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Neuroimmune interactions: the role of cytokines

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Introduction

The concept of the brain as an 'immune privileged' organ has been modified significantly with the realization that interactions between the nervous and immune systems are important in many aspects of disease and injury. Peripheral infection, inflammation and injury activate afferent neuronal and homoral signals to the brain, which in turn influence or regulate specific aspects of the host acute phase response. Many molecules and pathways associated with immune or inflammatory responses have been identified within the central nervous system and are activated in response to peripheral disease or injury and diverse neurological disorders. Cytokines are polypeptide mediators most widely associated with the inflammation and immunity in the periphery and play a key role in many of these interactions. This review will focus mainly on the 'proinflammatory cytokines', interleukin-1 (IL-1), IL-6 and tumour necrosis factor α (TNFα), which are expressed by, and act on the brain, and have been implicated in many aspects of neuroimmunology.

Central nervous system regulation of host defence responses to peripheral disease

The host defence response, also known as the acute phase response, includes changes on both local (eg inflammation within specific tissues) and systemic functions. The central nervous system regulates important aspects of this response including fever, anorexia, hypermetabolism, neuroendocrine changes (most notably activation of the hypothalamic-pituitary-adrenal, axis), alterations in behaviour, cardiovascular and reproductive function and even some aspects of immune activation. Much of our understanding of the local and afferent pathways regulating these changes has derived from studies on fever. Fever is still one of the most widely used diagnostic tools in clinical medicine, it is a phylogenetically old response which has even been observed in poikilotherms, can be readily and continuously monitored in free-moving subjects and animals by remote radiotelemetry, and appears to share common mechanisms with several central nervous system-dependent acute phase responses (Kluger, 1991; Roberts, 1991).

Studies on fever and other neuroimmune responses in rodents have most often used systemic (intraperitoneal or intravenous) administration of bacterial lipopolysaccharide as a stimulus, which has provided much valuable information on fever and other central nervous system responses to infection (eg see Kluger, 1991). However, this approach has several potential disadvantages. High doses of lipopolysaccharide are required to induce fever in rats and mice, so injected lipopolysaccharide could act at numerous sites including in the brain

itself, and it is not possible to study local pathways or mediators within specific sites of infection or inflammation. Nevertheless, lipopolysaccharide-induced fever is associated with dramatic increases in circulating IL-6 and release of cytokines in the brain and is inhibited by blocking IL-1 actions at both sites (Le May et al., 1990; Rothwell et al., 1991). We have previously demonstrated that a sterile abscess induced by an intramuscular injection of turpentine (which does not diffuse into circulation) also elicits marked fever in the rat and, like lipopolysaccharide, is associated with increases in circulating IL-6 of many orders of magnitude (Turnbull et al., 1992; Cooper et al., 1994; Miller et al., 1997b). Indeed circulating IL-6 levels correlate with the rising phase of fever, although there may be a threshold level for IL-6, or existence of co-factors which are required to act synergistically with IL-6 in pyrogenesis (Turnbull, 1993).

However, in these and many other experimental systems, little or no increase in circulating IL-1 is detected in circulation, although blocking IL-1 by injection of a neutralizing antibody or recombinant interleukin-1 receptor antagonist (IL-1ra) significantly attenuates fever (Long et al., 1990; Miller et al., 1997a). These data question the hypothesis that IL-1 is the primary circulating endogenous pyrogen, but nevertheless indicate an important role in fever and suggest that it may act locally within infected or inflamed tissue.

In order to address these issues we have studied the effects of administering pyrogens into a sterile, subcutaneous air pouch which allows sampling of local cytokine production and modification of cytokine activities within the air pouch without direct effects of the stimulus on distant tissues. Injection of lipopolysaccharide (100 μg kg^{-1}) into such an air pouch in the rat elicits marked fever, of comparable magnitude to that seen in response to intraperitoneal injection of lipopolysaccharide. No increases in bioactive IL-1 or TNFα are identified in circulation (Figure 1) in response to either stimulus, but the bioactivity of both of these cytokines increases dramatically (30–1000 fold) in fluid sampled from the air pouch after lipopolysaccharide (Miller, 1996; Miller et al., 1997a, b). TNFα is the first cytokine detected (by 30 min after lipopolysaccharide) in the air pouch, followed by significant increases in IL-1 and IL-6. In agreement with earlier data on related models of systemic infection or inflammation, circulating IL-6 is increased by over 60 fold in response to air pouch administration of lipopolysaccharide and the time course is consistent with its direct involvement in fever. Increased IL-6, but not IL-1 or TNFα bioactivity, is also detected in cerebrospinal fluid within 2 h of lipopolysaccharide administration (Miller, 1996). It is likely that at least some of the IL-6 found in circulation and in the cerebrospinal fluid derives from the air pouch itself. We have observed that human recombinant IL-6 injected into an air pouch (in the absence of lipopolysaccharide) can subsequently be measured in circulation and cerebrospinal fluid in significant quantities by an immunoassay which does not detect rat IL-6 (Miller, Rothwell, Pitcher & Luheshi, unpublished observations) and IL-6 is transported across the blood brain barrier (Banks et al., 1994; Luheshi et
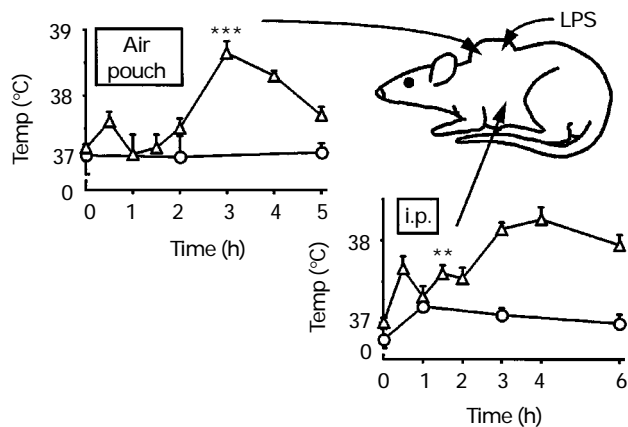
Figure 1 Cartoon depicting effect of injection of lipopolysaccharide (LPS) systemically (intraperitoneally) or into a subcutaneous air pouch injection on fever in the rat. Bacterial lipopolysaccharide ($\triangle$), LPS, $100 \, \mu g \, kg^{-1}$ or vehicle ($\bigcirc$) was injected after intraperitoneally (i.p.) or into a subcutaneous air pouch formed 6 days previously. Body temperature was recorded by remote, radiotelemetry in free-moving rats. Points shown are means and vertical lines indicate s.e.mean, $n = 8$.

al., 1994). Although IL-1 and TNF levels are not increased in cerebrospinal fluid, bioactivity of these cytokines is increased in push/pull perfusates from the hypothalamus of rats treated with lipopolysaccharide into an air pouch (Miller, Luheshi & Rothwell, unpublished data) or intraperitoneally (Klir et al., 1993).

Although IL-1 is probably not an important circulating endogenous pyrogen, it does nevertheless appear to participate directly in the development of fever. Injection of IL-1ra, a recombinant form of the naturally occurring IL-1 receptor antagonist, into the subcutaneous air pouch almost completely abolishes the increases in core temperature and circulating IL-6 in response to lipopolysaccharide (LPS, Miller et al., 1997a). Intraperitoneal injection of IL-1ra causes more modest inhibition of fever, which may be due to entry of the antagonist into the central nervous system, since intracerebroventricular (i.c.v.) injection of a 20 fold lower dose of IL-1ra also suppresses the febrile response to air pouch LPS, without affecting circulating IL-6 production (Miller et al., 1997a), and IL-1ra can enter the brain by an active transport mechanism (Gutierrez et al., 1994).

These data suggest that IL-1, TNFα and IL-6 are all produced locally within tissues in response to inflammation. IL-6 can be released into circulation and activate the brain either directly (via active transport into the central nervous system, Banks et al., 1994) or through release of other mediators. IL-1, TNFα and IL-6 have all been detected in and can be produced by cells in the brain (mainly glia) in response to systemic stimuli (Klir et al., 1993; Hopkins & Rothwell, 1995). These two cytokines probably interact to induce an increase in set point for body temperature via release of prostaglandins in the preoptic arterior hypothalamus.

The additional role of neural afferents in the activation of fever or other responses to a peripheral inflammation, pyrogens or cytokines has been proposed. We have shown that injection of capsaicin (to cause C-fibre deafferentiation) in the rat attenuates the early phase of the febrile response to turpentine, but not lipopolysaccharide (Turnbull et al., 1992). Several groups have shown that subdiaphragmatic vagotomy inhibits fever and behavioural responses to lipopolysaccharide or IL-1 in the rat, indicating that the vagus is an important pathway for afferent neuroimmune signals (eg Bluthe et al., 1994; Watkins et al., 1994). However, there is some inconsistency between data from different laboratories and we have observed that although subdiaphragmatic vagotomy abolishes

lipopolysaccharide or IL-1 induced behavioural changes in rats, it does not affect fever in the same animals (Luheshi, Bluthe & Dantzer, unpublished data).

Mechanisms of cytokine actions in the brain

The evidence that cytokines act directly in the brain to elicit biological responses such as fever is several fold. Firstly, injection, i.c.v. or into the brain parenchyma, of IL-1α, IL-1β, IL-6 or TNFα elicits maximal fever at doses several orders of magnitude lower than systemic pyrogenic doses. Secondly, inhibition of the actions of endogenous IL-1, IL-6 or TNF in the brain (by intracerebroventricular injection of IL-1ra or anti cytokine antibodies) reduces febrile responses to systemic pyrogenic stimuli (Klir et al., 1993; Cooper et al., 1994; Luheshi et al., 1997).

The primary site of action of the pyrogenic cytokines in the brain is presumed to be the preoptic arterior hypothalamus and the fever induced by all of these cytokines is reduced or prevented by co-administration of cyclo-oxygenase inhibitors (2) (see Kluger, 1991). However, the nature and location of brain IL-1 receptors which mediate such responses remains enigmatic.

Two IL-1 receptors have been identified. All known actions of the two IL-1 ligands (IL-1α and IL-1β) have been ascribed to interaction with the Type I (IL-1RI, 80 kDa) receptor, while the Type II IL-1RII (68 kDa) receptor is believed to act as a 'decoy', which is shed from the membrane and does not signal IL-1 actions (Sims et al., 1993). mRNA for the IL-1 RI has been identified in rodent brain, predominantly in the dentate gyrus with little, if any, message in the hypothalamus (Takao et al., 1990; 1992; 1993). Furthermore, radio-iodinated IL-1α or β show very little binding in rat brain and some specific binding in the mouse brain, but again not in the hypothalamus (Takao et al., 1990; 1992; 1993; Marquette et al., 1995). These seemingly discordant findings may reflect methodological problems and the relative insensitivity of radioligand binding, particularly since IL-1 can elicit biological responses in cells with as few as ten receptors. The failure to detect mRNA for IL-1RI in the hypothalamus may also reflect poor sensitivity of in situ hybridization and/or the existence of additional atypical or novel IL-1 receptors. An accessory protein has recently been identified which forms a dimer with the IL-1RI (Greenfeder et al., 1995). This accessory protein has been identified in the brain (including the hypothalamus), but does not co-localize with IL-1RI in all brain regions (Liu et al., 1996).

Using biotinylated IL-1ra, which may be more sensitive than binding of radioiodinated IL-1 and retains full biological activity, we have detected specific 'binding sites' in the rat hypothalamus. The binding of IL-1ra, which appears to be predominantly on neurones, is fully displaced by excess IL-1ra, IL-1α or IL-1β, indicating that it may reflect interaction with IL-1 'receptors' (Luheshi, Rothwell & Toulmond, unpublished data). It is not yet known if these are the IL-1RI or other novel receptors.

Several pieces of functional data are not consistent with the proposal that IL-1RI mediates IL-1 actions in the brain on fever. The dose-response profiles for development of fever in the rat are identical for recombinant rat IL-1α and β when these cytokines are injected systemically in the rat. However, when the same molecules are injected into the brain, IL-β is significantly more potent (Rothwell & Hopkins, 1995 and Figure 2). Furthermore, the actions of IL-1β in the brain on fever are blocked by co-administration (intracerebroventricular) of either a monoclonal antibody (ALVA42) raised to the IL-1RII (Luheshi et al., 1993), a corticotrophin releasing factor (CRF) receptor antagonist (Busbridge et al., 1989) or recombinant lipocortin-1 (Carey et al., 1990), while responses to IL-1α are unaffected by any of these treatments.

These data suggest that IL-1α and IL-1β may act on different brain receptors and through different mechanisms to
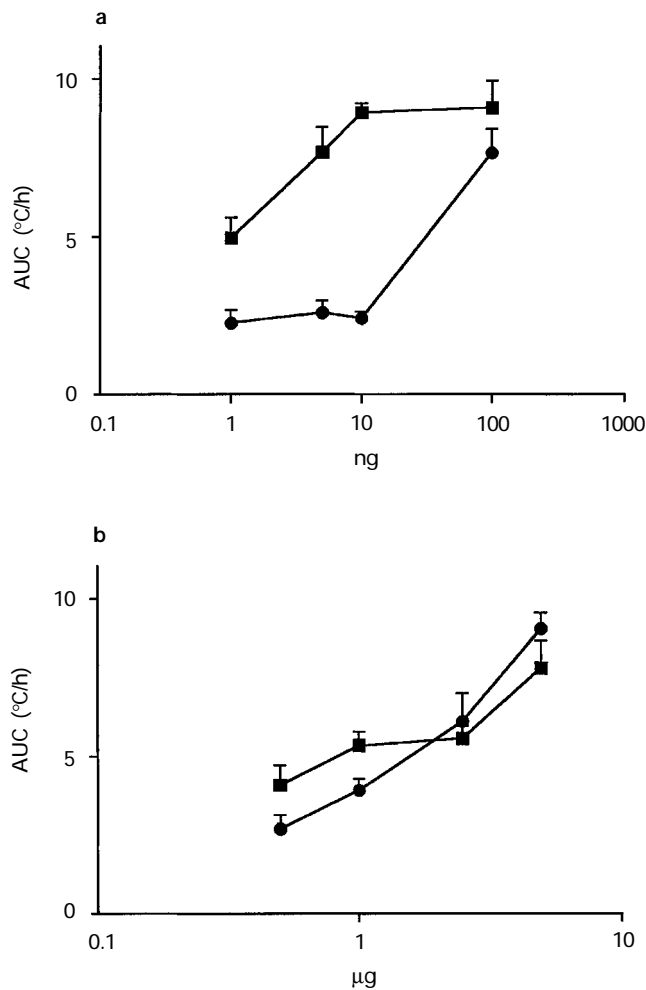
a

b

Figure 2 Comparison of effects of injection of various doses of recombinant rat interleukin-1α (IL-1α) (●) and IL-1β (■) either (b) intraperitoneally (i.p.) or (a) intracerbroventricularly (i.c.v.) on body temperature measured by remote radiotelemetry in the rat. Data are presented as area under the curve (AUC) for the temperature profile over the two hour period immediately after injection of IL-1. Points shown are means and vertical lines indicate s.e.mean, $n = 8 - 10$.

induce fever, possibly via novel and as yet unidentified receptors (for summary of actions of cytokines on fever see Figure 3).

Interactions between cytokines and the hypothalamic pituitary adrenal axis

It is well established that a number of cytokines are potent activators of the axis, which can act at the level of the hypothalamus, to induce expression and release of CRF, and at the pituitary release adrenocorticotrophic hormone (ACTH). In addition IL-1 can act through both of these mechanisms, and in some cases via direct actions in the adrenal, to stimulate glucocorticoid release (see Tkurnbull & Rivier, 1995; Buckingham, 1996). Glucocorticoids feed back as potent inhibitors of cytokine expression and action, not only on neuroendocrine responses, but also on fever (Coelho et al., 1995). The anti-pyretic effects of glucocorticoids are probably due, at least in part, to inhibition of prostaglandin synthesis and we have previously proposed that the peptide lipocortin-1 mediates suppressive effects of glucocorticoids on fever in the brain and periphery (Carey et al., 1990; Strijbos et al., 1993), which is consistent with the proposed actions of this peptide on the hypothalamic-pituitary adrenal axis (Buckingham, 1996).
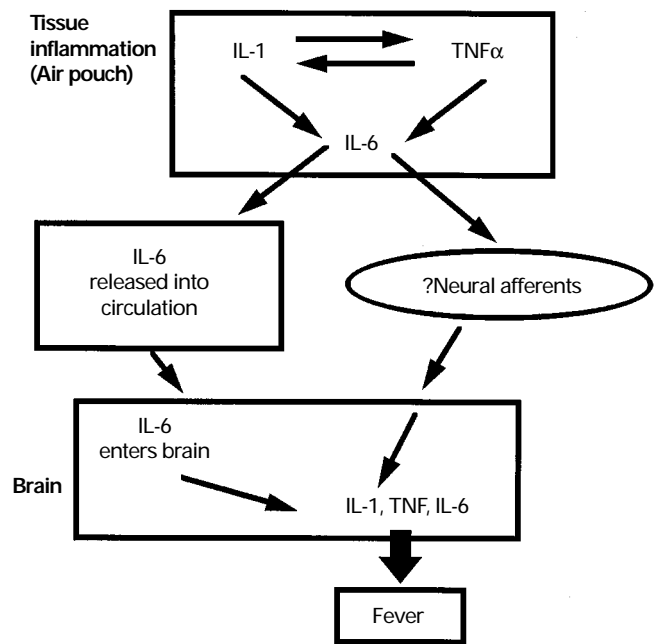

Figure 3 Figure indicating the role of proinflammatory cytokines within sites of infection in tissues, in circulation and in the brain, on the development of fever.

Glucocorticoids may also influence fever by suppression of the synthesis and/or release of CRF. The actions of some cytokines (IL-1β, IL-6 and IL-8) in the brain are dependent on CRF. Interestingly fever induced by IL-8 is not affected by cyclo-oxygenase inhibitors, but is reduced by dexamethasone (Coelho et al., 1995).

Genetically obese rodents (ob/ob mice and fa/fa Zucker rat) show marked alterations in hypothalamic-pituitary adrenal activity and their obesity is significantly attenuated by adrenalectomy, glucocorticoid receptor antagonists or i.c.v. infusion of CRF (see Rothwell, 1990). These mutants exhibit significantly impaired febrile responses to i.c.v. injection of IL-1β (Figure 4), but respond normally to IL-1α, and the reduced responses to IL-1β can be restored by adrenalectomy (Carnie et al., 1989; Busbridge et al., 1990). Recently, the obesity of the ob/ob mouse has been ascribed to a mutation in the 'ob gene' which results in a failure to produce its product, the peptide leptin (Zhang et al., 1994), while fatty Zucker rats and dlb/dlb mice have a mutation in the leptin receptor (Caro et al., 1996; Chen et al., 1996; Tartaglia et al., 1996). Leptin, produced by adipose tissue, is believed to regulate energy balance in normal mammals by acting on the hypothalamus to control appetite and energy expenditure (Frederich et al., 1995; Caro et al., 1996; Tartaglia et al., 1996). Several pieces of evidence suggest a possible relationship between leptin, cytokines and neuroimmune interactions.

The leptin receptor is a member of the Class I cytokine receptor family (including IL-6) (Tartaglia et al., 1996), suggesting that it may share actions with these cytokines. Indeed we find that leptin is a very potent pyrogen which, when injected i.c.v. in rats, causes marked increases in body temperature at doses which parallel those which induce hypophagia (Luheshi, Gardner & Rothwell, unpublished data). Furthermore, leptin expression is induced by lipopolysaccharide, IL-1 or TNF (Grunfield et al., 1996), and leptin increases expression of CRF in the hypothalamus (Schwartz et al., 1996). Thus, leptin may influence energy balance and body temperature in response to systemic infection and injury and, therefore, play a key role, with cytokines, in neuroimmune interactions and the metabolic effects of chronic disease, such as loss of appetite, hypermetabolism and cachexia.
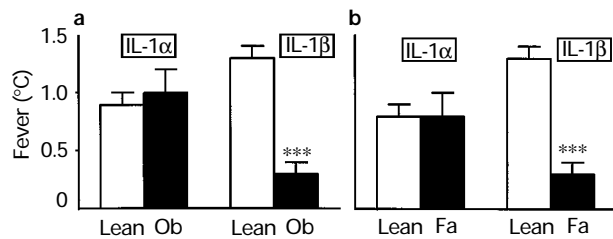
Figure 4 Effects of central (i.c.v.) injection of recombinant mouse IL-1α and IL-1β on body temperature measured by remote radio-telemetry in (a) genetically obese, ob/ob mice and (b) fatty (fa/fa) Zucker rats. Data are presented as area under the curve over the two hour period immediately after injection of recombinant cytokine. Vehicle has no effect. Means ± s.e.mean are shown, $n = 8$. ***$P < 0.001$ vs lean.

Figure 5 Effects of i.c.v. injection of recombinant interleukin-1β (IL-1β, 5 ng), vehicle (control), IL-1ra (10 μg) or an ICE inhibitor (ZVAD-DCB) on infarct volume (mm^3) measured histologically 24 h after focal cerebral ischaemia (middle cerebral artery occlusion in the rat). Means ± s.e.mean are shown, $n = 8-12$. ***$P < 0.001$ vs vehicle.

Cytokines and brain disease

In addition to the role of cytokines in neuroimmune interactions between peripheral tissues and the brain, these molecules also participate in acute and chronic disease and injury within the central nervous system itself. Constitutive expression of normal cytokines in the brain is low or barely detectable, but marked increases in several pro- and anti-inflammatory cytokines occur rapidly after acute insult (see Hopkins & Rothwell, 1995). In experimental animals, mRNA, protein and bioactive IL-1, IL-6, TNF and IL-8 are increased in response to cerebral ischaemia, brain trauma, excitotoxins or experimental inducers of inflammation such as lipopolysaccharide (see Hopkins & Rothwell, 1995). Similarly, numerous clinical studies have shown increases in these and other cytokines in cerebrospinal fluid or brain tissue at *post-mortem* from patients with acute or chronic neurological disease, including Alzheimer's, Parkinson's, multiple sclerosis and epilepsy as well as stroke, injury, infection and inflammation (see Hopkins & Rothwell, 1995). Increased expression of cytokines may of course be secondary to brain damage and not necessarily directly involved in the pathology. However, studies on experimental animals indicate that some cytokines, most notably IL-1 (particularly IL-1β), participate directly in acute neurodegeneration (see Rothwell & Relton, 1993; Rothwell & Hopkins, 1995; Rothwell, 1996; Rothwell et al., 1996). The expression of IL-1β in response to cerebral ischaemia, injury or excitotoxins in rat brain occurs within one hour of the insult, almost exclusively in microglia. Increased protein persists for many days with later expression detectable also in astrocytes and invading peripheral immune cells (Davies & Rothwell, unpublished data). Experimental interventions to increase or inhibit brain IL-1 activity dramatically influence the damage which ensues.

Intracerebroventricular injection of less than one picomol of IL-1β increases, by approximately 100%, the infarct volume resulting from focal cerebral ischaema (middle cerebral artery occlusion) in the rat (Figure 5, Relton & Rothwell 1992; Loddick & Rothwell, 1996). This exacerbation of damage is probably not due to the pyrogenic effects of IL-1, since it is not affected by cyclo-oxygenase inhibitors (Relton & Rothwell, unpublished data). Furthermore, intracerebroventricular injection of IL-6 also elicits fever, but in marked contrast to IL-1, inhibits rather than enhances damage (Loddick, Turnbull & Rothwell, unpublished data).

Inhibition of the processing or action of endogenous IL-1β by i.c.v. injection of an inhibitor of interleukin-1β converting enzyme (ICE which cleaves active IL-1β), or IL-1ra, reduces ischaemic brain damage by 50-70% (Figure 5; Loddick & Rothwell 1996; Loddick et al., 1996). Protection by IL-1ra is not associated with changes in body temperature or cardiovascular parameters and, unusually in middle cerebral artery occlusion damage, is reduced in the striatum as well as the cortex (Loddick & Rothwell, 1996). Separate studies have revealed that peripheral injection of higher doses of IL-1ra (50-
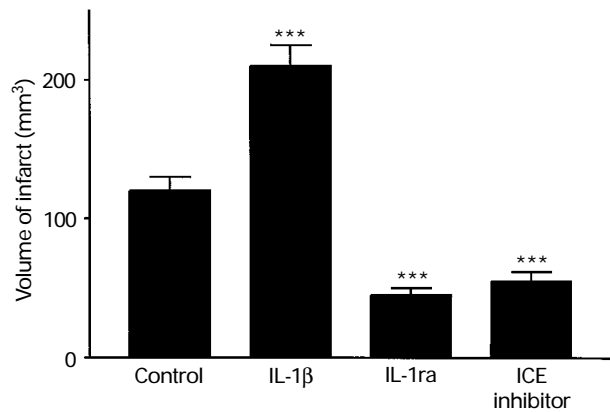
100 mg kg^{-1}) also reduces damage caused by middle cerebral artery occlusion damage in the rat and mouse, even when administered after the ischaemia. IL-1ra also inhibits oedema and neutrophil invasion, increases the number of surviving neurones and improves neurological score (Garcia et al., 1995; Relton et al., 1995 and see Rothwell et al., 1996 for review). Within the brain, the effects of IL-1 and IL-1ra on ischaemic damage appear to be highly site-specific, since IL-1 injected into the striatum enhances striatal and cortical damage, but is ineffective when injected into the cortex, whereas, striatal injection of IL-1ra protects the striatum and cortex from ischaemia, but does not reduce damage when administered into the cortex (Stroemer & Rothwell, 1997).

These data indicate that IL-1 participates directly in focal, permanent ischaemic brain damage, but further data show that inhibition of IL-1 also markedly reduces brain damage caused by global and reversible ischaemia in adult or neonatal rodents, traumatic injury (lateral fluid percussion) (Toulmond & Rothwell, 1995), excitotoxins (N-methyl-D-aspartate or AMPA/kainic agonists) (Relton & Rothwell, 1992), heat stroke (Lin et al., 1995) and clinical symptoms of experimental allergic encephalomyelitis (see Martin et al., 1996; Rothwell, 1996). Thus, IL-1 has been implicated in diverse forms of brain damage and may influence several processes which contribute to neurodegeneration (see Rothwell, 1996).

Mechanisms of action of IL-1 in neurodegeneration

The precise mechanisms of action of IL-1 are not known and may vary depending on the nature of the insult and probably involve effects of neurones, glia and brain endothelial cells (Figure 6). Some seemingly beneficial effects of IL-1 have been obtained including, for example, inhibition of calcium entry and glutamate release, enhanced α-aminobutyric acid (GABA) activity and induction of neurotrophins (see Hopkins & Rothwell, 1995; Rothwell, 1996). However, it seems that the over-riding effects of IL-1 are detrimental.

IL-1 is not neurotoxic *per se* to healthy, unchallenged neurones *in vivo* or *in vitro*. However, it markedly exacerbates ischaemic or excitotoxic brain damage *in vivo*, apparently through actions specifically in the striatum (see above). Interestingly, this region, like the hypothalamus, shows a high density of putative IL-1 receptors, as detected from the binding of biotinylated IL-1ra (Luheshi, Rothwell & Toulmond, unpublished data). IL-1 can also enhance apoptosis in cultured neurones and has been implicated directly in apoptosis (Friedlander et al., 1996). Many effects of IL-1 in the brain are exerted on glia and IL-1 is toxic to neurones co-cultured with
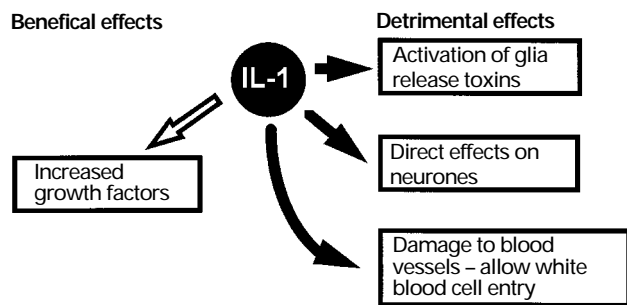
Figure 6 Actions of interleukin-1 (IL-1) in the brain which may have beneficial or detrimental effects on neurodegeneration.
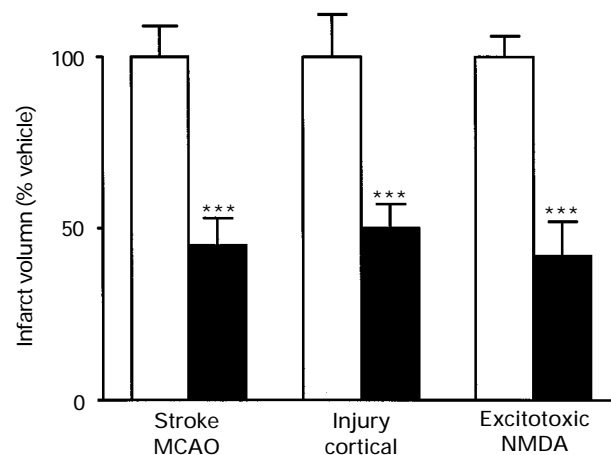

Figure 7 Effects of i.c.v. injection of a corticotrophin releasing factor (CRF) receptor antagonist on ischaemic, traumatic and excitotoxic brain damage in the rat. Data are from three separate studies in which infarct volume (expressed as percentage of volume in their respective vehicle treated group – open columns) was measured 24 h after middle cerebral artery occlusion (MCAO), 3 days after lateral, cortical, fluid percussion injury or 24 h after striatal infusion of an NMDA receptor agonist (cis 2, 4 methanoglutamate). CRF antagonist (25 μg αhelical CRF 9–41 or 10 μg D-Phe CRF, 2–41) was injected i.c.v. immediately after the insult. Means $\pm$ s.e.mean are shown, $n = 8 - 12$. ***$P < 0.001$ vs respective vehicle (treated group).

glia (Chao et al., 1996; Kim & Tauber, 1996). IL-1 can induce release of a variety of molecules from glia (eg nitric oxide, arachidonic acid and its products, β-amyloid precursor protein and complement), which may damage neurones directly or exacerbate other insults (see Rothwell, 1996; Rothwell et al., 1996). Furthermore, IL-1 could influence neurodegeneration through effects on the cerebrovasculature, where it may influence blood brain barrier integrity, cause release of nitric oxide and induce expression of adhesion molecules leading to neutrophil or macrophage invasion (see Rothwell & Relton, 1993; del Zoppo et al., 1996; Rothwell, 1996; Rothwell et al., 1996).

The mechanisms of IL-1 action on neurodegeneration appear to be distinct from those on fever. However, CRF has been implicated in both processes. Experimental focal cerebral ischaemia or brain trauma causes induction of CRF mRNA at the site of injury and in the armygdala (Wong et al., 1995; Roe, McGowan & Rothwell, unpublished data), and administration of CRF receptor antagonists inhibits ischaemic, excitotoxic and traumatic brain injury in the rat (Figure 7; Lyons et al., 1991; Strijbos et al., 1994; Wong et al., 1995; Roe & Rothwell, unpublished data). It is not yet known if the expression or actions of CRF in neurodegeneration are related directly to IL-1, though this is an attractive hypothesis given the relationship between these molecules in other responses to disease.

Therapeutic potential

Modification of cytokine expression and action has already attracted intense interest because of the accepted involvement of these molecules in so many diseases. The more recent demonstration of their key roles in neuroimmune interactions

has opened further therapeutic potential for modification of host defence responses to disease and for diverse neurological conditions.

The most obvious therapeutic strategies are inhibition of synthesis of proinflammatory cytokines or antagonism of their receptors. The former may lack specificity and the latter has, so far, yielded little success. However, experimental data have indicated several attractive approaches for modifying neuroimmune processes including endogenous modulators of cytokines (glucocorticoids, lipocortin, cytokine binding proteins, soluble receptors etc), specific inhibitors of processing (eg (ICE) inhibitors) or actions of cytokines and the use of endogenous 'anti-inflammatory cytokines' (eg IL-4, IL-10, IL-1ra). Research on neuroimmune interactions and the pharmacology of cytokines over the next few years may therefore lead to novel therapeutic approaches for the treatment of a number of peripheral and neurological disorders.

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