposure to this odor, by itself, had no effect on the mice.

Next, the odor was made to predict a significant biological event. After exposure to the odor, mice in an experimental group were given injections of a synthetic chemical called poly I:C (for polyinosinic-polycytidilic acid) that stimulates activity of natural killer cells. Mice in the control group did not receive the poly I:C.

How did researchers demonstrate a conditional immune response in mice?

For the experimental group, the odor of camphor was paired with exposure to Poly I:C nine times. In the 10th session, the mice were exposed only to the odor of camphor. Every mouse in the experimental group showed large increases in natural killer cell activity. Their bodies were "predicting" the injection of poly I:C and responding with immune system activity. In the control group, which was exposed only to the odor of camphor, no such response occurred.

This is typical of research on classical conditioning. It is capable of demonstrating remarkable, subtle biological effects. However, analyzing the exact mechanism can be difficult. How exactly does a mouse's "knowledge" that poly I:C is about to be delivered to its bloodstream stimulate the production of NK cells? If researchers knew that, perhaps they could help human patients boost production of NK cells when needed, as well.

Researchers suspect that neuroimmunomodulation takes place at every level of the nervous system. The word *neuroimmunomodulation*contains the word roots for *nerve* (neuro) and *immune* (immuno). So *neuroimmunomodulation* means modulating immune system activity with nervous system activity. The discipline of *psychoneuroimmunology*-arose in the 1970s and 1980s to study psychological influences on immune system functioning. However, research in this area has produced disappointing results. The positive effects of psychological intervention on health are easy to document, but evidence relating these benefits to immune system changes has been elusive (see the section on psychoneuroimmunology in Chapter 14).

Pavlovian conditioning of immune function: animal investigation and the challenge of human application

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Abstract

Pavlovian conditioning of immune functions provided early impetus to the rapidly expanding knowledge of bi-directional communication among the immune, endocrine, and central nervous systems. Since these early investigations, the phenomenology of this response has been well characterized. However the neural mechanisms and biological relevance of conditioned immunomodulation remain unclear. To this end, we present here data from our laboratories that have: (1) revealed some of the neural mechanisms and biological relevance of an animal model of conditioned immunomodulation; (2) demonstrated the conditionability and potential mechanisms of conditioned immune responses in healthy humans, and (3) investigated conditioned immunomodulation in a clinical sample. Together, these data demonstrate that animal models provide a basis for investigating mechanisms whereby conditioned changes in immune function may modulate health status in a clinical realm.

Author Keywords: Behavioral conditioning; Psychoneuroimmunology; Rat; Human; Sympathetic nervous system

Article Outline

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The learned immune response: Pavlov and beyond

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Abstract

The ability to associate physiological changes with a specific flavor was most likely acquired during evolution as an adaptive strategy aimed at protecting the organism while preparing it for danger. The behaviorally conditioned or learned immune response is an exquisite example of the bidirectional communication between the central nervous system (CNS) and the peripheral immune system. How is it possible that specific immuno-modulating properties of a drug or substance (unconditioned stimulus) can be re-enlisted just by the mere re-exposure to a particular taste, odor or environment (conditioned stimulus)? To answer this key question, we review the neurobiological mechanism mediating this type of associative learning, as well as the pathways and mechanisms employed by the brain to harness the immune system during the execution of the conditioned immune response. Finally, we focus on the potential therapeutic relevance of such learned immune responses, and their re-conceptualization within the framework of "*learned placebo effects*".

Keywords: Behavioral conditioning; Conditioned taste aversion; Placebo; Cyclosporine A; Noradrenaline; β-Adrenoceptors; Lymphocytes; Interleukin-2; Spleen

Article Outline

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Classical conditioning: the new hegemony

Article Abstract:

Data from different disciplines show that classical conditioning is involved in more human and animal behavior than was once thought. (Classical conditioning, exemplified in Pavlov's experiments on dogs, involves training an organism to produce a given response to a stimulus by always associating a given stimulus with that response.) Previous views that considered classical conditioning to involve only bodily secretions, reflexive actions, or emotions have been replaced. It is now thought that classical conditioning can be involved in problem-solving and other rule-governed processes. This new view has been accompanied by changes in how classical conditioning is conducted and evaluated. Such seemingly unrelated phenomena as the placebo effect, relapse to drug abuse by postaddicts, and the disease-fighting immune response appear to involve classical conditioning. Classical conditioning has been found in smaller and smaller organisms and has even been found in brain slices and in fetuses in the womb. Several research areas that use classical conditioning to explain phenomena can now be integrated, challenging traditional teleological interpretations of classical conditioning and offering some basic principles for testing conditioning in various areas.

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