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Effects of cytokines and infections on brain neurochemistry

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Abstract

Administration of cytokines to animals can elicit many effects on the brain, particularly neuroendocrine and behavioral effects. Cytokine administration also alters neurotransmission, which may underlie these effects. The most well studied effect is the activation of the hypothalamo–pituitary–adrenocortical (HPA) axis, especially that by interleukin-1 (IL-1). Peripheral and central administration of IL-1 also induces norepinephrine (NE) release in the brain, most markedly in the hypothalamus. Small changes in brain dopamine (DA) are occasionally observed, but these effects are not regionally selective. IL-1 also increases brain concentrations of tryptophan, and the metabolism of serotonin (5-HT) throughout the brain in a regionally non-selective manner. Increases of tryptophan and 5-HT, but not NE, are also elicited by IL-6, which also activates the HPA axis, although it is much less potent in these respects than IL-1. IL-2 has modest effects on DA, NE and 5-HT. Like IL-6, tumor necrosis factor-α (TNFα) activates the HPA axis, but affects NE and tryptophan only at high doses. The interferons (IFN's) induce fever and HPA axis activation in man, but such effects are weak or absent in rodents. The reported effects of IFN's on brain catecholamines and serotonin have been very varied. However, interferon-γ, and to a lesser extent, interferon-α, have profound effects on the catabolism of tryptophan, effectively reducing its concentration in plasma, and may thus limit brain 5-HT synthesis.

Administration of endotoxin (LPS) elicits responses similar to those of IL-1. Bacterial and viral infections induce HPA activation, and also increase brain NE and 5-HT metabolism and brain tryptophan. Typically, there is also behavioral depression. These effects are strikingly similar to those of IL-1, suggesting that IL-1 secretion, which accompanies many infections, may mediate these responses. Studies with IL-1 antagonists, support this possibility, although in most cases the antagonism is incomplete, suggesting the existence of multiple mechanisms. Because LPS is known to stimulate the secretion of IL-1, IL-6 and TNFα, it seems likely that these cytokines mediate at least some of the responses, but studies with antagonists indicate that there are multiple mechanisms. The neurochemical responses to cytokines are likely to underlie the endocrine and behavioral responses. The NE response to IL-1 appears to be instrumental in the HPA activation, but other mechanisms exist. Neither the noradrenergic nor the serotonergic systems appear to be involved in the major behavioral responses. The significance of the serotonin response is unknown.

Keywords: Cytokine; Interleukin; Interferon; Dopamine; Norepinephrine; Serotonin; Acetylcholine; Tryptophan; Fos; Neurochemistry; Behavior; HPA axis; Cyclooxygenase

1. Introduction

Once it had been accepted that the immune system communicated with the nervous system, and that the nervous system could exert important influences on the immune system, the important question became how. The 'how' is obviously complex: how does the immune system send signals to the central nervous system (CNS), and what are the effects on the brain? How does the CNS respond to those effects and communicate with the other organs in the body to implement any necessary responses, and how does the CNS signal the immune system and affect its functions? This chapter addresses these questions: what are the responses in the brain to signals from the immune system, and what effects do those responses induce?

The first indications that the immune system might affect brain neurochemistry arose from studies that indicated that neurophysiological changes in the brain occurred to immune challenges. A study of Besedovsky et al. indicated that an immune challenge to rats with red blood cells from

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sheep (SRBC) altered the firing of neurons in the hypothalamus [1], and some similar observations were reported by Klimenko [2]. This finding complemented earlier studies that showed that challenges with SRBC, trinitrophenyl-hemocyanin or trinitrophenyl-horse red blood cells elevated plasma concentrations of corticosterone [3]. Subsequent studies by Besedovsky et al. indicated that injection of SRBC also affected norepinephrine (NE) metabolism in the hypothalamus, specifically the SRBC challenge decreased the turnover of NE in the hypothalamus [4]. This was one of the earliest reports linking immune system function to neurochemical changes in the brain.

There are only two major mechanisms, by which organ systems can communicate, neural and endocrine (using endocrine in the broadest sense of a systemic chemical messenger). Thus, the immune system most likely uses an endocrine-like mechanism, sending messages to the brain, using chemical messengers released by immune cells or organs. By the 1980s, the immune system was known to synthesize and secrete a number of chemical messengers, which were known generically as cytokines (originally a distinction was made between lymphokines (from lymphocytes) and monokines (from monocytes), but this has now been abandoned in favor of calling all such factors cytokines). Thus, attention was immediately focused on cytokines as the immune messengers to the brain. Besedovsky et al. challenged lymphocytes in vitro with concanavalin A (ConA), and administered the supernatants to rats and observed an increase in plasma corticosterone [5]. It was also shown that similarly prepared supernatants when injected into rats reduced the concentrations of NE in the hypothalamus and brainstem [4]. Thus, they suggested that some soluble factor secreted by the immune cells in vitro (e.g. a lymphokine or cytokine) was responsible for this response.

A second seminal discovery, also arose from Besedovsky's laboratory, namely that purified recombinant interleukin-1 (IL-1) administered intraperitoneally (ip) to rats potently activated the hypothalamo–pituitary–adrenocortical (HPA) axis, elevating plasma concentrations of ACTH and corticosterone (the major glucocorticoid hormone in the rat) [6]. This property of IL-1 was rapidly confirmed by several other groups in several different species (see review [7]). Subsequently, Dunn, in mice [8], and Besedovsky's group, in rats [9], showed that ip IL-1 activated NE metabolism in the brain, especially in the hypothalamus. Because, NE had long been known to be involved in activation of the HPA axis [10,11], this immediately suggested that the NE activation was instrumental in the HPA activation. Dunn and Kabiersch et al. also showed that the neurochemical effects of IL-1 were not confined to NE, but serotonin (5-hydroxytryptamine, 5-HT) metabolism was also increased, as were concentrations of tryptophan (the essential precursor for 5-HT) were also increased throughout the brain [8,9].

2. Neurochemical responses to cytokines

(A summary of these effects appears in Table 1.)

2.1. Interleukin-1 (IL-1)

2.1.1. Effects on catecholamines

As indicated above, a key observation was that ip IL-1 administration to mice or rats increased the brain concentrations of the catabolites of NE, suggesting that the release of this neurotransmitter was increased [8,9,12,13]. The initial reports were based on an increase in the brain content of 3-methoxy,4-hydroxyphenylethyleneglycol (MHPG), a major catabolite of NE. This response occurred in every brain region studied, but the magnitude of the response was greatest in the hypothalamus, and other structures innervated by the ventral noradrenergic projection system (the ventral noradrenergic bundle, VNAB). It was smaller in those innervated by the dorsal noradrenergic bundle (DNAB), such as the cerebral cortex, hippocampus and cerebellum. Within the hypothalamus, the greatest response occurred in the medial part containing the paraventricular nucleus (PVN). The interpretation of these catabolite studies as reflecting increased neurotransmitter release were supported by subsequent studies using microdialysis which can directly assess extracellular concentrations of neurotransmitters. Microdialysate NE from the hypothalamus was increased following peripheral IL-1 administration [14–17]. Complementary data were

Table 1
Comparison of HPA and brain neurochemical responses to viral infection, LPS and some cytokines

Stimulus	Corticosterone	NE	DA	Tryptophan	5-HT
Influenza virus	+	+	0	+	+
LPS	+	+	+	+	+
IL-1α/IL-1β	+	+	0	+	+
IL-2	0	+	+	n.d.	0
IL-6	+	0	0	+	+
TNFα	+	(+)	0	(+)	0
IFNα	0	0	0	0	0

+, increased; 0, no change; n.d., not determined; (+), indicates increases only at high doses.