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Review

Sickness: From the focus on cytokines, prostaglandins, and complement factors to the perspectives of neurons

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ABSTRACT

Systemic inflammation leads to a variety of physiological (e.g. fever) and behavioral (e.g. anorexia, immobility, social withdrawal, depressed mood, disturbed sleep) responses that are collectively known as sickness. While these phenomena have been studied for the past few decades, the neurobiological mechanisms by which sickness occurs remain unclear. In this review, we first revisit how the body senses and responds to infections and injuries by eliciting systemic inflammation. Next, we focus on how peripheral inflammatory molecules such as cytokines, prostaglandins, and activated complement factors communicate with the brain to trigger neuroinflammation and sickness. Since depression also involves inflammation, we further elaborate on the interrelationship between sickness and depression. Finally, we discuss how immune activation can modulate neurons in the brain, and suggest future perspectives to help unravel how changes in neuronal functions relate to sickness responses.

Contents

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1. Inflammation: the body's response to infection and injury

We have all suffered from infections and injuries. When they occur, the body responds by triggering a series of cellular (e.g. recruitment and activation of immune cells) and vascular (e.g. increased blood flow and vascular permeability) responses, which are collectively known as inflammation (Schmid-Schonbein, 2006). While these changes are aimed to (1) resist invading pathogens, (2) remove cell debris, and (3) facilitate wound recovery, they can become harmful when over-exaggerated, as exemplified in diabetes mellitus (Esser et al., 2014), cardiovascular diseases (Mangge et al., 2014), rheumatoid arthritis (Yoshida et al., 2014), systemic lupus erythematosus (Dai et al., 2014), and neurodegenerative diseases (Glass et al., 2010).

In order to initiate inflammation, at least two criteria must be met, (1) the immune system has to sense invading pathogens and damaged tissues, and (2) immune molecules have to be produced to direct inflammatory changes toward pathogens and injured tissues but not to healthy self-tissues (Schmid-Schonbein, 2006). In respect to pathogens, innate immune cells (e.g. macrophages/monocytes, neutrophils, natural killer cells, and dendritic cells) can use their pattern recognition receptors (PRRs) to specifically recognize and bind to pathogen associated molecular patterns (PAMPs) from pathogens (Bianchi, 2007; Kawai and Akira, 2009; Lee and Kim, 2007). PAMPs are evolutionarily conserved motifs that reside only in pathogens but not in self-tissues, thereby allowing immune cells to differentiate "self" from "non-self". PRRs are membrane-bound or secretory receptors. Upon associating with PAMPs, PRRs can stimulate intracellular mitogen activated protein kinase (MAPK), nuclear factor-kappaB (NF-κB), and interferon regulatory factor (IRF) signaling cascades, leading to the transcription of inflammatory molecules (e.g. cytokines) (Kawai and Akira, 2008). For instance, toll-like receptor 4 (TLR4) on the cell surface of macrophages interacts with lipopolysaccharide (LPS), an outer membrane component of Gram-negative bacteria, to induce the activation of MAPK and NF-κB pathways and the release of proinflammatory cytokines (Lu et al., 2008). Another example, polyriboinosinic:polyribocytidylic acid (polyI:C), a viral mimetic for double-stranded RNA viruses, is sensed by an intracellular PRR toll-like receptor 3 (TLR3), and this triggers the production of type I interferons and proinflammatory cytokines through IRF3- and NF-κB-dependent signaling (Matsumoto and Seya, 2008). In addition to the TLRs, many other classes of PRRs have been discovered, including nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) (Saleh, 2011), C-type lectin receptors (CLRs) (Osorio and Reis e Sousa, 2011), and retinoic-acid-inducible gene I (RIG-I)-like receptors (RLRs) (Kawai and Akira, 2009; Liu and Gu, 2011). Collectively, the different classes of PRRs enable innate immune cells to sense and respond to various PAMPs from a wide range of pathogens. On the other hand, inflammation can take place in the absence of any pathogenic stimulus, i.e. a process referred to as sterile inflammation (Chen and Nunez, 2010). This can be demonstrated when one accidentally dips a finger into boiling water, redness and swelling soon develop around the finger. The mechanisms by which sterile inflammation occur have been less studied. It is believed that injured and dead cells release endogenous danger signals known as alarmins, which can activate receptors and intracellular signaling cascades similar to those used by PAMPs (Bianchi, 2007; Rosin and Okusa, 2011). A good illustration of an alarmin is that high mobility group box-1 (HMGB1), a protein normally inside the nucleus to assist DNA bending, can be released from necrotic cells to induce NF-κB-dependent transcription of cytokines through TLR2 and TLR4 (Park et al., 2006a).

As mentioned, inflammatory mediators are required to regulate inflammatory responses to infections and injuries. For instance, IL-1β is a proinflammatory cytokine produced during inflammation that can stimulate human monocytes to elevate the expression of cyclooxygenase-2 (COX-2), i.e. the rate limiting enzyme involved in prostaglandins E2 (PGE_2) synthesis, and the downstream release of PGE_2 (Porreca et al., 1996). PGE_2 serves as a vasodilator to upregulate the local blood flow (Petersen et al., 2010), thereby bringing more immune cells and blood borne nutrients to facilitate the removal of pathogens and cell debris. Aside from controlling local inflammatory changes, inflammatory mediators may also act on distant organs, particularly when they enter the blood stream, i.e. systemic inflammation. A good example is that circulating interleukin-6 (IL-6) can take effect on the liver to promote the production of acute phase proteins such as C-reactive protein and serum amyloid-A (Banks et al., 1995; Betts et al., 1993; Bode et al., 2012; Streetz et al., 2001). These acute phase proteins are critical mediators in the complement cascade, and are important in helping phagocytes to clear up pathogens and cell debris.

In summary, inflammation is a set of physiological responses to infection and injury. It is orchestrated by different types of immune cells and a variety of inflammatory mediators (e.g. cytokines, prostaglandins, and complement factors). These inflammatory molecules not only act locally on neighboring immune cells to trigger their recruitment/activation, and on nearby vasculature to induce vasodilation and increase vascular permeability, but also communicate over great distances to other organs such as the liver to further boost up the immune response. This leads to another question: If systemic inflammatory mediators can act remotely to increase inflammation in other tissues and organs, is it possible for them to trigger inflammation in the brain?

2. Systemic inflammation causes brain inflammation

It is now quite clear that systemic inflammation can induce brain inflammation, or also known as neuroinflammation. In past literature, neuroinflammation was often defined by (1) elevated levels of cytokines (e.g. IL-1β, TNF-α, IL-6) and COX-2 in the brain (Cunningham et al., 2005; Huang et al., 2008; Lund et al., 2006), and by (2) an increased abundance of activated microglia (Chang et al., 2009; Kettenmann et al., 2011; Perry, 2010; Venneti et al., 2009). For example, a peripheral challenge of LPS not only leads to increased cytokines at the periphery (Kemna et al., 2005; Sadeghi et al., 1999), but also up-regulates cytokines and COX-2 expression in the brain (Cunningham et al., 2009; Czapski et al., 2010; Eriksson et al., 2000; Konsman et al., 2004; Murray et al., 2012; Quan et al., 1998; Skelly et al., 2013; Teeling et al., 2010; Teeling et al., 2007; van Dam et al., 1995; van Dam et al., 1992), and induces morphological shifts of microglia into an activated phenotype (Kozlowski and Weimer, 2012). Similarly, a systemic injection of poly(I:C) can increase cytokines and type I interferons at the periphery (Cunningham et al., 2007; Field et al., 2010; Starkhammar et al., 2012; Stowell et al., 2009) and in the brain (Cunningham et al., 2007; Field et al., 2010; Konat et al., 2009; Yamato et al., 2014). Although it is possible for LPS (Obuchowicz et al., 2014; Singh and Jiang, 2004) and poly(I:C) (Ott et al., 2012) to act directly on the brain to lead to neuroinflammation, several studies have indicated that systemic injection of cytokines (e.g. IL-1β, TNF-α) alone is sufficient to trigger inflammatory changes in the brain (Cao et al., 1996; Konsman et al., 2004; Skelly et al., 2013). Furthermore, injury in peripheral tissues per se can cause brain inflammation. This can be exemplified by the bile duct ligation and resection procedure, which has been studied in rodents to induce liver injury. It is characterized by a prolonged period (i.e. weeks) of hepatic inflammation together with elevated levels of circulating cytokines (Fernandez-Martinez et al., 2006). Following this procedure, mice display an increased abundance of morphologically activated microglia in the periventricular and perivascular areas in the brain, and a greater