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Further evidence for the depressive effects of cytokines: Anhedonia and neurochemical changes

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Abstract

Although human studies have emphasized a role for IL-2 in depressive illness, limited attention has been devoted to the behavioral and neurochemical effects of this cytokine in animal studies. The present review assesses the behavioral effects of IL-2 in rodents, in counterpoint to the effects of interleukin-1β (IL-1β), necrosis factor-α (TNF-α) and endotoxin challenge. Unlike IL-1β, systemic IL-2 provokes modest effects on hypothalamic-pituitary–adrenal (HPA) functioning, and does not provoke marked signs of illness or anxiety. In some respects, however, IL-2 elicits effects reminiscent of traditional stressors, including anhedonia (diminished pleasure gained from otherwise rewarding stimuli). Additionally, when chronically administered, IL-2 may impact on cognitive processes, including spatial working memory. While IL-2 may induce depressive-like symptoms, the available data are sparse, have hardly considered the impact of chronic cytokine treatment, only assessed behavior in a narrow range of tests, and it remains to be established whether the effects of IL-2 are modifiable by antidepressant treatments. Finally, as the effects of IL-2 on CNS processes vary in a biphasic fashion, and may also engender neurotoxic effects, further analyses are necessary to discern under what conditions this cytokine provokes depressive-like behavioral outcomes.

Keywords: Interleukin-2; Interleukin-1; Lipopolysaccharide; Depression; Anxiety; Dopamine; Norepinephrine; Serotonin

1. Introduction

Increasing attention has focused on the proposition that cytokines, like neurotransmitters and hormones, may contribute to the provocation or exacerbation of affective disorders. To a considerable extent, this view was reinforced by the realization that communication occurs between the immune, endocrine, autonomic, and central nervous system, and that immune activation (or products of an activated immune system, e.g., cytokines) profoundly influences neuroendocrine and central neurotransmitter processes (Blalock, 1994; Dantzer et al., 2001; Dunn, 1995). There are, of course, several potential routes of communication between the immune system and the CNS, including stimulation of vagal afferents (Dantzer et al., 2001; Maier, Goehler, Fleshner, & Watkins, 1998) or brainstem neurons (Zhang, Lu,

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Elmquist, & Saper, 2000), and by a cascade of neuroendocrine and neuropeptide regulators (Turnbull, Lee, & Rivier, 1998).

While not dismissing alternatives, the view has been entertained that macrophage-derived cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α), as well as IL-2 secreted from T cells, may act in a signaling capacity between the immune and central nervous system. Moreover, by affecting central neurotransmitter functioning, these cytokines may come to affect mood states (including affective illnesses). It is premature to conclude that any one cytokine is pivotal in relation to depression, particularly as these cytokines may have additive or synergistic actions (e.g., Brebner, Hayley, Merali, & Anisman, 2000; Plata-Salaman, Sonti, Borkoski, Wilson, & Ffrench-Mullen, 1996).

2. Cytokines as stressors

In addition to its other functions, the immune system may act in a signaling capacity, informing the brain of antigenic challenge (Blalock, 1994). Given the similarity between the neurochemical changes exerted by stressors and those elicited by proinflammatory cytokines, it may be that the brain interprets these signals as if they were stressors (Anisman & Merali, 1999; Dunn, 1995, 2001). Certainly the effects of systemic stressors (e.g., viral insults or endotoxins) and those of processive stressors (i.e., those involving higher-order sensory processing, e.g., fear conditioning) are distinguishable from one another (Herman & Cullinan, 1997). Nevertheless, the immune system may be part of a regulatory loop that contributes to the symptoms of mood and anxiety-related disorders (Anisman & Merali, 1999; Griffiths, Ravindran, Merali, & Anisman, 2000; Kronfol & Remick, 2000; Licinio & Wong, 1999; Maes, 1999). Moreover, there is reason to suppose that stressful events influence the response to cytokine challenges (and vice versa) and thus affective changes elicited by cytokines may be influenced by the backdrop upon which they are applied.

Despite the similarities between some of the neurochemical effects of cytokines, stressors, and those presumed to subserve depressive illness, there is still a paucity of data concerning the potential behavioral and neurochemical effects of some cytokines. Curiously, while the human experimentation supporting a role for cytokines in depression have come from correlational studies involving IL-2 and IL-2 receptors (and other cytokines), as well as from trials of IL-2 or IFN-α immunotherapy, the animal studies have focused on the effects of IL-1β, and to a lesser degree IL-6 and TNF-α. Remarkably little information is available, however, concerning the behavioral effects of IL-2. The sections that follow provide a brief overview of the effects of cytokines on depressive-like behaviors in rodents and their relationship to central monoamine and to neuroendocrine factors. While the present review focuses on the effects of IL-2, they are contrasted with those of proinflammatory cytokines, endotoxins, and stressors.

3. Central presence of cytokines

The de novo syntheses of cytokines and their receptors have been identified in several brain regions (Hanisch & Quirion, 1996; Rothwell, 1999). The presence of some cytokines (e.g., IL-1) within the brain are particularly marked following a variety of insults, including concussive brain injury, cerebral ischemia, seizure, bacterial endotoxin, and viral challenge, psychological factors (e.g., stressors) and by physical insults, and appear to be elevated in neurodegenerative disorders (Dunn, 2001; Licinio & Wong, 1999; Plata-Salaman, 2000; Reichlin, 2001; Rothwell, 1999; Rothwell & Luheshi, 2000).

Like other cytokines, IL-2 and IL-2R are endogenous to the brain (Araujo & Lapchak, 1994; Araujo, Lapchak, Collier, & Quirion, 1989; Lapchak, 1992; Lapchak, Araujo, Quirion, & Beaudet, 1991; Pettito & Huang, 1994, 1995; Pettito, Huang, Raizada, Rinker, & McCarthy, 1997a; Seto, Hanisch, Villemain, Beaudet, & Quirion, 1993; Hanisch, 2001) and various insults or pathological conditions may be associated with increased central IL-2 (Hanisch, 2001). The function of this cytokine within the brain is not known as yet, but it may support the survival of neurons in cortical and subcortical regions (Hanisch, 2001). Moreover, in addition to its constitutive expression, IL-2 may gain entry to the brain at certain sites, such as the circumventricular organs (Banks, 1999, 2001) and may cross the blood–brain-barrier by altering cerebrovascular permeability (Banks & Kastin, 1992; Ellison, Krieg, & Povlishock, 1990). Damage to the blood–brain barrier was reported following repeated IL-2 treatment (Ellison et al., 1990) and repeated central administration of IL-2 may engender neurotoxic-like effects