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Invited Minireview

Sociality and sickness: Have cytokines evolved to serve social functions beyond times of pathogen exposure?

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ABSTRACT

During pathogen exposure or some forms of stress, proinflammatory processes induce an array of motivated and behavioral adjustments termed "sickness behaviors". Although withdrawal from social interactions is a commonly observed sickness behavior, the relation between social behavior and sickness is much more complex. Sickness can suppress or stimulate social behavior. Sickness can serve as a social cue. Stressors that are social in nature can induce sickness behaviors, and sickness behavior can be readily suppressed by meaningful social stimuli. The nature, context, and timing of these effects together suggest that cytokine-induced behavior may play a role in mediating social interactions in various non-pathological conditions.

1. Introduction

The acute phase response, or "sickness", refers to an initial response of the innate immune system to a broad range of potentially infectious agents. It comprises a systemic inflammatory reaction mediated by proinflammatory factors such as the cytokines Interleukin-1 (IL-1), IL-6, and tumor necrosis factor alpha (TNFα). "Sickness behavior" is the term used to describe an array of behaviors exhibited as part of the acute phase response. Sickness behaviors include inactivity, lethargy, disinterest in surroundings, reduced intake of food and water, sleepiness, a hunched or curled body posture, shivering, piloerection, and cognitive impairment (Hart, 1988; Kelley et al., 2003). Rather than simple debilitating effects due to the action of a replicating pathogen, sickness behaviors are considered to be motivated responses induced by proinflammatory cytokines. In other words, cytokines are thought to engender a central state that organizes perception and action to serve adaptive functions related to recuperation (Aubert, 1999). Many sickness behaviors support fever either by increasing, or slowing the loss of, body temperature (e.g., shivering, hunched posture) or by conserving energy needed for thermogenesis (e.g., inactivity, sleepiness). Fever, in turn, is a key response in promoting recovery. Whereas there is still debate about the specific function of all sickness responses (e.g., cognitive impairment), sickness behaviors are considered highly adaptive and to have evolved as one component of the innate immune system's first line of defense. The specific behaviors exhibited by particular species may vary, but sickness behaviors appear to be nearly universal among vertebrates (Hart, 1988).

Although originally conceptualized as pathogen-induced, it has since become clear that some stressors can also induce components of the acute phase response, including sickness behaviors (Maier and Watkins, 1998). Much of the current literature on stress-induced sickness behavior focuses on how enhanced proinflammatory signaling triggered by stress might promote the development of depression. Indeed, the study of stress-induced sickness behavior may serve as a useful model for this purpose. Yet, sickness behavior is fundamentally an adaptive response. The specific adaptive benefit of sickness behaviors can be more difficult to discern when occurring in the context of stress rather than sickness, but some functions, most notably conserving energy, are relevant to both conditions. Indeed, increased energy demand during both stress and sickness, together with the capacity of sickness behaviors to conserve energy, may help explain the occurrence of these responses in both situations (Maier and Watkins, 1998).

Evidence indicates that centrally acting cytokines are responsible for both pathogen-induced and stress-induced sickness behavior. Cytokines expressed peripherally in response to a

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pathogen can either enter the brain directly through sites where the blood–brain barrier is weak or absent, or via specialized transport systems. Cytokines can also signal the brain through indirect mechanisms involving peripheral nerves such as the vagus, hypoglossal, and glossopharyngeal, or through interaction with endothelial and perivascular cells. In turn, microglia and other central cells can manufacture cytokines that then act on neural tissue to produce the behavioral outcome (e.g., Banks and Erickson, 2010; McCusker and Kelley, 2013; Serrats and Sawchenko, 2009). In the case of stress-induced sickness, neural signals may directly activate central proinflammatory release or do so through a more-indirect route involving stress-hormone facilitated release of peripheral danger signals (Danger-Associated Molecular Patterns; DAMPs) such as HSP72 or HMGB1, that in turn activate peripheral cytokine release that then triggers central proinflammatory signaling (Fleshner, 2013). The fact that cytokines—peptides associated with immune regulation—can affect behavior as well as respond to stressors is not surprising given the extensive interaction and broad overlap of effects of peptides classically considered components of either the immune, neural or endocrine systems (e.g., Rothwell and Hopkins, 1995).

The loss of interest in surroundings exhibited by sick animals typically extends to their social environment. Indeed, reduced social behavior and diminished responsiveness to social companions are considered to be characteristic sickness behaviors. A reduction in the time spent investigating an unfamiliar conspecific is a commonly used measure of sickness behavior in rats and mice (e.g., Arakawa et al., 2009; Fishken and Winslow, 1997). Similarly, sickness disrupts sexual behavior of rats, at least that of females (Avitsur and Yirmiya, 1999). Nonetheless, the relation between sickness and social behavior is much more complex than these findings would suggest. Suppression of social behavior is not an invariant outcome of sickness. Sickness can serve as a social cue. Some stressors that are social in nature can induce an inflammatory cascade with sickness behavior, and certain social interactions can suppress sickness responses (Fig. 1). Here we will briefly review these various relations between social behavior and sickness with an emphasis on the suppressive, or "buffering" effects of social conditions on sickness responses. These findings will be considered in the context of the hypothesis that mechanisms of sickness behavior may also mediate the behavior of healthy individuals under ordinary conditions.

2. Suppression of social behavior is not an invariant outcome of sickness

Whether sickness suppresses social behavior depends on both subject and environmental variables. Sex differences in the sexual behavior of male and female rats is a case in point. In females, an injection of the proinflammatory cytokine IL-1 suppressed sexual receptivity, proceptive behavior, preference for a gonadally intact male, and a general measure of activity in the open field. In males, however, a dose sufficient to suppress general activity had no effect on sexual behavior or preference for a receptive female (Yirmiya et al.,1995). Thus, for males but not females, the motivation to mate appears to outweigh motivation to engage in sickness behavior. These results might be understood in the context of the greater offspring investment by females than by males together with the risk of diminished fitness resulting from infection during pregnancy. That is for males, mating, even while infected, offers an opportunity for successful reproduction with little investment; while for females, pregnancy and lactation represent significant investment in what may well be a litter with substantially reduced chances of survival to reproductive age. In a somewhat related fashion, how lactating mice respond during sickness varies with ambient temperature and the state of their pups. Aubert et al. (1997) injected mothers with lipopolysaccharide (LPS), a component of the cell wall of gram negative bacteria that potently elicits the acute phase response. Under standard temperature conditions, a dose of LPS sufficient to induce signs of sickness also disrupted nest building and pup retrieval. But when ambient temperature was reduced so that the need of the pups for warmth was increased, the nest-building and retrieval of LPS-injected dams did not differ from that of controls. In this case, environmental conditions determined whether social (i.e., maternal) behaviors took precedence over sickness behaviors. Together, these now classic examples of how sickness behavior can be adapted or suspended to meet environmental demands also emphasize that whether or not social behaviors are disrupted by sickness can be determined by variables related to reproductive success and fitness. While nearly all studies of sickness behavior have been conducted with captive or domesticated animals, the little information available on animals in the wild supports the notion that individuals will forego the expression of sickness behavior when doing so accrues a selective advantage. That is, LPS was found to elicit sickness responses in free-living male song sparrows during the non-breeding season, but to have no detectable effect during the active breeding season when sickness behavior would likely jeopardize mating opportunities (Owen-Ashley and Wingfield, 2006).

In addition, dominance status can modulate the effect of sickness on social behavior. In male mice housed in dyads, treating the dominant partner with LPS reduced the time it spent in the agonistic behaviors that enforce dominance, whereas treating the subordinate with LPS had no discernible effect on defensive or other social behavior (Cohn and de Sá-Rocha, 2006). Moreover, it appears that central cytokine activity may respond to differences in social status. In adult male rats housed in pairs, the member of the pair found to be subordinate in a food competition task also had markedly higher levels of IL-1 expression in the hypothalamus (Barnum et al., 2008), raising the possibility that central cytokine signaling might contribute to some of the behavioral differences

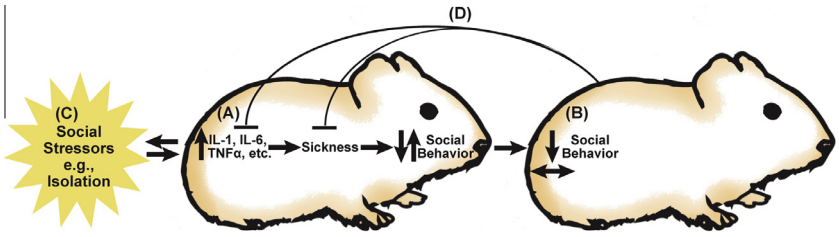

Fig. 1. Illustration of some of the complexity of relations between sickness and social behavior. (A) Increased proinflammatory cytokine signaling increases sickness, including sickness behavior, but social behavior may be either reduced or increased. (B) Exposure to a sick individual may reduce or have no effect on a partner's interactions with the sick animal. (C) Social stressors, such as isolation, can be powerful stimulators of increased proinflammatory signaling, and sickness and proinflammatory activity can induce feelings of isolation. (D) Meaningful social partners can reduce or "buffer" cytokine signaling and sickness.