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Connection between inflammatory processes and transmittor function—Modulatory effects of interleukin-1

Stefan Spulber [1], Marianne Schultzberg *

Department of Neurobiology, Care Sciences and Society, Division of Neurodegeneration, Karolinska Institutet, SE-141 86 Stockholm, Sweden

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ABSTRACT

Cells in the nervous system can respond to different kinds of stress, *e.g.* injury, with production and release of inflammatory molecules, including cytokines. One of the most important proinflammatory cytokines is interleukin-1, affecting most organs of the body. The high constitutive expression of interleukin-1 in the adrenal gland provides a source for local and systemic actions, in addition to activated monocytes. In the brain, the constitutive expression is low, but activated microglia produce and release interleukin-1 during pathological conditions such as neurodegenerative disorders (*e.g.* stroke, traumatic brain injury, Alzheimer's disease, Parkinson's disease). Interleukin-1 has an important role in mediating 'sickness symptoms' such as fever, in response to infections. Its role in neurodegeneration is not fully elucidated, but there is evidence for involvement in both amyloidosis and tau pathology, major neuropathological hallmarks of Alzheimer's disease. The interleukin-1 family at present consists of 11 members, one of which is the endogenous receptor antagonist. Overexpression of this antagonist in the CNS in a transgenic mouse strain, Tg hsIL-1ra, has allowed studies on morphological and functional effects of blocking interleukin-1 receptor-mediated activity in the brain. Marked alterations of brain morphology such as reduced hippocampal and cortical volume correlate with behavioural deficits. Decreased anxiety and impaired long-term memory are among the consequences. Intact interleukin-1 signalling is important for the brain's ability to adapt to acute and chronic neuroinflammation. Increased amplitude and prolongation of proinflammatory cytokine production underly the behavioural alterations characteristic for ageing. Moreover, deregulated expression of interleukin-1 is associated with ageing-related chronic neurodegenerative disorders.

Contents

Abbreviations: AD, Alzheimer's disease; Arc, activity-regulated cytoskeleton-associated protein; Aβ, β-amyloid; BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; IL-1, interleukin-1; IL-1F, interleukin-1 family; IL-1R, interleukin-1 receptor; IL-1ra, interleukin-1 receptor antagonist; Tg hsIL-1ra, transgenic mouse strain with overexpression of human soluble IL-1ra.

* Corresponding author at: Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Novum, Floor 5, SE-141 86 Stockholm, Sweden. Tel.: +46 8 585 83889, fax: +46 8 585 83880.
E-mail address: Marianne.Schultzberg@ki.se (M. Schultzberg).
[1] Present address: Department of Neuroscience, Karolinska Institutet, SE-171 77 Stockholm, Sweden.

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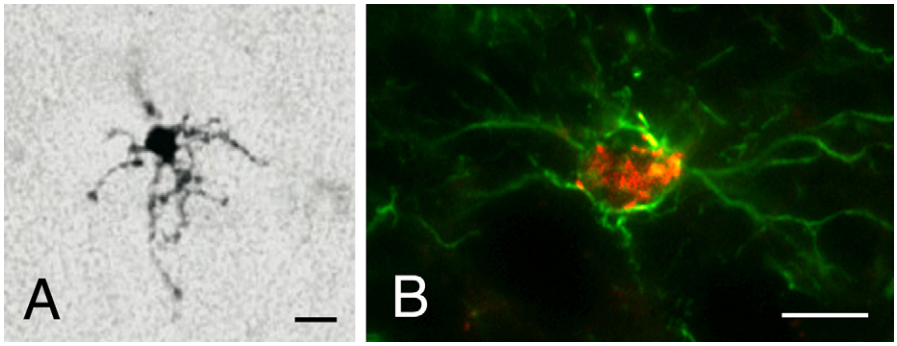

Fig. 1. (A and B) Micrographs of an activated microglial cell containing IL-1β (A) and an astrocyte with transgenic expression of hsIL-1ra (B). (A) Shows a microglial cell activated by systemic administration of kainic acid (KA) in the rat. (B) The transgene hsIL-1ra (red) is co-localized with the astrocytic protein GFAP (green) in the brain of the transgenic mouse strain Tg hsIL-1ra (Lundkvist et al., 1999). Scale bar 10 μm.

1. Introduction

The nervous system has been considered an 'immune-privileged site'. However, more recently evidence has emerged that the brain and other parts of the nervous system can mount an inflammatory response. Thus, it is now well accepted that certain cells in the nervous system can respond to different kinds of stress, including injury with production and release of inflammatory molecules, such as cytokines. The major cell type responsible for this in the brain is microglia, but also astrocytes are known to produce and secrete inflammatory factors upon activation in response to different stressful stimuli.

Many proteins act on or 'move' cells, hence cyto-kines, but this term has come to include mainly those proteins involved in immune responses. Cytokines may have either proinflammatory or anti-inflammatory activity, interleukin-1 (IL-1) being the most well-known and best studied proinflammatory cytokine (see Dinarello, 1994). IL-1 has multiple actions, both in the immune system and other systems and organs, notably the nervous system. Many aspects regarding the role of IL-1 in the nervous system remain to be clarified, and here we will analyse some of these aspects, both in relation to normal and to pathological conditions.

1.1. The IL-1 system

Initially known as a family of two isoforms, IL-1α and IL-1β, there is now at least 11 known members of the IL-1 family (IL-1F1–11), interacting with IL-1 receptor proteins IL-1R1–9 or related proteins (see Arend et al., 2008; Dinarello, 2009; O'Neill, 2008). IL-1α (IL-1F1) and IL-1β (IL-1F2) are synthesised as 31 kDa precursor proteins, which are cleaved by specific proteases to 17 kDa proteins. IL-1β-converting enzyme (ICE), or caspase-1, cleaves the IL-1β precursor to its active secreted form. In contrast, pro-IL-1α is also biologically active and, in the human, IL-1α is mainly considered to have an autocrine role, presumably through binding to intracellular receptors (Dinarello, 2009). Murine cells do secrete IL-1α, but further studies are required to distinguish, at each location, which isoform is responsible for the bioactivity.

Both IL-1α and IL-1β bind to the type I and type II receptors (IL-1RI or IL-1R1, and IL-1RII or IL-1R2), and both of these receptors occur in a membrane-bound and a soluble form. The soluble IL-1RII (sIL-1RII) serves as one of the regulatory factors of IL-1-mediated activity, by binding IL-1 and preventing its binding to the signalling, membrane-bound IL-1RI. In order for signal transduction to occur following this binding, the receptor has to interact with the IL-1R accessory protein (IL-1RAcP). IL-1-mediated activity is inhibited by an endogenous receptor antagonist, IL-1ra, that upon binding to IL-1RI prevents the interaction with IL-1RAcP. The existence of these two endogenous regulators of IL-1 bioactivity emphasizes the potency of this cytokine and the need to control its actions.

1.2. Location of IL-1 synthesis

The main source of IL-1 in the periphery is monocytes, which upon activation secrete the cytokine. In the nervous system, microglial cells (see Fig. 1), the equivalent of peripheral monocytes, is the predominant source. Microglial production of IL-1, and other cytokines, is induced upon different kinds of stress such as mechanical injury and cerebral ischemia (see below). IL-1 production has also been documented in neurons and astrocytes as well as pericytes (see Dinarello, 1994). Under normal conditions, the levels of IL-1 are low, both in the circulation and in the CNS, whereas upon infection, injury or other types of insults/stimuli, an abrupt but transient increase in the IL-1 levels occurs, and in a healthy, young mouse brain the levels of expression of IL-1 return to normal within 8 h (see Rooker et al., 2006). However, IL-1 binds to its receptors with high affinity and hence only low concentrations are required for a biological response. Interestingly, comparatively high basal levels of IL-1 are found in the adrenal gland (Schultzberg et al., 1989, 1995). Both IL-1α and IL-1β, as well as the endogenous receptor antagonist are produced in quantifiable levels in both adrenal medulla and cortex of the rat, albeit with different distribution (Schultzberg et al., 1989, 1995). IL-1α is localized to the noradrenergic chromaffin cells, *i.e.* cells lacking phenyl-N-methyltransferase (PNMT), the enzyme converting noradrenaline to adrenaline. This is also the case in the mouse adrenal gland, although some adrenaline chromaffin cells seem to produce the cytokine. IL-1β and IL-1ra have a complementary distribution to IL-1α, both mainly produced in the adrenaline cells (Schultzberg et al., 1995). The occurrence of IL-1 in adrenal chromaffin cells thus adds to the list of bioactive peptides/proteins, such as enkephalin (Schultzberg et al., 1978) and neuropeptide Y (NPY) (Lundberg et al., 1986) that are colocalized with catecholamines. The expression of IL-1 in the adrenal gland is elevated by bacterial lipopolysaccharides (LPS), along with enkephalin (Nobel and Schultzberg, 1995). The cholinergic agonists nicotine and carbachol increase IL-1α mRNA levels in the rat adrenal gland, but decrease IL-1α protein levels (Andersson et al., 1992), suggesting that the adrenal gland is a source of this cytokine in situations when adrenal catecholamines are released. Depletion of IL-1 from the rat adrenal chromaffin cells by reserpine also indicates release concomitant with the catecholamines (Schultzberg et al., 1989). Recent studies have shown that IL-1β stimulates catecholamine release from mouse chromaffin cells through NPY (Rosmaninho-Salgado et al., 2007).