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Cytokine-Induced Sickness Behavior: Where Do We Stand?

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Sickness behavior refers to the coordinated set of behavioral changes that develop in sick individuals during the course of an infection. At the molecular level, these changes are due to the effects of proinflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNFα), in the brain. Peripherally released cytokines act on the brain via a fast transmission pathway involving primary afferent nerves innervating the body site of inflammation and a slow transmission pathway involving cytokines originating from the choroid plexus and circumventricular organs and diffusing into the brain parenchyma by volume transmission. At the behavioral level, sickness behavior appears to be the expression of a central motivational state that reorganizes the organism's priorities to cope with infectious pathogens. There is clinical and experimental evidence that activation of the brain cytokine system is associated with depression, although the exact relationship between sickness behavior and depression is still elusive.

INTRODUCTION

As pointed out by Keith W. Kelley in his presidential address (Kelley, 2001), the discovery of the effects of cytokines on brain functions forms a cornerstone in the field of psychoneuroimmunology. This interdisciplinary field, which began with the study of brain influences on immunity, has developed to the point where we are beginning to understand the important reciprocal relationship between immune products and brain functions. It is now evident that the proinflammatory cytokines that are released by activated macrophages and monocytes during an infection are located in the brain and mediate the central components of the host response to infection in what is called sickness behavior (Hart, 1988). Since it was demonstrated in the late 1980s and early 1990s that proinflammatory cytokines induce sickness behavior (Kent, Bluthe, Kelley, & Dantzer, 1992), much has been learned about the way these mediators alter brain functions and of the molecular and cellular mechanisms that are involved in these actions. The objective of this article is not to review the entire field of cytokines and behavior. It is much more focused and aims at presenting the newest data on the brain processes that mediate cytokine-induced sickness behavior and discussing the possible relevance of these processes to the psychopathology of depression.

THE CONCEPT OF SICKNESS BEHAVIOR

Nonspecific symptoms of infection and inflammation include fever and profound physiological and behavioral changes. Sick individuals experience weakness, malaise, listlessness, and inability to concentrate. They become depressed and lethargic, show little interest in their surroundings, and stop eating and drinking. Their range of preoccupations is limited to their own body and the suffering they are experiencing. This constellation of nonspecific symptoms is collectively referred to as ''sickness behavior.'' Due to their commonality, symptoms of sickness are frequently ignored by physicians. They are considered as an uncomfortable, but rather banal, component of the pathogen-induced debilitation process that affects a sick organism.

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This view has, however, turned out to be incorrect. The behavioral symptoms of sickness represent, together with the fever response and the associated physiological changes, a highly organized strategy of the organism to fight infection (Hart, 1988). Fever is an adaptive homeostatic state that is characterized by an elevated set point in body temperature regulation (Kluger, 1991). A feverish individual feels cold even in neutral environmental temperatures. The person therefore not only seeks warmer temperatures but also enhances heat production (increased thermogenesis) and reduces heat loss (decreased thermolysis). The higher body temperature that is achieved in this way stimulates proliferation of immune cells and is unfavorable for the growth of many bacterial and viral pathogens. In addition, the reduction of plasma levels of zinc and iron that occurs during fever decreases the availability of these minerals for growth and multiplication of microorganisms.

The amount of energy that is required to increase body temperature during the febrile process is quite high since, in human beings, metabolic rate increases by 13% for a rise of 1°C in body temperature. Because of the high metabolic cost of fever, there is little room for activities other than those favoring heat production (e.g., shivering) and minimizing thermal losses (e.g., rest, curl-up posture, and piloerection).

The necessary synchrony between metabolic, physiological, and behavioral components of the systemic response to infection is dependent on the same molecular signals as those that are already responsible for the local inflammatory response. These signals are proinflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-α (TNFα), and the interferons (IFNs). Proinflammatory cytokines are released by activated monocytes and macrophages. These soluble mediators act on the brain in two successive waves. The first wave is triggered by activation of primary afferent neurons innervating the body site where the inflammatory reaction takes place. The second wave involves slowly diffusing cytokines from the circumventricular organs and choroid plexus to brain targets such as the amygdaloid complex.

Although sickness behavior is a normal response of the host to pathogens that are recognized by the innate immune system, there is evidence that the mechanisms that contribute to the development of sickness behavior may play in the role in the pathophysiology of depression.

CYTOKINES INDUCE SICKNESS BEHAVIOR

Systemic or central infusion of recombinant cytokines induces the full-blown repertoire of nonspecific symptoms of sickness in both experimental animals (Table 1) and human beings. The same effects are obtained in response to the administration of molecules that induce the synthesis of endogenous cytokines [e.g., lipopolysaccharide (LPS), the active fragment of endotoxin from Gram-negative bacteria].

The behavior of animals injected with LPS or cytokines at the periphery or into the lateral ventricle of the brain has been studied extensively (Dantzer, Bluthe, Castanon, Chauvet, Capuron, Goodall, Kelley, Konsman, Layé, Parnet, & Pousset, 2001; Kent, Bluthe, Kelley et al., 1992). In general, these animals display depressed locomotor activity, decreased exploration of their physical and social environment, reduced food and water intake, and impaired learning and memory. Decreased social exploration of juvenile conspecifics has been used as a convenient way to assess sickness behavior in laboratory rodents. It involves olfactory sampling of the partner and offers the advantage of being reproducible and quantifiable. The use of juvenile conspecifics

TABLE 1
Range of Behavioral Effects Observed in Laboratory Rodents Injected Systemically or Centrally with Proinflammatory Cytokines and the Cytokine Inducer Lipopolysaccharide

Behavioral effects
Decreased general activity
Decreased exploratory behavior
Decreased social and sexual behavior
Decreased food and water intake
Decreased preference for saccharin
Decreased brain self-stimulation
Decreased body care activities
Impaired learning and memory

allows us to get rid of other behavioral patterns such as sexual behavior or aggression that normally occur with adult partners. Systemic administration of LPS, IL-1β, and TNFα to adult rats and mice decreased time adults spent in exploration of juveniles (Bluthe, Dantzer, & Kelley, 1992; Bluthe, Pawlowski et al., 1994).

Another important component of sickness behavior is the decreased intake of food that develops in sick individuals. Systemic administration of IL-1β and TNFα consistently suppresses feeding. This effect has been observed using various measurements of food intake and *ad libitum* as well as deprived conditions (Kent, Bret-Dibat, Kelley, & Dantzer, 1996; Plata-Salaman, 1999). In contrast to the decrease in social exploration that takes about 2 h to develop, the cytokine-induced suppression of food intake occurs within 1 h following treatment.

NEUROANATOMICAL BASIS OF SICKNESS BEHAVIOR

Our understanding of the way sickness behavior is organized in the brain is based on several methodological approaches (Dantzer, Konsman, Bluthe, & Kelley, 2000). Molecular biology studies have demonstrated that peripheral cytokines induce the synthesis and release of cytokines in the brain. LPS, for instance, induces expression of IL-1α, IL-1β, and TNFα, followed by that of IL-6 and the specific antagonist of IL-1 receptors, IL-1ra (Gatti & Bartfai, 1993; Laye, Parnet, Goujon, & Dantzer, 1994) (Fig. 1). The main cellular sources of IL-1 are represented by microglial cells and perivascular and meningeal macrophages (van Dam, Brouns, Louisse, & Berkenbosch, 1992). These locally produced cytokines are responsible for the central components of the host response to infection, as demonstrated by pharmacological experiments making use of cytokine antagonists or cytokine receptor antagonists. For instance, administration of the IL-1 receptor antagonist (IL-1ra) into the lateral ventricle of the brain to block brain IL-1 receptors abrogated the depressive effect of peripherally administered IL-1 on social exploration in rats exposed to a juvenile (Kent, Bluthe, Dantzer et al., 1992). Using expression of the early gene *c-fos* or its protein product Fos as a marker of neuronal activation in those brain areas that are activated by stressors, neuroanatomists have identified the brain targets of peripheral immune stimuli (Fig. 2). Peripheral administration of LPS activates the primary projection area of the vagus nerves in the brain, which is represented by the nucleus tractus solitarius (NTS), and the secondary projections of these nerves, including the para-

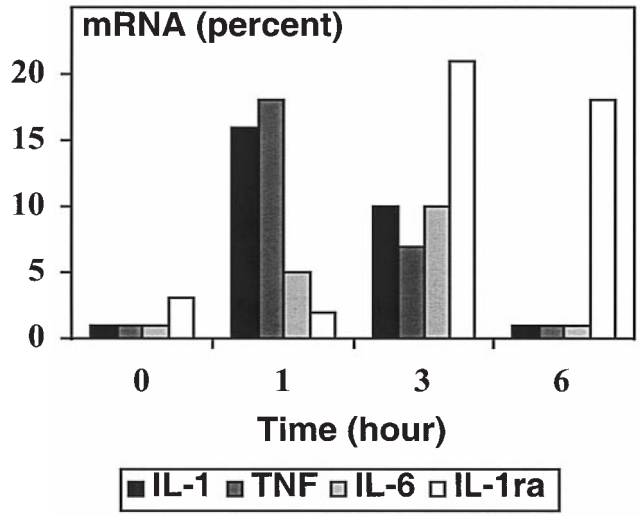

FIG. 1. Induction of cytokine expression in the mouse brain in response to systemic LPS (10 μg/mouse, ip). Mice were injected with LPS at time 0 and killed by decapitation 1, 3, and 6 h later. The brain was dissected out and hypothalamic mRNAS were measured by comparative RT–PCR. Each value corresponds to the mean of two to three different experiments with a minimum of five mice in each experiment. Data are expressed as a percentage of β-2 microglobulin mRNA expression used as an internal control.

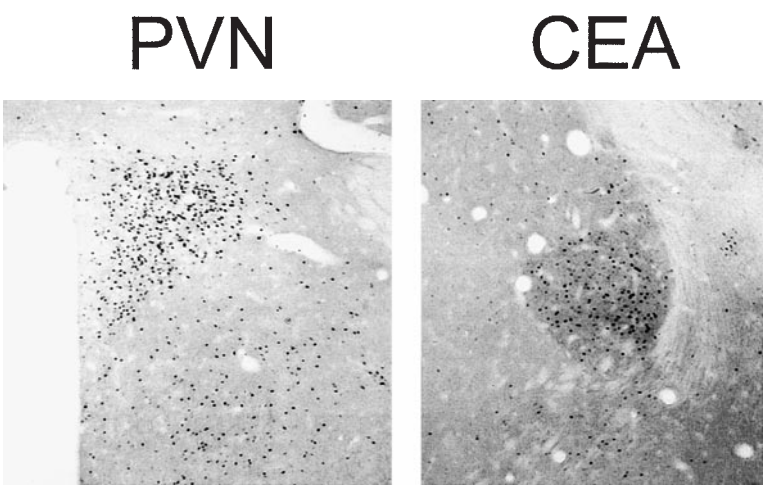

FIG. 2. LPS induces the expression of Fos in the paraventricular nucleus (PVN) and central nucleus of the amygdala (CEA). Rats were injected with LPS (250 μg/kg, ip) and killed 2 h later. Brain coronal sections were made at the level of the PVN and CEA and Fos expression was revealed by immunohistochemistry. There was no Fos expression in saline-treated rats (data not shown) (modified from Konsman, 2000).

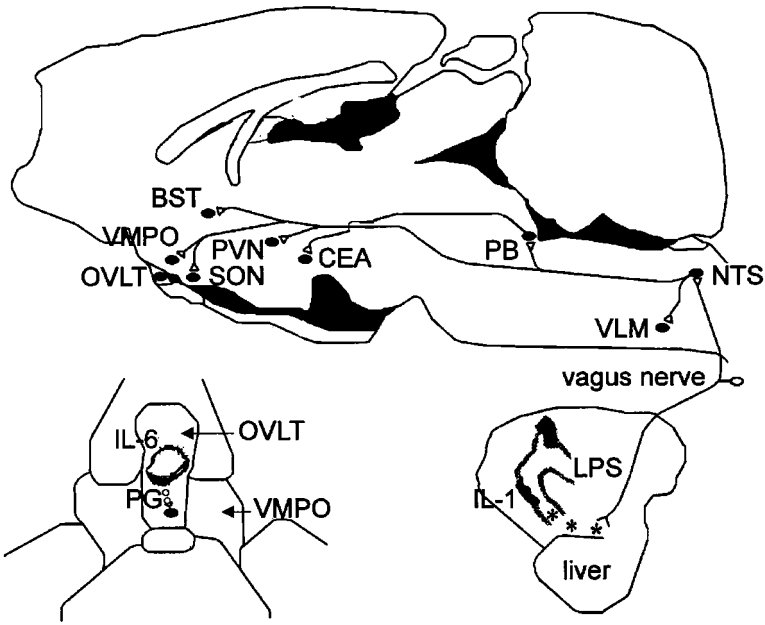

FIG. 3. Fast immune-to-brain signaling mediated by vagal nerve conduction. A systemic injection of LPS induces FOS expression in the primary and secondary projection areas of the brain via projection pathways that are illustrated on a sagittal section of the rat brain. At the periphery LPS induces the expression of IL-1 in Kuppfer cells of the liver. This results in activation of the vagus nerve that projects to the nucleus tractus solitarius (NTS) and, from there, to the ventrolateral medulla (VLM), the prabrachial nucleus (PB), the central nucleus of the amygdala (CEA), the hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus (SON), the ventromedial part of the preoptic nucleus (VMPO), and the bed nucleus of the stria terminalis (BST). Note that neural projections from the organum vasculosum of the lamina terminalis (OVLT) to the VMPO can be activated by circulating IL-6 or by prostaglandins synthesized by endothelial cells (modified from Konsman et al., 1999).

brachial nucleus, the hypothalamic paraventricular and supraoptic nuclei, the central nucleus of the amygdala, and the bed nucleus of the stria terminalis (Hare, Clarke, & Tolchard, 1995; Sagar, Price, Kasting, & Sharp, 1995; Tkacs & Li, 1999; Tkacs, Li, & Strack, 1997; Wan, Wetmore, Sorensen, Greenberg, & Nance, 1994) (Fig. 3). Sectioning of the vagus nerves just beneath the diaphragm abrogates expression of Fos in these brain areas (Wan et al., 1994). The key role of the vagal nerves in the transmission of peripheral immune signals to the brain was further confirmed by the demonstration that vagotomy attenuates the behavioral actions of peripheral cytokines (Bluthe, Michaud, Kelley, & Dantzer, 1996; Bluthe, Walter et al., 1994) and abrogates the induction of IL-1β in the brain in response to peripheral LPS or IL-1β (Hansen, Taishi, Chen, & Krueger, 1998; Laye et al., 1995).

The abdominal vagal nerves have the important peculiarity of being associated with immune cells that express IL-1β in response to local inflammation (Goehler et al., 1999). This locally produced IL-1β binds to vagal fibers and increases vagal discharge activity. Glutamate is released at the level of the nucleus tractus solitarius where vagal fibers terminate (Mascarucci, Perego, Terrazzino, & De Simoni, 1998). Glutamate acts on catecholaminergic neurons of the NTS that project to the paraven-

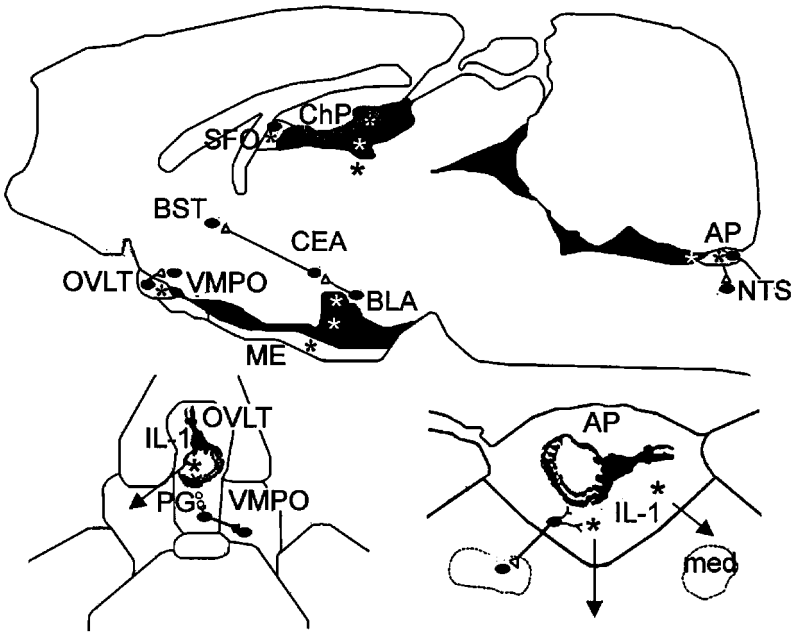

FIG. 4. Diffusion of IL-1β from the circumventricular organs and the choroid plexus into the brain parenchyma by volume diffusion. IL-1β (asterisks) diffuses from the area postrema (AP) into the NTS that it can activate directly or indirectly, via neurons projecting from the AP to the medial NTS. In the OVLT, IL-1β can diffuse into the VMPO or activate it via prostaglandins that act on neurons projecting from the OVLT to the VMPO. IL-1β originating from the choroid plexus (ChP) can reach the basolateral amygdala, resulting in activation of the CEA and BST (modified from Konsman, 2000).

tricular and preoptic nuclei of the hypothalamus (Ericsson, Kovacs, & Sawchenko, 1994; Sawchenko & Swanson, 1982). The central nucleus of the amygdala can be reached via this pathway or, more probably, via the parabrachial nuclei (Tkacs & Li, 1999). These pathways appear to be responsible for the activating effects of inflammatory stimuli on the hypothalamic–pituitary–adrenal (HPA) axis and their depressive effects on behavior. However, the pyrogenic activity of inflammatory stimuli involves still another pathway represented by prostaglandin synthesis by cyclooxygenase-2 around blood vessels (Cao, Matsumura, Yamagata, & Watanabe, 1997).

The brain production of IL-1β in response to peripheral inflammatory stimuli is first restricted to the choroid plexus and circumventricular organs (Konsman, Kelley, & Dantzer, 1999). IL-1β then slowly diffuses to the brain side of the blood–brain barrier by volume transmission (Fig. 4). Direct activation of neurons by slowly diffusing IL-1β takes place in the basolateral amygdala and the area postrema. Projections from the basolateral amygdala mediate the depressive effects of IL-1β on social exploration, whereas those from the area postrema contribute to activation of the HPA axis (Konsman, 2000). The observation that a late (4 h post-LPS) infusion of IL-1ra into the lateral ventricle of the brain attenuates the depressive effects of systemic LPS on social exploration concomitantly with an abrogation of Fos expression in the central amygdala and bed nucleus of the stria terminalis points to the role of these two structures in cytokine-induced behavioral depression.

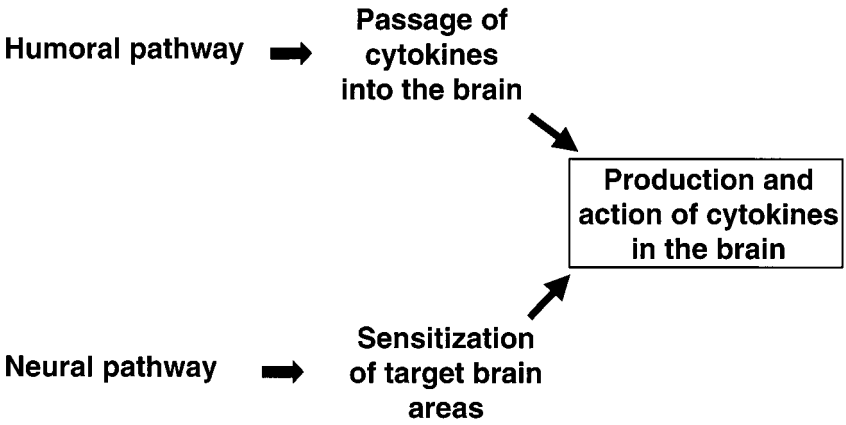

FIG. 5. Convergence of humoral and neural pathways in the transmission of the peripheral immune message to the brain. The possibility that neural pathways activated by peripheral immune stimuli sensitize target brain areas to the action of cytokines that propagate throughout the brain by volume diffusion remains to be tested.

In summary, activation of afferent nerve fibers by peripherally released cytokines represents a fast pathway of transmission of immune signals from the periphery to the brain. This pathway certainly sensitizes the brain target areas to the action of brain-produced cytokines that relay and amplify the action of peripheral cytokines (Fig. 5).

MOTIVATIONAL ASPECTS OF SICKNESS BEHAVIOR

As emphasized earlier in this article, sickness behavior is usually viewed by physicians as the result of debilitation and physical weakness, which inevitably occur in an organism in which all resources are engaged in a defensive process against pathogens. An alternative hypothesis is that sickness behavior is the expression of a highly organized strategy that is critical to the survival of the organism in the face of infectious pathogens (Fig. 6). If this is the case, then it follows that sick individuals should be able to reorganize their behavior depending on its consequences and the internal

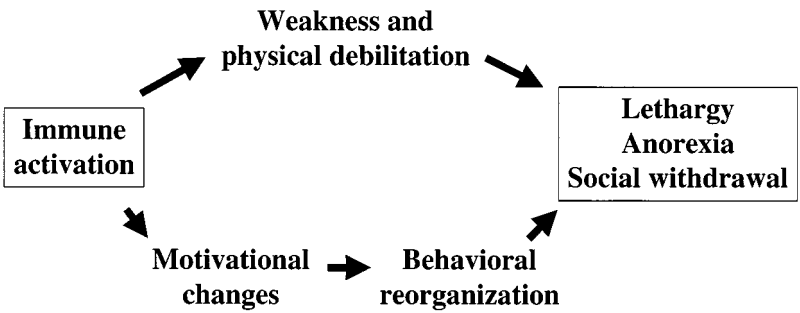

FIG. 6. Motivational interpretation of sickness behavior. Sickness behavior is not the consequence of weakness and physical debilitation caused by the disease process but the expression of a highly organized strategy enabling the organism to fight infectious microorganisms.

and external constraints to which they are exposed. This flexibility is characteristic of what psychologists call motivation. A motivation can be defined as a central state that reorganizes perception and action. A typical motivational state is fear. In order to escape a potential threat, a fearful individual must be attentive to everything that is occurring in his environment. At the same time and according to the circumstances, the person must be ready to engage in the most appropriate defensive behavioral pattern that is available in his or her behavioral repertoire. In other words, a motivational state does not trigger an inflexible behavioral pattern. Instead, it enables a person to uncouple perception from action and therefore to select the appropriate strategy depending on the eliciting situation (Bolles, 1974).

The first evidence that sickness behavior is the expression of a motivational state rather than the consequence of weakness was provided by Neal Miller in a series of experiments initially designed to search for the motivational signal for thirst (Miller, 1964). He showed that rats injected with bacterial endotoxin stopped pressing a bar for water but, when given water, imbibed substantial amounts but to a lesser extent than normally. This effect was not specific to thirst since the endotoxin treatment also reduced bar pressing for food and even blocked responding in rats trained to press a bar for the rewarding effects of electrical stimulation in the lateral hypothalamus. Interestingly enough, when rats were trained to turn off an aversive electrical stimulation in this brain area by pressing a bar, endotoxin also reduced the rate of responding, but to a lesser extent than bar pressing for a rewarding brain stimulation. However, when rats were placed in a rotating drum that could be stopped for brief periods by pressing a lever, endotoxin treatment resulted in an increase rather than a decrease in response rate. The mere fact that endotoxin treatment resulted in a decreased or increased behavioral output depending on the consequences of the behavior under study gave strong support to the motivational interpretation of the behavioral effects of such a treatment. The effects of LPS on macronutrient intake in rats provide a clear-cut example of behavioral reorganization in response to sickness. When rats are given the opportunity to select macronutrient components of their diet, their selection pattern reflects the organism's nutritional and energetic requirements. To determine whether this selection pattern is altered during sickness, rats were submitted to a dietary self-selection protocol in which they had free access to carbohydrate, protein, and fat diets for 4 h a day (Aubert, Goodall, & Dantzer, 1995). After a 10-day habituation to this regimen, they were injected with LPS or IL-1β. Under the effect of this treatment, they decreased their total food intake as expected, but reorganized their self-selection pattern so as to ingest relatively more carbohydrate and less protein. Fat intake remained constant. This change in macronutrient intake contrasts with the increased consumption of fat that occurs in rats exposed to cold. Although eating fat would be a better way for feverish animals to cope with their increased energy requirements, it cannot be very profitable since cytokines have adverse metabolic effects resulting in increased lipolysis and hypertriglyceridemia (Grunfeld & Feingold, 1996). Under these conditions, an increased intake of fat would actually be counterproductive since it would further enhance hyperlipidemia without positively contributing to lipid metabolism.

An important characteristic of a motivational state is that it competes with other motivational states for behavioral output. The normal expression of behavior requires a hierarchical organization of motivational states that is continuously updated according to fluctuations in the internal state and occurrence of external events. When

an infection occurs, the sick individual is at a life-or-death juncture and his or her physiology and behavior must be altered so as to overcome the disease. However, this is a relatively long-term process that needs to accommodate more urgent needs, when necessary. It is easy to imagine that if a sick person lying in bed hears a fire alarm ringing in the house and sees flames and smoke coming out of the basement, the person should be able to momentarily overcome sickness behavior to escape danger. In motivational terms, fear competes with sickness, and fear-motivated behavior takes precedence over sickness behavior. The observation that the depressive effects of IL-1β on behavior of mice are more pronounced when experimental animals are tested in the safe surroundings of their home cage than when they are placed into a new environment (Dantzer et al., 2001) provides a good example of the motivational competition between fear and sickness.

The previous example lacks specificity since the attenuated behavioral effects of cytokines can be easily explained by the increased levels of circulating glucocorticoids that develop in animals exposed to stressors (Goujon et al., 1995). A better demonstration of the motivational aspects of sickness behavior is represented by the effects of cytokines on maternal behavior. If fitness is the key issue, it is evident that dams should care for their infants despite sickness. In motivational terms, the components of maternal behavior that are crucial for the survival of the progeny should be more resilient, i.e., less sensitive to the depressive effects of pyrogens, than those behavioral patterns that are less important. In accordance with this prediction, administration of LPS to lactating mice at a dose that induces the full spectrum of sickness behavior does not disrupt pup retrieval after pups have been removed from the nest (Aubert, Goodall, Dantzer, & Gheusi, 1997). Nest building is suppressed in this condition. This was no longer the case, however, when the dams and their litters were exposed to 4°C instead of 20°C, so as to increase the fitness value of nest building (Aubert, Goodall et al., 1997) (Fig. 7).

In order to show that sickness does not interfere with the subject's ability to adjust behavioral strategies with regard to its needs and capacities, the effects of LPS were assessed on food hoarding and food consumption in rats receiving a food supplement in addition to the amount of food they obtained in the same situation (Aubert, Kelley, & Dantzer, 1997). Rats were trained to obtain food for 30 min in an apparatus consisting of a cage connected to an alley with free food at its end. In this apparatus, rats normally carry back to their home cage the food that is available at the end of the alley, and the amount of food they hoard is lower when they receive a food supplement than when they have no supplement. In response to LPS, food intake was decreased to the same extent whether or not rats received a food supplement. However, food hoarding was less affected in rats that did not receive a food supplement compared to rats provided with the food supplement. These results indicate that the internal state of sickness induced by LPS is more effective in suppressing the immediate response to food than the anticipatory response to future needs.

SENSITIZATION AND CONDITIONING OF CYTOKINE-INDUCED SICKNESS BEHAVIOR

The range of stimuli that trigger a given motivational state can be considerably expanded by processes of sensitization and classical or Pavlovian conditioning. Sensitization occurs after initial exposure to motivational stimuli that are either exaggerated in terms of magnitude or frequency or take place at a sensitive time in ontogeny.

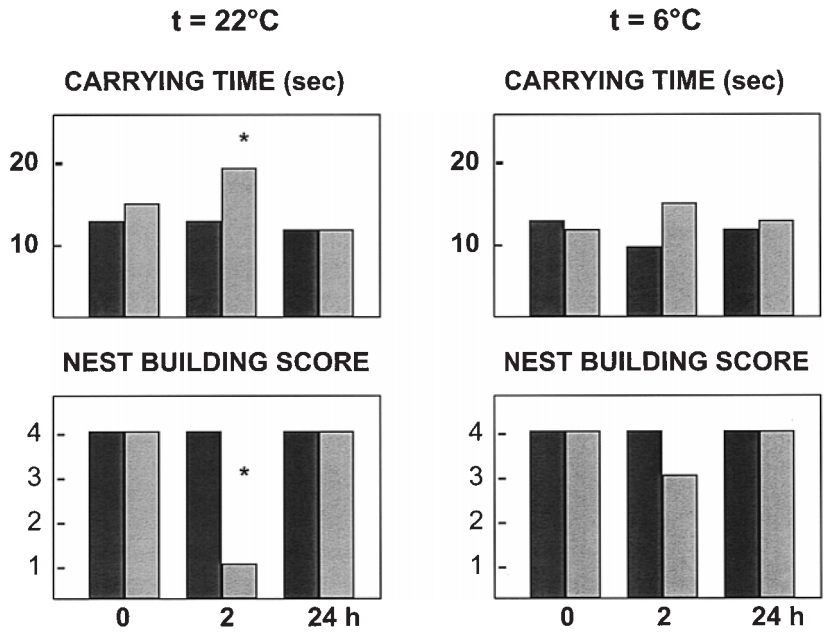

FIG. 7. Effects of LPS on mouse maternal behavior. Mice were given saline (dark columns) or LPS (400 μg/kg, ip) (gray columns) at time 0 and tested for their maternal behavior immediately before the injection and 2 and 24 h later. Note that at an ambient temperature of 22°C, LPS-treated dams retrieved all their pups after they had been removed from the nest, but they took longer to do that than saline-treated dams. However, they did not build a nest after their nest had been removed and replaced by cotton wool. When mice were tested at 6°C, they retrieved their pups at the same speed whatever the treatment and built a fully enclosed nest (from Aubert et al., 1997).

It results in a higher than normal response to stimuli than stimuli that normally trigger the motivational state or are just below its threshold, and it can be responsible for an increased response to stimuli of another motivational class (cross-sensitization) (Fig. 8). Instances of cross-sensitization between cytokines and nonimmune stressors have been reported using the pituitary–adrenal response as an end point. Adult rats injected with a single dose of IL-1β and exposed 1 to 2 weeks later to a novel environment displayed heightened reactivity of the pituitary–adrenal axis to novelty (Tilders & Schmidt, 1999). Similarly, long-lasting (1–12 weeks) sensitization of the pituitary–adrenal axis response to IL-2 has been reported in humans (Denicoff et al., 1989). In the first case, the enhanced reactivity of the HPA axis has been shown to be mediated by an increased expression of vasopressin in the hypothalamic neurons that normally express predominantly corticotropin-releasing hormone (CRH) (Tilders & Schmidt, 1999)

The possibility that sickness behavior can be triggered by nonimmune stimuli has been studied using mainly behavioral conditioning. Most of the studies have focused on the febrile response to LPS. In a typical experiment carried out in rats, LPS was used as an unconditioned stimulus in a taste aversion model using the taste of a saccharin solution as the unconditioned stimulus. LPS induced an initial fall in body temperature followed by an increase. The same pattern was observed in rats reexposed to the saccharin taste solution 2 weeks after conditioning, although it was less

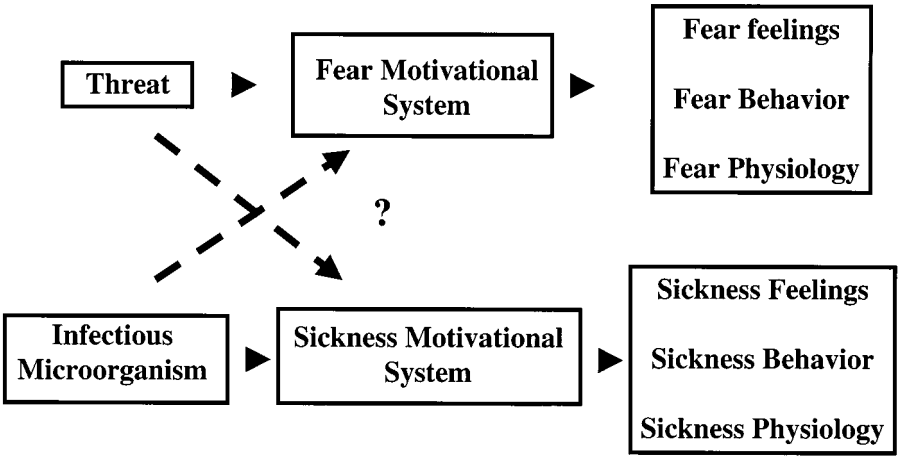

FIG. 8. Implications of the motivational hypothesis of sickness. Sickness, as a motivational state, is normally triggered by perception of infectious microorganisms by the immune system, just as fear is triggered by the perception of potential or real threats. Repeated activation of one of these motivational systems is theoretically able to make it responsive to other classes of stimuli, a phenomenon called cross-sensitization. Note that cross-sensitization does not necessarily trigger the whole range of motivational changes that are normally induced by the original stimuli.

marked (Bull, Brown, King, & Husband, 1991). Conditioning of the febrile response has also been observed in mice exposed to a camphor odor paired with administration of the interferon-α inducer poly I:C (Hiramoto, Ghanta, Rogers, & Hiramoto, 1991). In this study, one conditioning session was sufficient to increase body temperature in young and old mice, and this conditioned response was quickly extinguished following a second exposure to the conditioned stimulus. The possibility that conditioning extends to other components of the sickness response has been examined in a number of studies. Rats exposed to saccharin previously paired with LPS displayed a conditioned decrease in food intake (Exton, Bull, & King, 1995) and a conditioned suppression of splenocyte IL-2 production and splenic norepinephrine content concomitantly with a conditioned enhancement of plasma corticosterone levels (Janz et al., 1996). Apparently, all components of the sickness response to LPS cannot be conditioned to the same extent. Rats reexposed to saccharin paired with LPS displayed a conditioned febrile response but not the typical increased slow-wave sleep and decreased REM sleep observed in LPS-treated animals on the conditioning day (Bull, Exton, & Husband, 1994). However, the problem with this experiment is that it was carried out during the light portion of the dark–light cycle. Therefore, the possibility that the somnogenic components of the acute phase response are subject to classical conditioning was retested by reexposing rats to the saccharin taste solution during the dark portion of the light–dark cycle (Exton, Bull, King, & Husband, 1995). This resulted in a conditioned increase in slow-wave sleep but no change in REM sleep.

All these findings appear at first glance to provide a demonstration of the possibility of conditioning the sickness response. However, the interpretation of this phenomenon is not as straightforward as it appears *a priori*, especially since at least in the case of body temperature, conditioned changes in body temperature can be observed

in rats exposed to saccharin paired with lithium chloride instead of LPS (Bull et al., 1991). Hence there is clearly a need for further investigation of the modalities and specificity of conditioning influences on sickness behavior.

PSYCHOPATHOLOGICAL IMPLICATIONS OF THE EXISTENCE OF A MOTIVATIONAL STATE OF SICKNESS

The demonstration that the immune system influences behavior and mental states has important implications for our understanding of the relationships between psychological factors and disease. In the case of cancer, for example, such psychological features as the feelings of hopelessness and helplessness that are commonly associated with the onset and progression of the disease might be secondary to the effects on the central nervous system of factors released by immune or tumor cells during the early stage of tumor growth. The same possibility applies to the relationship between psychological factors and autoimmune and inflammatory diseases. The possible causal role of cytokines in the mental and behavioral symptoms that occur in various pathological conditions is only beginning to be explored. There is already evidence demonstrating that proinflammatory cytokines are responsible for the development of subjective and behavioral symptoms of sickness during infection with a bacterial or viral pathogen. For instance, patients treated with IFN-α show fever, anorexia, fatigue, headache, myalgia, and arthralgia. These symptoms culminate in lethargy and withdrawal from the surroundings. The same symptoms are observed in volunteers injected with low doses of LPS. The possibility that the release of cytokines accounts for more subtle changes in cognition and performance has been assessed by Smith et al. (1988). On the basis of earlier work showing that infection with upper respiratory viruses decreased the efficiency with which psychomotor tasks were performed, volunteers of both sexes were injected with IFN-α. Volunteers injected with the larger dose were significantly slower at responding in a reaction time task when they were uncertain when the target stimulus would appear. Simultaneously, the subjects displayed fever and experienced feelings of illness. However, they were not impaired in the pursuit of a tracking task or with a syntactic reasoning task. These effects were similar to the alterations in performance observed in patients with influenza (Smith et al., 1988). More recently, and in line with the inflammatory hypothesis of atherosclerosis (Ross, 1999), Appels proposed that the association between feelings of exhaustion and acute coronary events observed in patients suffering from coronary heart disease is mediated by inflammation-induced release of cytokines such as IL-1β and TNFα (Appels, 1999).

The possibility that proinflammatory cytokines have relatively specific effects on cognitive processes has been investigated in animal models. IL-1β, but not IL-6, impaired spatial navigation learning in rats (Oitzl, van Oers, Schobitz, & de Kloet, 1993). A similar deficit in spatial learning was observed in mice injected with IL-1β or infected with the pathogenic agent *Legionella pneumophilia* (Gibertini, Newton, Friedman, & Klein, 1995). Interference of cytokines with formation of new memories has also been demonstrated in an autoshaping task in which rats learned to press a lever that was introduced into the cage before food delivery (Aubert, Vega, Dantzer, & Goodall, 1995). These effects of cytokines appeared to be independent of their pyrogenic activity since they were observed regardless of whether body temperature increased or decreased.

Cytokines have also been proposed to mediate the profound fatigue and neurasthe-

nia that are experienced by patients suffering from viral infections or chronic fatigue syndrome. Evidence for a role of cytokines in chronic fatigue syndrome is very sketchy, probably as a consequence of the heterogeneity of the disease. In the scientific community, the interest in cytokines in psychopathology has recently shifted from somatic to mental disorders. Fatigue symptoms such as lack of energy and loss of interest occur very frequently in depressed patients. These symptoms are actually incorporated in the basic description of depressive episodes. In the 10th revision of the *International Classification of Disease* the entry for ''Depression'' begins with the statement that ''the subject suffers from a lowering of mood, reduction of energy, and decrease in activity. Capacity for enjoyment, interest and concentration are impaired, and marked tiredness after even minimum effort is common.'' The possibility that activation of peripheral blood monocytes and T lymphocytes plays a role in the etiology of major depression has been proposed by Maes et al. (1995) and further elaborated in an impressive number of publications from this group. In addition to the evidence pointing out the profound effects of cytokines on behavior and the HPA axis, this hypothesis is based on the observation of an increased production of cytokines by monocytes and T lymphocytes from depressed patients. For example, elevated levels of acute-phase proteins and increased concentrations of IL-6 and its soluble receptor have been found in the plasma of subjects with major depression and there was a close relationship between IL-6 levels and acute-phase proteins. However, such results are not consistently found by other research groups, and more research is still needed before a specific role of immune products in the pathogenesis of depressive symptoms can be accepted (Dantzer, Wollman, Vitkovic, & Yirmiya, 1999). The observed immune alterations appear to be a trait rather than a state marker of depression since they persist even when depressive symptoms regress. In addition, the possible contribution of antidepressant treatment to the changes in immune functions in depressed patients remains to be established.

Whereas the evidence in favor of an association between depression and an activation of the cytokine system is still contradictory, it is well recognized that administration of cytokines to nonpsychiatric patients induces the development of true depressive episodes in a large proportion of patients (Meyers, 1999). Immunotherapy is commonly used for the medical treatment of malignancies and chronic viral infection. The flu-like symptoms that occur very early in all of the patients are followed more or less rapidly by depressed mood and alterations in cognition. Severe depression develops in about one-third of the patients. Patients treated with IL-2 become clinically depressed after a few days of treatment, whereas patients treated with IFN-α become depressed after a few weeks (Capuron, Ravaud, & Dantzer, 2000) (Fig. 9). The risk of developing a depressive episode is positively correlated to the score of depressed mood at initiation of treatment despite the fact that the initial scores are within the normal range (Capuron & Ravaud, 1999). There is preliminary evidence that the mood changes that are induced by IFN-α immunotherapy can be prevented by pretreatment with fluoxetine (Miller, Pariante, & Pearce, 1999).

The possibility of a role of cytokines in depression has also been studied in animal models of depression. In the absence of any knowledge on the causal factors of depression, most animal models of depression are based on behavioral and pharmacological analogies. At the behavioral level, the two main symptoms that are usually considered include the deficit in escape/avoidance learning and anhedonia, or more precisely the diminished capacity to experience pleasure, which are typically dis-

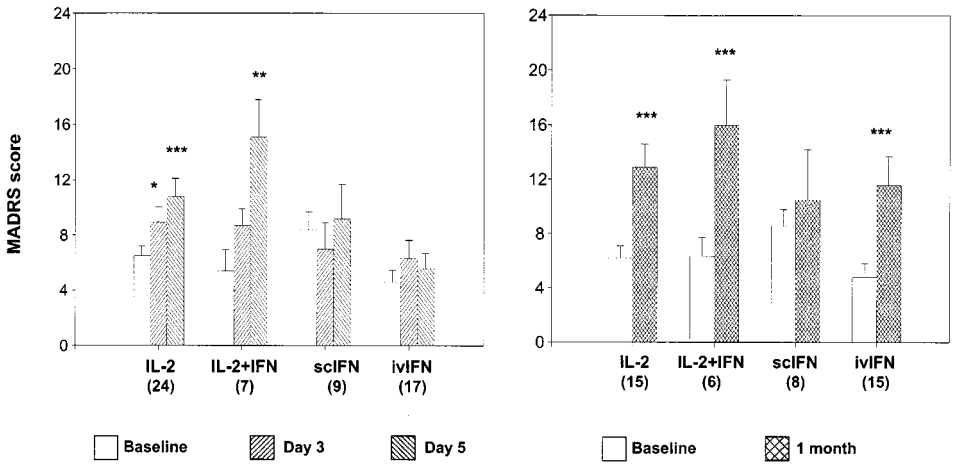

FIG. 9. Differential effects of IL-2 and IFN-α on mood in cancer patients. Patients with kidney cancer or melanoma were treated with IL-2 and/or IFN-α, IFN-α being injected subcutaneously or intravenously. In response to immunotherapy, patients displayed increased scores in the Montgomery and Asberg Depression Rating Scale (MADRS) after a few days of treatment with IL-2, whereas the effects of IFN-α required a few weeks to develop (modified from Capuron et al., 2000).

played by experimental animals exposed to uncontrollable electric shocks. At the pharmacological level, chronic but not acute treatment with antidepressant drugs blocks the development of these symptoms. A number of studies provide some evidence for a role of cytokines in animal models of depression. Intracerebroventricular administration of the interleukin-1 receptor antagonist (IL-1ra), which blocks the access of endogenous IL-1 to its receptors, attenuated the escape-avoidance deficit induced by inescapable electric shock in rats (Maier & Watkins, 1995). In a different series of experiments, cytokine treatment was found to induce anhedonia in rats, as evidenced by decreased responding for rewarding lateral hypothalamic self-stimulation in response to IL-2 and LPS, but not to IL-1β and IL-6 (Anisman & Merali, 1999), and attenuated preference for a saccharin solution in response to LPS (Yirmiya, 1996). This last effect was antagonized by chronic but not acute treatment with the antidepressant drug imipramine (Yirmiya, 1996). The behavioral effects of LPS were attenuated by pretreatment with chronic but not acute imipramine (Yirmiya et al., 1999). The atypical antidepressant drug tianeptine had the same action. It attenuated the effects of LPS and IL-1β injected peripherally on behavior and pituitary–adrenal activity, but it failed to alter the behavioral effects of LPS and IL-1β when these molecules were injected into the lateral ventricle of the brain (Castanon, 2001; Castanon, Konsman, Medina, Chauvet, & Dantzer, in preparation) (Fig. 10).

CONCLUSION

Sufficient evidence is now available to accept the concept that cytokines are interpreted by the brain as molecular signals of sickness. Sickness can actually be considered as a motivation, that is, a central state that organizes perception and action in face of this particular threat that is represented by infectious pathogens. A sick individual does not have the same priorities as one who is in good health, and this reorganization of priorities is mediated by the effects of cytokines on a number of peripheral

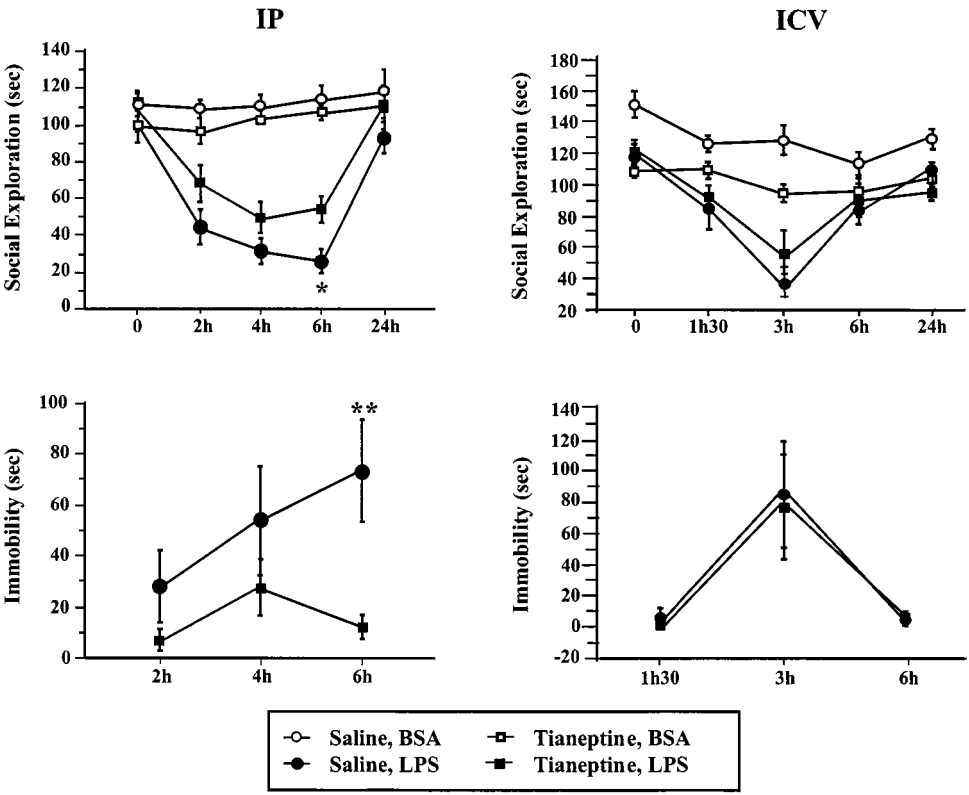

FIG. 10. Protective effects of chronic tianeptine treatment on the behavioral effects of LPS. Rats that had been chronically injected with the antidepressant tianeptine (10 mg/kg ip twice a day for 14 days) were treated with ip (250 μg/kg) or icv (0.1 μg/rat) LPS. Sickness behavior was assessed by decrease in social exploration and appearance of immobility periods. Note that tianeptine attenuated the effects of ip but not icv LPS (modified from Castanon et al., 2001).

and central targets. The elucidation of the mechanisms that are involved in these effects should give new insight into the way sickness and recovery processes are organized in the brain.

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