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Twenty years of research on cytokine-induced sickness behavior

Robert Dantzer [a,b,*], Keith W. Kelley [a]

[a] *Integrative Immunology and Behavior Program, Laboratory of Integrative Immunophysiology, Department of Animal Sciences, University of Illinois at Urbana-Champaign, IL 61801, USA*
[b] *Integrative Immunology and Behavior Program, Laboratory of Integrative Immunophysiology, Department of Medical Pathology, University of Illinois at Urbana-Champaign, IL 61801, USA*

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Abstract

Cytokine-induced sickness behavior was recognized within a few years of the cloning and expression of interferon-α, IL-1 and IL-2, which occurred around the time that the first issue of Brain, Behavior, and Immunity was published in 1987. Phase I clinical trials established that injection of recombinant cytokines into cancer patients led to a variety of psychological disturbances. It was subsequently shown that physiological concentrations of proinflammatory cytokines that occur after infection act in the brain to induce common symptoms of sickness, such as loss of appetite, sleepiness, withdrawal from normal social activities, fever, aching joints and fatigue. This syndrome was defined as sickness behavior and is now recognized to be part of a motivational system that reorganizes the organism's priorities to facilitate recovery from the infection. Cytokines convey to the brain that an infection has occurred in the periphery, and this action of cytokines can occur via the traditional endocrine route via the blood or by direct neural transmission via the afferent vagus nerve. The finding that sickness behavior occurs in all mammals and birds indicates that communication between the immune system and brain has been evolutionarily conserved and forms an important physiological adaptive response that favors survival of the organism during infections. The fact that cytokines act in the brain to induce physiological adaptations that promote survival has led to the hypothesis that inappropriate, prolonged activation of the innate immune system may be involved in a number of pathological disturbances in the brain, ranging from Alzheimer's disease to stroke. Conversely, the newly-defined role of cytokines in a wide variety of systemic comorbid conditions, ranging from chronic heart failure to obesity, may begin to explain changes in the mental state of these subjects. Indeed, the newest findings of cytokine actions in the brain offer some of the first clues about the pathophysiology of certain mental health disorders, including depression. The time is ripe to begin to move these fundamental discoveries in mice to man and some of the pharmacological tools are already available to antagonize the detrimental actions of cytokines.
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1. Introduction

The first paper on sickness behavior was published in *Brain, Behavior, and Immunity* (BBI) by Aubert et al. (1995). Since then, 39 papers on sickness behavior have been published in the journal, which represent 20 percent of the 192 papers published on cytokine-induced sickness behavior that are listed in PubMed. Despite some risk of overlap, it would be fair to add to these statistics the 14 papers on cytokines and depression that were published in BBI in 2002. Although the familiar phrase that "statistics lie and statistician's use statistics" is apropos in the sense that statistics can be used to describe nearly anything one wants them to tell, it is clear from this cursory quantitative review of the literature that BBI has been instrumental in promoting the concept of cytokine-induced sickness behavior. This conclusion becomes even more obvious when these figures are compared to the 52 papers on cytokines and the brain that were published by BBI and contrast with the 15,382 papers listed by PubMed in this field (as of July 27, 2006).

* Corresponding author.
E-mail address: dantzer@uiuc.edu (R. Dantzer).

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BBI has not been the home journal of those scientists who study the expression and actions of cytokines in the brain. Its niche is clearly at the interface between immunity and behavior in physiological and pathological conditions. The objective of this article is not to add another paper on cytokine-induced sickness behavior to the list of those already published by BBI but to show why it was and remains logical for BBI to play an instrumental role in the publication of the results on cytokine-induced sickness behavior.

2. Before 1987: The history of sickness behavior

The study of sickness has a rich history in psychology and behavioral pharmacology (Fig. 1). In psychology, research on the concept of sickness started in the mid-fifties with Garcia's work on bait shyness (Garcia et al., 1955). Garcia explained the fact that rodents cannot be poisoned very easily by their propensity to develop learned aversions to the new taste of any compound that induces gastro-intestinal malaise. At the time this research was carried out, the laws of learning were dominated by knowledge gained from the study of classical conditioning and operant conditioning. It was believed that learning could only take place if a very short interval, on the order of a few seconds, separated the conditioned stimulus (the taste) from the unconditioned stimulus (the malaise experienced in response to poisonous food). In operant conditioning, the operant response could be learned only if the reward immediately followed the operant response or if secondary reinforcers were present to maintain the conditioned response. Because conditioned taste aversions could still be learned despite the long delay—several hours—between the taste and illness, and illness could only be conditioned to interoceptive stimuli (e.g., a taste or a smell), but not to exteroceptive stimuli (e.g., a tone or a light). Garcia proposed that the laws of classical conditioning applied only to the exteroceptive defense system that developed to protect organisms from predators. In contrast, the laws of conditioned taste aversion apply to the interoceptive defense system that developed to protect organisms from ingested poisons (Garcia et al., 1974). According to this evolutionary perspective, the ability to form learned taste aversions is an important advantage for an eclectic gastronomic animal since it helps the animal to distinguish those foods that are noxious from those that are safe and possibly health promoting. Of course, this strategy is functional only if the eclectic gastronomic animal displays neophobia and ingests only very small amounts of a new food (i.e., a nibbler). This aspect of sickness was somewhat neglected in Garcia's theoretical elaboration. Since psychology often develops in waves of controversy, it is not surprising that this view was used to challenge the concept proposed by Garcia that food aversions are learned. It was argued by others that the so called conditioned taste aversions could just represent a summation of neophobic responses, the novelty of the sensory experience associated with the poisonous food and the new experience of gastrointestinal malaise (Mitchell et al., 1975).

Formation of a conditioned taste aversion implies that the subject is able to monitor its internal state and to associate with it not only an affective (bad versus good) but also a quantitative value (a little versus a lot). The malaise induced by lithium chloride is not necessarily the same as the malaise induced by the muscarinic cholinergic receptor agonist pilocarpine. In terms of cognition, this means that

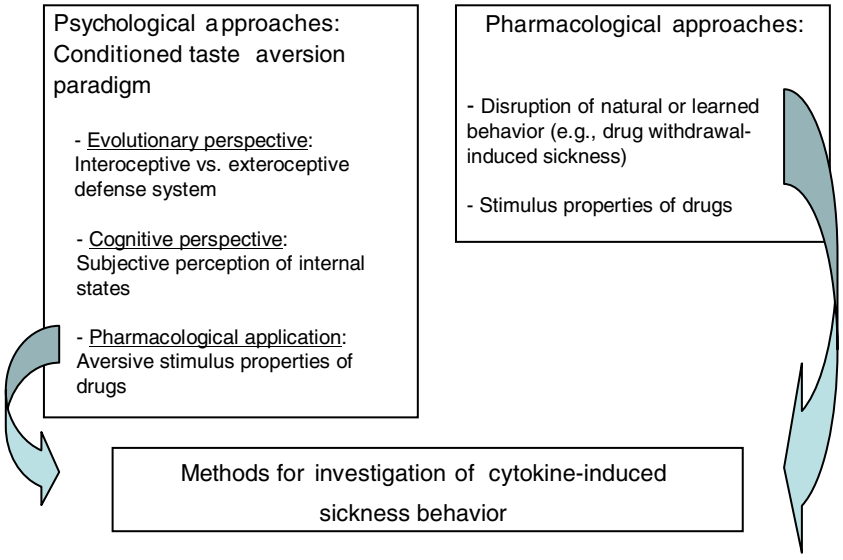

Fig. 1. The natural history of concept of sickness. Psychological and pharmacological roots of the concept of sickness behavior. In behavioral sciences, the ability of animals to relate sickness and malaise to the nature of the nutrients they ingest was studied within the context of the conditioned taste aversion paradigm. This ability was further elaborated in terms of advantages during evolution and cognitive abilities. Some pharmacologists used the conditioned taste aversion paradigm for studying the aversive stimulus properties of drugs. However, this type of approach was miniscule when compared to the huge scientific and industrial investment in the systematic study of the stimulating properties of psychoactive drugs based on operant conditioning technology. The sickness-inducing properties of certain treatments were mainly quantified indirectly, via the disruption of natural or learned behavior. These two different lines of research, especially the last one, gave rise to the methodology currently used for studying cytokine-induced sickness behavior.