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Review article

How cytokines can influence the brain: A role for chemokines?

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Abstract

Following inflammation or infection, cytokines are released in the blood. Besides their effect on the immune system, cytokines can also act in the brain to modulate our behaviors, inducing for example anorexia when produced in large amount. This review focuses on our current knowledge on how cytokines can influence the brain and the behaviors through several possible pathways: modulating peripheral neurons which project to the brain through the vagus nerve, modulating the levels of hormones such as leptin which can act to the brain through the humoral pathway and possibly acting directly in the brain, through the local production of cytokines and chemokines such as SDF-1α/CXCL12.
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Keywords: Cytokines; Chemokines; Hypothalamus; Inflammation; LPS; Neurons

Contents

1. Introduction

Infection and inflammation result in a number of metabolic changes that are often characterized by negative energy balance, increased thermogenesis and anorexia (Dantzer and Kelley, 2007; Johnson, 1998). In experimental animals, these changes can be induced by exposure to the bacterial cell wall product lipopolysaccharide (LPS), which suppresses appetite and triggers a number of other behavioral responses including sleep, general malaise and fever. These responses are mediated by cytokines, a family of immune products induced by LPS that can act to activate sickness-type behavior (Konsman et al., 2002). Cytokines produced during inflammation or infection can affect the brain by several pathways (Fig. 1): they can act on peripheral tissues producing hormones such as leptin which influence the activity of the brain; they can act on peripheral neurons which project to the brain through the vagus nerve; they can also directly enter the brain and act locally, as the permeability of the blood brain barrier (BBB) is increased by LPS (Wispelwey et al., 1988). The aim of this review is to summarize

Abbreviations: ATP, adenosine tri-phosphate; BBB, blood brain barrier; CCK, cholecystokinin; GIRK, G-protein activated inward rectifier potassium; GPCRs, G protein coupled receptors; IL, interleukin; ip, intraperitoneal; LHA, lateral hypothalamus; LPS, lipopolysaccharide; MCH, melanin-concentrating hormone; MCP1, monocyte attractant protein 1/CCL2; NO, nitric oxide; POMC, pro-opiomelanocortin; ROS, reactive oxygen species; SDF-1α, stromal cell-derived factor 1α/CXCL12; TNF, tumor necrosis factor.

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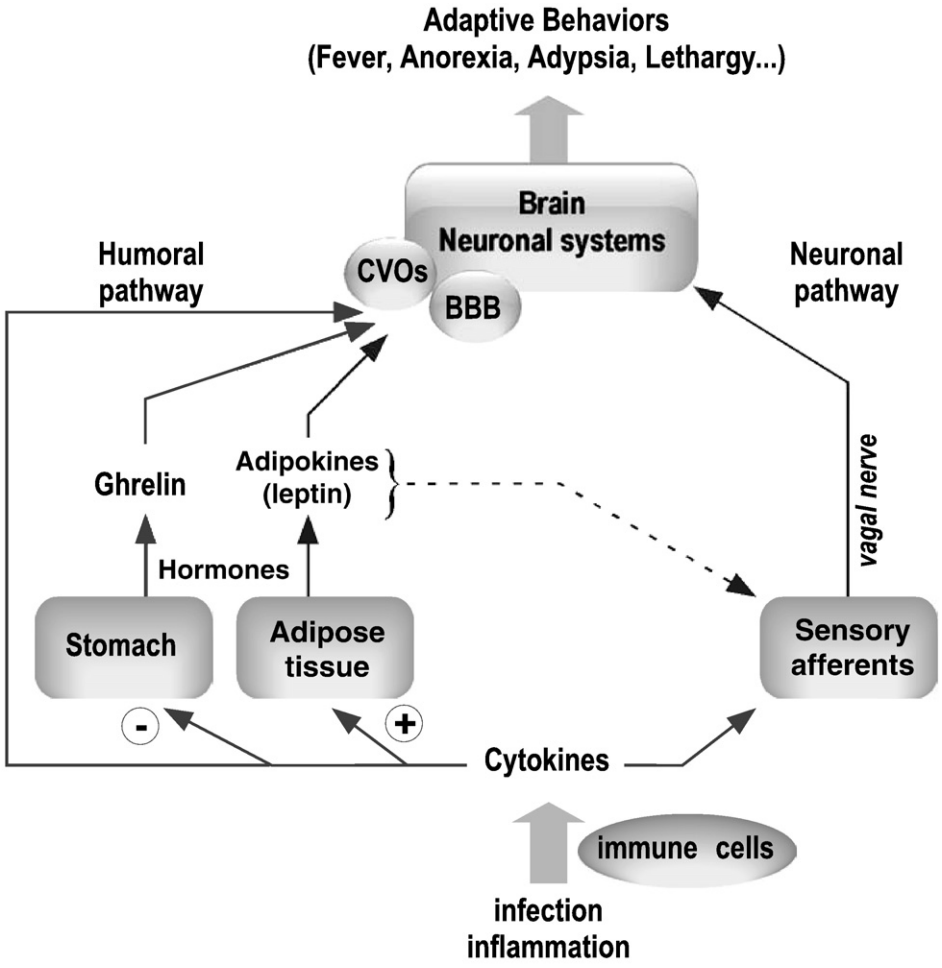

Fig. 1. Infection and inflammation can influence the brain through different pathways. Cytokines produced by immune cells can act on peripheral sensory afferents which project to the brain (neuronal pathway). Cytokines can also induce the modification of hormone release (ghrelin, adipokines such as leptin) in the blood by peripheral tissues (stomach or adipose tissue). These hormones can reach the brain and act on the various neuronal systems regulating adaptive behaviors and/or modify the activity of sensory afferent neurons. Finally, cytokines can directly affect the brain activity at the level of the circum ventricular organs (CVOs) or can enter the brain through the blood brain barrier (BBB). The increase in cytokine concentration in the brain leads to perturbations in the activity of several neuronal systems controlling adaptive behaviors.

recent data showing that cytokines and chemokines can modulate the activity of several neuronal populations which may have a role under physiological and/or pathological conditions.

2. Cytokines can affect the level of hormones which modulate brain neuronal activity

Adipokines are cytokines secreted by adipose tissue which can play important roles in modifying appetite, but also insulin resistance and atherosclerosis (MacDougald and Burant, 2007; Monzillo et al., 2003). Members include: leptin, adiponectin, chemerin, interleukin-6 (IL-6), resistin, tumor necrosis factor-alpha (TNF-α), and visfatin. They are the subjects of intense research, as they may be modifiable causes of morbidity in people with obesity (Yudkin, 2007).

Leptin is transported into the brain where it decreases appetite and increases body temperature. LPS is known to increase leptin synthesis and secretion at the periphery (Sachot et al., 2004). Leptin is able to modulate in a coordinated manner the activity of neurons of the hypothalamus expressing leptin receptor, stimulating neurons of the arcuate nucleus producing anorexigenic peptides such as such Pro-opiomelanocortin (POMC) neurons and inhibiting neurons producing orexigenic peptides such as NPY neurons.

Similarly, LPS injections increase resistin and cholecystokinin (CCK) plasma levels (Lu et al., 2002; Weiland et al., 2005), both peptides being anorexigenic (Hayes and Covasa, 2005; Tovar et al., 2005). In the same way, LPS increases insulin levels (Kim et al., 2007). By contrast, ghrelin is a peptide hormone produced by the stomach with a potent orexigenic effect and plasma levels that are inversely correlated with the fed state. Intraperitoneal (ip) injections of LPS to rats decrease ghrelin levels in fasted rats compared to those observed post-prandially (Basa et al., 2003). IL-1α or β and prostaglandin pathways are part of the early mechanisms by which LPS suppresses fasted plasma ghrelin (Wang et al., 2006). Therefore, inflammation can lead to variation in the concentration of various hormones and peptides in the blood which can influence the brain.

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