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Invited minireview

The neurobiology of aggression and rage: Role of cytokines

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Abstract

Recent studies have suggested an important relationship linking cytokines, immunity and aggressive behavior. Clinical reports describe increasing levels of hostility, anger, and irritability in patients who receive cytokine immunotherapy, and there are reports of a positive correlation between cytokine levels and aggressive behavior in non-patient populations. On the basis of these reports and others describing the presence or actions of different cytokines in regions of the brain associated with aggressive behavior, our laboratory embarked upon a program of research designed to identify and characterize the role of IL-1 and IL-2 in the hypothalamus and midbrain periaqueductal gray (PAG)—two regions functionally linked through reciprocal anatomical connections—in the regulation of feline defensive rage. A paradigm involved cytokine microinjections into either medial hypothalamus and elicitation of defensive rage behavior from the PAG or vice versa. These studies have revealed that both cytokines have potent effects in modulating defensive rage behavior. With respect to IL-1, this cytokine facilitates defensive rage when microinjected into either the medial hypothalamus or PAG and these potentiating effects are mediated through 5-HT2 receptors. In contrast, the effects of IL-2 are dependent upon the anatomical locus. IL-2 microinjected into the medial hypothalamus suppresses defensive rage and this suppression is mediated through $GABA_A$ receptors, while microinjections of IL-2 in the PAG potentiate defensive rage, in which these effects are mediated through NK-1 receptors. Present research is designed to further delineate the roles of cytokines in aggressive behavior and to begin to unravel the possible signaling pathways involved this process.

Keywords: Cytokines; Interleukin-1; Interleukin-2; Aggression; Defensive rage; Serotonin; GABA; NK-1

1. Introduction

There is a consensus that the immune and central nervous systems (CNS) communicate in a bi-directional manner. A fundamental principle of psychoneuroimmunology is that this communication helps regulate an orchestrated immune response (Dantzer et al., 1999). This notably includes: (1) activation of neuroimmune feedback loops, and (2) stimulation of central neurochemical alterations that in turn underlie adaptive behavioral and physiological responses (i.e., the classic symptoms of sickness behavior). Cytokines released during the course of an immune response act as messengers that help modulate sickness behavior by influencing relevant neurotransmitter systems, and in some cases, by directly acting within the brain (Maier et al., 2001).

Since cytokines also act as endogenous neuromodulators, it is possible to study their relationship to behavior independent of an ongoing immune response. In this context, it has been recently shown that cytokines are present in brain regions, such as the hypothalamus and midbrain periaqueductal gray (PAG), that are known to be associated with aggression and rage behavior (Siegel et al., 1999). Moreover, there is evidence that anger and hostility are increased in patients receiving repeated cytokine immunotherapy, supporting the view that cytokines may facilitate the expression of aggressive behavior. Accordingly, the following review will discuss research investigating the

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relationship between cytokines, immunity, and aggressive behavior. This includes studies detailing the immunological consequences of an aggressive confrontation, the relationship between cytokines and aggressive behavior, links between social status and immune function and effects of immune responding on the animal's response to an aggressive challenge. We will also discuss our research program that uses an established model of feline aggressive behavior to directly determine the role of brain cytokines (notably interleukin (IL)-1β and IL-2) on the expression of defensive rage behavior, which is a close animal analog of a parallel form of human aggression. This approach allows us to identify specific brain sites wherein cytokines may modulate aggressive behavior, systematically determine the nature of their effects, and identify specific cytokine-neurotransmitter receptor mechanisms that underlie these effects.

2. Cytokines, immunity and aggressive behavior

The relationship between cytokines, immunity, and aggressive behavior has been studied on many levels in human and infrahuman populations. In this section, we will present an overview of representative studies examining the aggression–immunity relationship. This includes: (a) human studies that evaluate anger/hostility in patients receiving repeated cytokine immunotherapy, or coordinate assessments of anger/hostility and endogenous cytokine or immune cell activity in non patient populations; and (b) animal studies examining immunological profiles of aggressive and submissive individuals, and the relationship between strain, social status and immunity.

In recent years, an increasing amount of attention has focused on psychiatric abnormalities associated with cytokine administration (notably interferon (IFN)α-2b and/or interleukin (IL)-2), which are used in the treatment of cancer, AIDS, and hepatitis C, among other disorders (e.g., Capuron et al., 2004). Studies have shown that cytokine immunotherapy results in a facilitation of aggressive behavior. Specifically, measures of anger/hostility and irritability are increased in patients receiving cytokine immunotherapy (e.g., Kraus et al., 2003; McHuthison et al., 1998). It is important to consider that various factors may have contributed to these observations, including comorbid psychiatric abnormalities and processes related to the underlying disorder being treated. Indeed, patients also display depression, anxiety, and cognitive difficulties, among other psychiatric disturbances. Moreover, it is possible that an interaction between cytokine treatment and the disease process (e.g., chronic infection and subsequent alterations of cytokine activity) influences the expression of aggressive behavior. Support for this suggestion stems from a study by Kraus et al. (2003) who evaluated anger/hostility in patients with chronic hepatitis C infection before and after onset of IFN therapy. They found that anger/hostility was increased in patients before onset of cytokine treatment and that these increases were further augmented following onset of therapy. To be sure, one must temper one's conclusions concerning the relationship between cytokines and measures of aggressive behavior pending analyses of the possible contributions of other factors, including actual regimens of cytokine therapy, the use of other treatments, and certain demographic factors, among other factors.

Studies using non-patient populations also suggest a link between aggressive behavior and cytokines. In these studies, measures of aggressive behavior are related to endogenous blood cytokine production. For example, Suarez et al. (2004), using healthy subjects, showed that Cook–Medley Hostility scores are increased coincident with an enhancement of LPS-stimulated production of proinflammatory cytokines by blood monocytes. Consistent with these findings, Kiecolt-Glaser and colleagues (2005) showed that higher levels of hostile marital interactions are associated with increased production of plasma proinflammatory cytokines.

Taken together, these studies show that a positive association exists between cytokines, immune cell activity, and various measures of aggressive behavior in patient and non-patient populations. Increases in aggressive behavior have also been linked to enhancements of cytokine production and immune cell activity in animal studies. For example, Petitto et al. (1994) showed that IFNγ, IL-2 production, and T cell proliferation were higher in mice bred for high aggression (based on frequency of attacks after contact) than mice bred for low aggression. Inasmuch as these effects were not related to differences in post-weaning social experience or to gender differences, the authors suggested that a genetic linkage exists for genes associated with aggression and immunity.

It is important to consider that aggressive confrontations can result in both immunoenhancing and immunosuppressive effects. Avitsur and colleagues (2002) used a paired fighting model to determine the effects of fighting on measures of splenic cell distribution and function. They found that six daily sessions resulted in an increase in monocytes and neutrophils, and a decrease in lymphocyte measures. These effects occurred coincident with a state of glucocorticoid resistance in splenocytes. The authors suggested that the immune alterations associated with aggressive confrontations may be related, at least in part, to wound healing.

Another model of social stress that has been used to examine the aggression–immune relationship is the social confrontation model or resident-intruder confrontation. In this model, an intruder is placed into an aggressive animal's home cage. The intruder is typically attacked and defeated, and tends to show submissive or subdominant behavior. Stefanski and Ben-Eliyahu (1996) used this model to study the consequences of social confrontation on tumor retention. They found that rats receiving mammary tumor cells one hour into a seven hour confrontation had increased tumor retention, and that this effect was blocked by a β adrenergic antagonist. Studies have also examined the effects of social status on measures of immunity. Typically, subdominant animals are immunosuppressed and show an