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Invited Review

Liver–brain interactions in inflammatory liver diseases: Implications for fatigue and mood disorders

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ABSTRACT

Chronic inflammatory liver diseases are often accompanied by behavior alterations including fatigue, mood disorders, cognitive dysfunction and sleep disturbances. These altered behaviors can adversely affect patient quality of life. The communication pathways between the inflamed liver and the brain that mediate changes in central neural activity leading to behavior alterations during liver inflammation are poorly understood. Neural and humoral communication pathways have been most commonly implicated as driving peripheral inflammation to brain signaling. Classically, the cytokines TNFα, IL-1β and IL-6 have received the greatest scientific attention as potential mediators of this communication pathway. In mice with liver inflammation we have identified a novel immune-mediated liver-to-brain communication pathway whereby $CCR2^+$ monocytes found within the peripheral circulation transmigrate into the brain parenchyma in response to MCP-1/CCL2 expressing activated microglia. Inhibition of cerebral monocyte infiltration in these mice significantly improved liver inflammation associated sickness behaviors. Importantly, in recent work we have found that at an earlier time point, when cerebral monocyte infiltration is not evident in mice with liver inflammation, increased monocyte:cerebral endothelial cell adhesive interactions are observed using intravital microscopy of the brain. These monocyte:cerebral endothelial cell adhesive interactions are P-selectin mediated, and inhibition of these interactions attenuated microglial activation and sickness behavior development. Delineating the pathways that the periphery uses to communicate with the brain during inflammatory liver diseases, and the central neurotransmitter systems that are altered through these communication pathways (e.g., serotonin, corticotrophin releasing hormone) to give rise to liver inflammation-associated sickness behaviors, will allow for the identification of novel therapeutic targets to decrease the burden of debilitating symptoms in these patients.

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1. Introduction

Systemic inflammatory diseases are commonly accompanied with alterations in behavior which result from changes in central neurotransmission. These changes in behavior, which include fatigue, increased anxiety, loss of appetite, sleep disturbances and loss of social interest are collectively termed sickness behaviors. During acute systemic infections, sickness behaviors can serve an adaptive purpose. However, during chronic inflammation increased prevalence of sickness behaviors can greatly affect patient quality of life (Dantzer et al., 2008; DMello and Swain, 2011). Despite the high incidence of sickness behaviors and mood disorders in patients with chronic inflammatory diseases (e.g., rheumatoid arthritis, inflammatory bowel disease, inflammatory liver disease), they have received little attention due to a limited understanding of how these changes within the CNS develop in the setting of peripheral organ centered inflammation. Furthermore, changes in central neural activity that give rise to behavioral alterations can occur in the absence of any pathological CNS tissue damage. In order to mediate changes within the brain during systemic inflammation, pathways of communication must exist between the periphery and the brain. This review outlines how the inflamed liver communicates with the brain and the changes in behavior, specifically fatigue and mood disorders, that likely occur as a result of this communication. Observations made in clinical studies involving patients with hepatitis C (Hep C) and the cholestatic liver disease primary biliary cirrhosis (PBC) are mainly discussed.

2. Unique immunological environment of the liver

The liver is a unique anatomical and immunological site. It serves as a barrier between the gut and the body and is constantly exposed to low levels of endotoxin and dietary antigens present in the blood and arriving from the gut via the portal vein. Hepatocytes occupy ~80% of the total liver tissue. The remaining population of

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non-parenchymal cells is diverse and includes sinusoidal endothelial cells, Kupffer cells, biliary cells, stellate cells and intrahepatic lymphocytes (Bogdanos et al., 2013).

T cell biology in the liver is unlike that of any other organ. The liver contains a population of resident lymphocytes that includes conventional $CD4^+$ and $CD8^+$ T cells. $CD8^+$ T cells usually outnumber $CD4^+$ T cells in the liver and the frequency of effector/memory cells is higher than in the blood. Natural Killer (NK) T cells are more abundant in the human liver compared to other organs constituting up to 15% of the lymphocyte population. NKT cells have been observed to crawl within the liver sinusoids (Lee et al., 2010). On activation, NKT cells produce large amounts of cytokines including interferon (IFN)-γ (Th-1 type), interleukin (IL)-4 (Th-2 type) and IL-17 (Th-17 type) and thereby have important immunoregulatory roles (Swain, 2008). The production of Th-1 cytokines such as IFN-γ can mediate activation of other cell types within the liver, including NK cells and macrophages. NK cells are also enriched within the liver. On activation, NK cells can produce pro-inflammatory cytokines such as IFN-γ (Vermijlen et al., 2002). Unconventional T cells that do not express NK cell markers include the γδ T cells and make up ~20% of T cells in the liver, thereby making the liver one of the richest sources of γδ T cells in the body (Bogdanos et al., 2013). γδ T cells are suggested to play a prominent role in innate defenses against viral and bacterial infections and against tumors (Hou et al., 2013).

Kupffer cells constitute the largest population of tissue macrophages, accounting for about 80–90% of tissue macrophages present in the body. They are found immobilised mainly in the hepatic sinusoids with extensions in as many as five sinusoids (Lee et al., 2010). Kupffer cells can produce a broad range of pro-inflammatory cytokines including tumor necrosis factor (TNF)-α, IL-1β and IL-6, as well as anti-inflammatory mediators such as IL-10 (Bogdanos et al., 2013). Kupffer cells have been reported to have significant immunomodulatory roles in models of liver inflammation as described below. They can influence the recruitment of immune cells into the liver as was demonstrated in mice with liver inflammation induced by bile duct ligation, where depletion of Kupffer cells resulted in reduced infiltration of $Ly6C^{hi}$ monocytes (Duwaerts et al., 2013). Depletion of Kupffer cells has also been associated with a reduction in chemokine and adhesion molecule expression within the liver as was evident in a rat model of biliary obstruction and repair where Kupffer cell depletion was associated with reduced hepatic CXCL-1 and ICAM-1 expression, together with reduced hepatic infiltration of neutrophils (Harty et al., 2008). Kupffer cells can also influence the activity of cells recruited into the liver during liver inflammation. This was demonstrated in mice with liver inflammation induced by bile duct ligation where $Ly6C^{hi}$ infiltrating monocytes from Kupffer cell depleted mice were observed to produce lower amounts of TNFα, and the chemokines KC, MIP-2 and MCP-1/CCL2 compared to $Ly6C^{hi}$ monocytes from mice without Kupffer cell depletion (Duwaerts et al., 2013). In addition, interactions between Kupffer cells and other hepatic resident immune cells, such as NK cells, have been observed to play significant roles in regulating inflammation within the liver. Depletion of Kupffer cells suppressed activation of NK cells in mice with liver inflammation induced by bile duct ligation (Cheng et al., 2011). Furthermore, in vitro studies with Kupffer cells and hepatic NK cells demonstrated that Kupffer cell IL-6 production was dependent on NK cell production of IFN-γ (Cheng et al., 2011). It should also be mentioned that in addition to Kupffer cells, depletion of other hepatic resident immune cells, such as NK cells (Cheng et al., 2011) or NKT cells (Philip Wintermeyer et al., 2009), is also associated with modulation of inflammation in models of liver inflammation. For instance, depletion of NKT cells was shown to affect hepatic KC and IL-4 levels and was also associated with increased hepatic recruitment of neutrophils in mice with liver inflammation induced by bile duct ligation (Philip Wintermeyer et al., 2009). Therefore, the interaction between different cell types within the liver can drive chemokine and cytokine production within the liver, which in turn regulates cellular recruitment into the liver and the inflammatory process in general during liver inflammation.

3. Potential routes of communication between the periphery and the brain

Much of our understanding of how the periphery communicates with the brain comes from animal models that have examined central changes induced by systemic administration of the gram negative bacterial cell wall component lipopolysaccharide (LPS). LPS is a potent inducer of a range of cytokines; however three cytokines in particular have received the most attention as mediating communication between the periphery and the CNS; namely, TNFα, IL-1β and IL-6. Administration of endotoxin or cytokines to healthy subjects or rodents results in the development of sickness behaviors and depressed mood (Dantzer et al., 2008; Hannestad et al., 2012). It is likely that the mechanisms promoting changes within the brain share common processes in different systemic inflammatory settings. In patients with a range of peripheral organ inflammatory diseases including chronic liver disease (Neuman et al., 2002), psoriasis (Roussaki-Schulze et al., 2005), inflammatory bowel disease (Louis et al., 1997), diabetes (Lasselin et al., 2012) or rheumatoid arthritis (Riccio et al., 2012), circulating levels of cytokines such as TNFα or IL-6 are reported to be elevated. Furthermore, peripheral administration of cytokine antagonists improves sickness behaviors in a number of inflammatory diseases, thereby highlighting the importance of peripheral cytokines in communicating with the brain to mediate sickness behavior development. For instance, treatment with an IL-6R or an anti-TNFα antagonist is associated with improvement in fatigue in patients with rheumatoid arthritis (Strand et al., 2012) or inflammatory bowel disease (Lichtenstein et al., 2002) respectively. Possible similarities in periphery-to-brain communication pathways promoting sickness behaviors is also highlighted in a model of murine stress (i.e., social defeat) and in mice with central inflammation induced by intracerebral IL-1β administration. In mice subjected to social defeat, the monocyte mediated periphery-to-brain communication pathway seen in mice with liver inflammation (described below) has also been observed. In mice subjected to social defeat, recruitment of monocytes into the brain was evident and was found to be integral for mediating anxiety-like behaviors (Wohleb et al., 2013). Furthermore, circulating TNFα plays a key role in communication between the periphery and the brain in mice with liver inflammation (described below). In rodents with intracranial IL-1β or LPS induced central inflammation, neutralization of circulating TNFα using etanercept treatment was associated with a reduction in cerebral neutrophil recruitment (Campbell et al., 2007b).

Communication between the periphery and the brain is likely to occur via four main pathways (1) neural pathways, (2) signaling via cerebral endothelial cells (CECs), (3) signaling via circumventricular organs (CVOs) and (4) cerebral infiltration of monocytes (Fig. 1).

3.1. Neural pathway

Several organs in the body, including the liver, are innervated by vagal afferents. Vagal nerve afferents express cytokine receptors, including IL-1R, and have macrophages interspersed between vagal fibers that could also respond to cytokines (Ek et al., 1998). Rodents treated with LPS intraperitoneally show increased Fos (protein expressed by the immediate early gene c-fos; used as an indicator of neuronal activation) expression in the vagal afferent

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