Neuroscience and Biobehavioral Reviews 34 (2010) 782–790

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Early attachment-figure separation and increased risk for later depression: Potential mediation by proinflammatory processes

Michael B. Hennessy [a,*], Terrence Deak [b], Patricia A. Schiml-Webb [a]

[a] Department of Psychology, Wright State University, 335 Fawcett Hall, Dayton, OH 45435, United States
[b] Department of Psychology, Binghamton University, Binghamton, NY 13902, United States

ARTICLE INFO

Keywords:
Depression
Separation
Attachment
Proinflammatory activity
Cytokines
Hypothalamic–pituitary–adrenal
Corticotropin-releasing factor

ABSTRACT

Early maternal separation and other disruptions of attachment relations are known to increase risk for the later onset of depressive illness in vulnerable individuals. It is suggested here that sensitization involving proinflammatory processes may contribute to this effect. This argument is based on: (1) current notions of the role of proinflammatory cytokines in depressive illness; (2) evidence that proinflammatory cytokines mediate depressive-like behavior during separation in a rodent model of infant attachment; and (3) comparisons of the effects of early proinflammatory activation versus maternal separation on later proinflammatory activity and biobehavioral processes related to depression. The possible interaction of proinflammatory processes and corticotropin-releasing factor in the sensitization process is discussed.

Contents

1. Introduction

In recent years, there has been a concerted effort to better understand the relationship between stress and depression. Stress promotes depression in vulnerable individuals in at least two ways. First, periods of major stress frequently precipitate the onset of depressive bouts (Bonde, 2008; Caspi et al., 2003; Chadda et al., 2007; Gotlib et al., 2008). Second, exposure to stressors during early life—often stressors involving disruption of attachment relations (i.e., separation, abuse, neglect)—increases the risk for the onset of depressive illness in later life (Agid et al., 1999; Bernet and Stein, 1999; Gilman et al., 2003; Reinherz et al., 1999; Takeuchi et al., 2002).

The association between early attachment-figure separation and depression was suggested by the work of Spitz and others in the 1940s and 50s, which demonstrated that children often exhibited depressive-like behavior during prolonged separation from their parents in hospitals or other institutional settings (Bowlby et al., 1952; Robertson, 1953; Spitz, 1946). Studies of nonhuman primates that then followed firmly established the importance of the attachment figure in infancy for healthy psychological functioning (Harlow and Harlow, 1969; Mineka and Suomi, 1978) and identified a stage of behavioral response to maternal separation that was marked by passivity and withdrawal. Behavior during this passive or "despair" stage clearly resembled the depressive behavior of separated children (Kaufman and Rosenblum, 1967; Mineka and Suomi, 1978) and soon was established as an early animal model of depressive illness (McArthur and Borsini, 2006). Later studies by Levine and others in both nonhuman primates and rodents demonstrated the variety

* Corresponding author. Tel.: +1 937 775 2943; fax: +1 937 775 3347.
E-mail address: michael.hennessy@wright.edu (M.B. Hennessy).

0149-7634/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neubiorev.2009.03.012

of essential physiological functions [e.g., cardiovascular, hypothalamic–pituitary–adrenal (HPA)] and behaviors of the infant that were, as a matter of course, controlled and regulated by the presence of the maternal figure (e.g., Hofer, 1987; Mason and Berkson, 1975; Rosenfeld et al., 1992; Schanberg et al., 2003).

In humans, retrospective studies began to document a positive correlation between early attachment-figure separation and increased risk for depression in adulthood (Birtchnell, 1972; Brown et al., 1977). As the association of early attachment disruption and later depression has progressively become more firmly established in the literature (e.g., Kessler et al., 2008; Widom et al., 2007), studies attempting to identify the mechanisms responsible have proliferated as well. Research has implicated the HPA and serotonergic systems among others (Gillespie and Nemeroff, 2007; Spinelli et al., 2007), though the bulk of attention has focused on corticotropin-releasing factor (CRF). A number of lines of evidence suggest that CRF acting at both hypothalamic and extra-hypothalamic sites is a crucial factor determining the effect of early stressors on later depression and anxiety disorders (Bradley et al., 2008; Coplan et al., 1996; Heim et al., 2008; Keen-Rhinehart et al., 2008). Enhancement or sensitization of CRF action on, for instance, HPA, sympathetic, and central monoamine systems as a result of the early trauma provides a unifying mechanism for "stress diathesis" models for the development of depressive illness (Gold et al., 1988; Heim and Nemeroff, 2001), and has helped build a case for current attempts to develop CRF antagonists as anti-depressants (Binneman et al., 2008; Holsboer and Ising, 2008; Valdez, 2006).

This paper will suggest that the association of early attachment disruption with the later onset of depression might also involve a sensitization of proinflammatory pathways; that is, a neuroimmune process. This notion was prompted by ongoing research in our laboratories indicating that proinflammatory activity mediates depressive-like behavior in an animal model of attachment-figure separation. The present paper places these findings in the context of: (1) the now extensive literature documenting that proinflammatory processes can contribute to depressive illness; and, (2) evidence that increased proinflammatory activity in the CNS can exert long-term effects on both behavior and stress-related physiological systems that are relevant to the development of depressive illness. Specifically, the current paper will suggest that stress-induced activation of proinflammatory activity during attachment-figure separation (or possibly other forms of attachment disruption) in early life may increase proinflammatory activity or its effects on other stress-related systems in later life, and thereby increase the chances of depressive illness. Such a process, if confirmed, might be incorporated within the broader framework of the stress-diathesis model of depression and its proposed mediators (e.g., CRF). Others have proposed that stressors and increased proinflammatory activity can cross-sensitize neural circuits underlying depression (Anisman et al., 2003; Tilders and Schmidt, 1999). We build on this idea as it applies to a specific form of an early psychosocial stressor (attachment-figure separation) thought to be particularly potent at promoting the development of depression in later life.

In the following sections we first will provide a brief overview of relevant findings regarding the role of proinflammatory activity in depressive illness. Second, we will present evidence primarily from our own comparative work indicating that proinflammatory processes underlie depressive-like behavior during maternal separation. Third, comparisons of the lasting effects of increased proinflammatory activity and maternal separation on relevant biobehavioral measures and proinflammatory activity in later life will be made. Finally, conclusions from these sets of data, as well as limitations and qualifications of the proposal, will be discussed.

2. Proinflammatory processes in depressive illness

The notion that proinflammatory processes can play an important role in at least some forms of depressive illness has gained widespread acceptance during the last decade. A complete review of the role of proinflammatory activity in depression is beyond the scope of the present paper. A number of more-comprehensive recent reviews of this topic are available (e.g., Dantzer et al., 2008; Dunn et al., 2005; Miura et al., 2008; Schiepers et al., 2005). The purpose here is to provide the basic framework of this idea, to illustrate the kinds of data that support it, and to demonstrate how relevant proinflammatory processes appear to be linked to stress in ways that are amenable to study in laboratory animals.

Proinflammatory cytokines [interleukin-1 (IL-1), IL-6, tumor necrosis factor-α (TNF-α), and interferon-α (INF-α) among others] are peptides secreted by monocytes/macrophages and microglia upon detection of antigens as part of the innate immune response. The peptide signalers orchestrate a systemic inflammatory response known as the acute phase response, or sickness, that constitutes a first line of defense against pathogen replication (Baumann and Gauldie, 1994). The acute phase response consists of both physiological components such as fever, shifts in the production of proteins by the liver, and HPA activation, as well as behavioral changes. In general, active behaviors are diminished and passive responses predominate. "Sickness behaviors" include reductions in feeding, drinking, socio-sexual activity, and overall interaction with the environment, as well as the seeking of warmth, shivering, piloerection, sleepiness, cognitive impairments, and the assumption of a hunched posture (Hart, 1988; Yirmiya, 1996). The responses largely appear to be motivated behaviors rather than simply the result of debilitation (Aubert, 1999), and seem to be adaptive during times of illness by supporting the production of fever, conserving energy, etc. (Hart, 1988). Interestingly, sick animals can also appear "depressed", i.e., disengaged, asocial, and, in some cases, projecting an impression of sadness.

Evidence that increased proinflammatory cytokine activity contributes to human depression stems from several sources. For instance, levels of circulating cytokines and other markers of the acute phase response have been found to be elevated in depressed patients (Kronfol, 2002). Chemotherapy with proinflammatory cytokines, in particular INF-α, provokes depressive reactions in a substantial proportion of patients (e.g., Miyaoka et al., 1999; Raison et al., 2006), and the depressive effect of cytokines can be reduced with anti-depressants (Musselman et al., 2001). Further, exposing laboratory animals to stressors has been found to elicit increased proinflammatory activity and aspects of an acute phase response, including depressive-like, sickness behavior (Maier and Watkins, 1998). Indeed, it has been suggested that cytokine activation in response to stressors may be a major factor accounting for the onset of stress-induced depression (Miura et al., 2008). Thus, study of stress-induced sickness behavior offers a potential framework in which to consider the ability of periods of stress to precipitate depressive episodes. During stressor exposure, increased proinflammatory activity may alter metabolism of tryptophan to reduce central serotonin, enhance HPA activity, and increase central neurotoxic activity (Hayley et al., 2005; Miura et al., 2008). In other words, stress-induced cytokine activity may promote depression by its action on other putative mechanisms of depressive illness, namely: reduced serotonergic activity, HPA hyperactivity, and increased neurotoxic action. Moreover, Koo and Duman (2008) and Goshen et al. (2008) recently reported that stressor-induced behavioral signs of depression and associated reductions in neurogenesis in mice were reversed by central antagonism of the IL-1 receptor. These latter findings not only fit