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Brief Commentary

Malaise, melancholia and madness: The evolutionary legacy of an inflammatory bias

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ABSTRACT

Evolutionary imperatives bred a vigorous and highly orchestrated behavioral and immune response to the microbial world that served to promote species survival and propagation. The resultant legacy is an inflammatory bias which goes largely unchecked in the modern world and is provoked not only by pathogens but also now by people. In this commentary, the authors' contributions to the special issue on *Inflammation* and *Mental Health* are described, beginning with the origins of the inflammatory bias, its roots in genetic predispositions to behavioral adaptations and ultimately maladaptations, and its consequences on the developing brain. In addition, the mechanisms by which the immune system engages behavior are described including a central role for the inflammasome which may serve to link psychological stress with inflammatory and behavioral responses. Neurotransmitter systems that mediate effects of the immune system on behavior are also described along with interactions of the inflammatory bias with depression and their convergent impact on the response to stress and medical illness. Finally, translational implications are discussed including data from a clinical trial using a cytokine antagonist in depressed patients, which suggests an interaction of the inflammatory bias with other evolutionary legacies including those related to food consumption and their modern consequences of obesity and the metabolic syndrome. Taken together, the articles offer a sampling of the rich literature that has evolved regarding the role of the immune system in behavioral disorders. The grounding of this relationship in our evolutionary past may serve to inform future research both theoretically and therapeutically.

1. Introduction

As we have learned more about interactions between the brain and the immune system, it is increasingly apparent that cytokines and other immune molecules and cells play a Janus-faced role in central nervous system (CNS) function. Indeed, immune system molecules and cells are an essential component of numerous processes that are fundamental to the maintenance of neuronal integrity including neurogenesis, synaptic remodeling, and neurotransmission (Yirmiya and Goshen, 2011). For example, inhibition of cytokines through the use of antagonists or gene targeting is associated with significant impairments in learning and memory in conjunction with deficits in the elemental processes that support these functions including long-term potentiation (Yirmiya and Goshen, 2011). Similar results have been found following removal of cellular components of the immune system including T cells and microglia (Kipnis et al., 2004; Sierra et al., 2013; Ziv et al., 2006). Recent data suggest that even the healing effects of antidepressants may be in part dependent upon the induction of an immune response (Warner-Schmidt et al., 2011).

Side-by-side with these sustaining influences of the immune system on neuronal function is the specter of a destructive force driven by an overactive immune response or inflammation that in its attempt to contain and control a perceived assault can wreak havoc on the body and the brain, ultimately affecting behavior (Dantzer et al., 2008; Miller et al., 2009). While the short-term goal to enact protective responses at the cellular and organismic level is essential to survival, in the long run, chronic immune activation and inflammation, comes at a high cost, contributing to the immense personal and economic burden of neuropsychiatric disorders as well as other illnesses in our society. Much attention has appropriately been paid to the mechanisms of the effects of inflammation on the pathways to pathology in mental illnesses. However, it is important to recognize that there is a method to the madness, beginning with the need to survive in a hostile microbial environment in ancestral times, and ultimately resulting in the legacy of an inflammatory bias which when triggered or fostered by environmental conditions can lead to a host of maladies that are overrepresented in the modern world including allergic disorders, cardiovascular disease, diabetes, cancer and neuropsychiatric disorders (Couzin-Frankel, 2010). In this special issue of *Brain*

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Behavior Immunity, we will begin with human evolution and through a series of papers will expand upon the basis of the inflammatory bias, its genetic representations, the dire consequences on a developing brain, the mechanisms impacting CNS function, the role of environmental triggers and ultimately translational relevance (Fig. 1).

2. Man meets microbe: the evolutionary imperative

Natural selection favors those individuals who can survive to reproductive age. In the ancestral world, infant mortality secondary to infectious diseases was one of the primary sources of evolutionary pressure applied to the human race (Volk and Atkinson, in press). As a result, individuals with a more vigorous or targeted immune response to prevailing pathogens were the ones most likely to survive and propagate the species (Raison and Miller, 2013). So important was the need to fend off these microbial assaults, data suggest that European and Asian peoples were the beneficiaries of a critical immunologic boost through interbreeding with Neanderthals and other now extinct human sub-species (Abi-Rached et al., 2011). Indeed, analysis of modern human DNA reveals the presence of genes derived from Neanderthals that cluster in the human major histocompatibility locus and are associated with a more aggressive immune response to pathogens including viruses

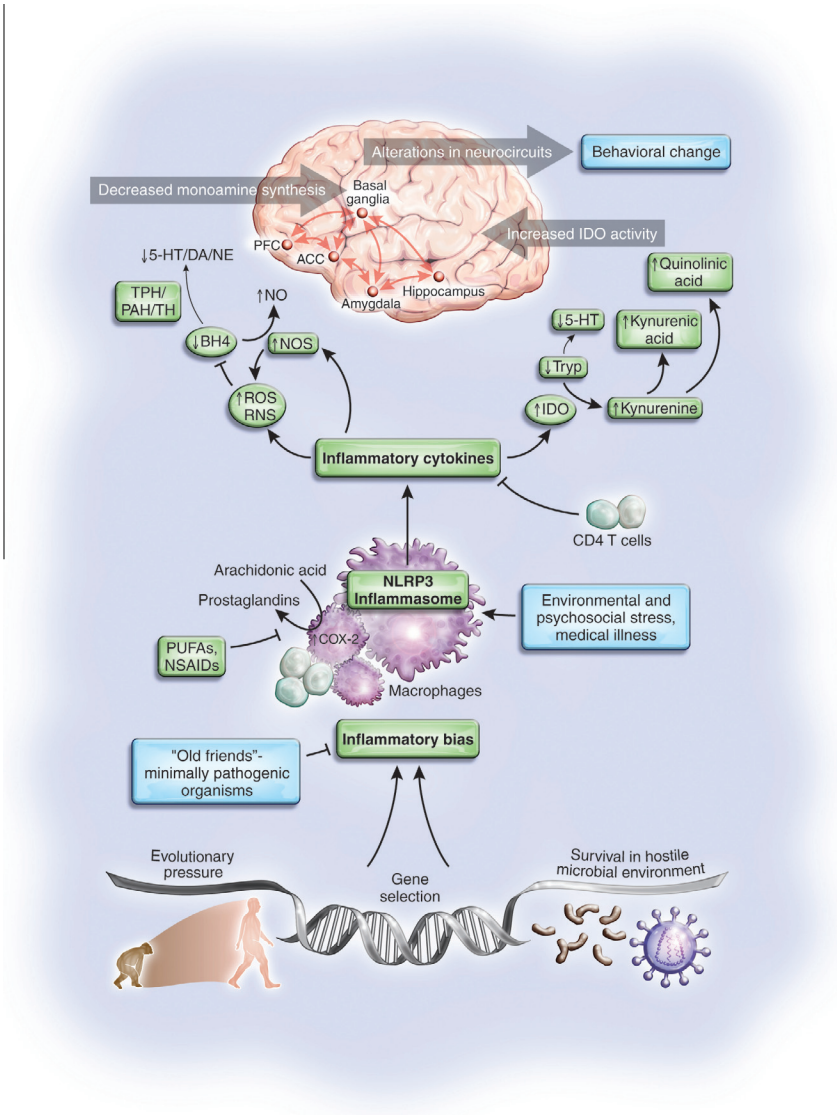

Fig. 1. Mechanisms and consequences of the evolutionary legacy of an inflammatory bias. Survival in the ancestral world was contingent upon successful negotiation of a hostile microbial environment which ultimately contributed to a genetically-based inflammatory bias. This inflammatory bias, while essential for survival against pathogens and predators, has in the modern world (in the absence of temperance by exposure to minimally pathogenic organisms and the elaboration of immunomodulatory T cells) been expanded to include the response to psychosocial challenge. This capacity is achieved through immune mechanisms such as the inflammasome, which can respond to a variety of environmental stressors beyond pathogens including psychosocial stress. Once activated, the inflammasome can trigger the release of inflammatory cytokines which in turn stimulate enzyme pathways such as indoleamine 2,3 dioxygenase (IDO) as well as the production of reactive nitrogen and oxygen species (RNS and ROS). Activation of these pathways can then lead to the release of neurotoxic metabolites of kynurenine including quinolinic acid, while also disrupting the synthesis of monoamine neurotransmitters including serotonin (5-HT), dopamine (DA) and norepinephrine (NE) through effects on the availability of monoamine precursors such as tryptophan (Tryp) and tyrosine as well as tetrahydrobiopterin (BH4), which is an essential enzyme co-factor for phenylalanine hydroxylase (PAH), tryptophan hydroxylase (TPH) and tyrosine hydroxylase (TH). These actions of inflammatory cytokines ultimately contribute to alterations in neurocircuits in the brain including the basal ganglia, the anterior cingulate cortex (ACC) and the prefrontal cortex (PFC) which elaborate a host of behavioral changes that are an essential complement to the integrated immune and behavioral response to pathogens and predators which ultimately aid survival. However, in the context of chronic or overwhelming psychosocial challenge, these same responses can contribute to the malaise, melancholy and madness which are the inflammatory legacy of our evolutionary past. NLRP3, NACHT domain-, leucine-rich repeat-, and pyrin domain-containing protein 3; NO, nitric oxide; NOS, nitric oxide synthase; NSAIDS, non-steroidal anti-inflammatory drugs; PUFAs, polyunsaturated fatty acids.