

Review

Connecting cytokines and brain: A review of current issues

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Summary. Cytokines have been a multi-disciplinary research focus for over 2 decades. To date, there have been more than 15000 articles published concerning the relationship between cytokines and the central nervous system (CNS). Over half of these articles have been published in the last 5 years. From such vast number of studies, two major topics emerge as the critical issues: 1) how do cytokines modulate the functions of the CNS? 2) what is the role of cytokines in the pathogenesis of neurological diseases? Thus far, it has been clearly established that cytokines can alter the functions of the CNS in specific manners, invoking CNS-controlled autonomic, neuroendocrine, and behavioral responses. Induced expression of cytokines has also been found in the CNS during brain injury and infection, contributing to the immunological processes at this "immunologically privileged" site. Furthermore, increasing evidence points to the potential involvement of cytokines in the induction and modulation of an array of neurological diseases ranging from Alzheimer's disease to chronic fatigue syndrome. Despite such progress, however, substantial obstacles remain for both the basic understanding and the potential clinical exploitation of how cytokines interact with CNS. In this review, we will attempt to synopsise the current theories and evidence regarding the answers to the above-mentioned critical questions. These issues will be reviewed not only in isolation, as most of the original reports focused on only one of the questions, but also in parallel such that inter-issue insights may be gained.

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How do cytokines modulate the functions of the central nervous system?

That cytokines may be potent neural active substances was postulated almost immediately after the discovery of the existence of this set of molecules (Dinarello, 1979). Initially identified as the intercellular signal molecules among immune cells (Dinarello and Mier, 1986), cytokines were suspected to act as crucial mediators between the immune system and the central nervous system (CNS). The key observation that germinated this idea is that immunological activities of the host are often associated with changes in behavior (sickness behavior, sleep), body temperature (fever or hypothermia), and neuroendocrine activities, all of which are regulated by the CNS. The presumed functions of the CNS-mediated responses during infection are to enhance immunity, conserve energy, and prevent hyperinflammation. The viewpoint of the integrated physiology, therefore, is that cytokines, which are induced during immune responses, modulate the functions of the CNS to recruit physiological, behavioral, and endocrine mechanisms to combat infection. An elegant early demonstration that substantiated such integrated physiological view was by Kluger et al. in 1975. They found that in lizard, a cold-blood animal that regulates its body temperature by moving to warmer environments, the generation of febrile responses significantly increased immunity and survival following bacterial infection. It was known then that fevers were induced by endogenous pyrogens, later to be identified as cytokines.

Direct evidence for the neural activities of cytokines was first obtained after injections of various cytokines systemically or into the cerebral ventricles (i.c.v.). These studies established that cytokines can activate the hypothalamus-pituitary adrenal (HPA) axis (Berkenbosch et al., 1987; Besedovsky and del Rey, 1987; Sapolsky et al., 1987), induce fever (Duff and Durum, 1983), prolong slow wave sleep (Krueger et al., 1984), reduce food (McCarthy et al., 1986) and water

intake (Chance and Fischer, 1991), and decrease motility (Crestani et al., 1991). These effects were evident not only in experimental animals but also in humans who received cytokine injections for cancer treatment (Smedley et al., 1983; Spriggs et al., 1987). The most tested cytokine in this regard is interleukin-1 (IL-1), although other cytokines such as the tumor necrosis factor (TNF) (Kapas et al., 1992; Kapas and Krueger, 1992), interferon (IFN) (Dinarelo et al., 1984; Kimura et al., 1994), IL-6 (LeMay et al., 1990), macrophage inflammatory protein-1 (MIP-1) (Davatelis et al., 1989), IL-12 (Atkins et al., 1997) and IL-2 (Ribeiro et al., 1993) can all induce one or several of the above-mentioned responses.

The neural actions of cytokines have important implications both physiologically and clinically. Cytokine-induced febrile response for example, can dramatically increase T helper cell activity, leading to increases in both cell-mediated and humoral immunity (Hanson, 1997). On the other hand, prolonged and high-temperature fevers can certainly be deleterious or even fatal. Thus, cytokine-mediated CNS effects can become the limiting factors for clinical use of high doses of cytokines (Ribeiro et al., 1993). A clear understanding of how cytokines affect CNS, therefore, is essential not only for basic cytokine biology but also for the development of cytokine medicine.

Achieving such an understanding, however, proves to be a daunting task due to the enormous complexities in both the immune and the nervous systems, and the structural separation between them. From the origin of cytokines in the immune system to their actions in the CNS, the following topics have been studied: 1) what is the relationship between different cytokines in regards to their ability to affect CNS? 2) what are the pathways via which cytokine signals are related across the blood-brain barrier (BBB)? 3) how do cytokines activate specific neural circuits to induce appropriate CNS-mediated responses? Although no simple answers can be found for any of these questions after examination of the literature in detail, a somewhat unexpected general modality of cytokine-to-CNS signal transmission does emerge.

The relationship between different cytokines in regards to their ability to affect CNS

Before evaluating the CNS effects of any given cytokine, it should be noted that, *in vivo*, an increase in the level of any single cytokine is most likely accompanied by changes in other cytokines. This is partly because that many cytokines are themselves the inducer of other cytokines (Olsson, 1993), and partly because multiple cytokines are required in a single immune response (Viguier, 2000). Generally, multiple cytokines are produced sequentially and/or in parallel to coordinate the initiation (inflammation, antigen presentation, acute phase responses) (Choy and Panayi, 2001), evolution (T cell activation, B cell activation, antibody production) (Callard, 1989; Moriggl et al.,

1999), and resolution (immunosuppression) of an immune response (Standiford, 2000). Multiple cytokines share bioactivities in peripheral immune system, resulting in functional redundancy (Rubinstein et al., 1998). Furthermore, the immunological action of a specific cytokine may be enhanced (Ostensen et al., 1989) or masked (Arend et al., 1987) depending upon the presence of other cytokines. The totality of such complexity found in cytokine biology in the immune system suggests that the CNS actions of any given cytokine should not be considered in isolation.

An illuminating example here is the induction of febrile responses in patients after they were treated with high doses of recombinant IL-2. Unlike IL-1 and TNF, IL-2 does not stimulate the synthesis of prostaglandins, which was thought to act at the anterior hypothalamus as the necessary downstream mediator of circulating pyrogens (Cocceani and Akarsu, 1998). Therefore, when it was found that high levels of IL-2 induced the production of IL-1 and TNF, it was concluded that IL-2 induces febrile responses indirectly through the actions of IL-1 and/or TNF (Mier et al., 1988). Further examination of this mechanism, however, revealed otherwise. Unlike IL-1- and TNF-induced fever, IL-2 induced fever was not suppressible by indomethacin (Chapman et al., 1988), a prostaglandin synthesis inhibitor. Therefore, IL-2 may have induced fever by its own direct action in the CNS or by inducing cytokines that activate febrile responses through prostaglandin-independent pathways. Two cytokines of this type, preformed pyrogenic protein (PFPP) (Zampronio et al., 2000) and macrophage inflammatory protein-1 (MIP-1) (Davatelis et al., 1989), have been identified recently. Hence, IL-1 and TNF are unlikely to be the mediators of IL-2 induced fever. This is clinically important because it suggests that combined IL-2 and IL-1 receptor antagonist (IL-1ra) therapy is not likely to reduce IL-2-induced fever. From a basic science point of view, this example shows that multiple cytokines may contribute to a common CNS-mediated effect, but the modalities of cytokine-CNS interactions may vary dramatically from one cytokine to another.

It is also important to note that interactions among cytokines are dynamic rather than static. A static view of the cytokine cascade is that there is a definite chain of cytokine induction such that a certain sequence (cytokine A to X) can be established as the pathway via which a given CNS effect is induced. This hypothesis has been tested using specific cytokine inhibitors or using animals that are deficient of a certain cytokine or its receptor (knockouts). Numerous CNS-mediated effects after peripheral immune challenge have been shown to be significantly attenuated by infusion of IL-1ra into the cerebral ventricle (*i.c.v.*). These include fever (Luheshi et al., 1997; Miller et al., 1997), prolonged slow wave sleep (Imeri et al., 1993), food-motivated behavior (Kent et al., 1996), reduced food and water intake (Linthorst et al., 1995). These results suggest that peripheral immune activities may ultimately affect the

CNS through the central effects of IL-1. This conclusion, however, is not supported by studies using transgenic animals. For example, fever induced by intraperitoneal (i.p.) injection of the bacterial endotoxin lipopolysaccharide (LPS) was only slightly reduced in either IL-1 β (Kozak et al., 1995) or IL-1 receptor knockout animals (Leon et al., 1996). Similarly, i.p.-LPS-induced fever was not reduced in transgenic animals that over-expressed IL-1ra in the CNS (Lundkvist et al., 1999). On the other hand, in IL-6 knockout animals, low-dose LPS induced fever was completely absent (Kozak et al., 1998). IL-6 knockout animals are also resistant to IL-1-induced fever (Chai et al., 1996). Therefore, these results suggest that IL-6, not IL-1, is the final common cytokine for fever induction. The discrepant results generated by these two approaches, viz., inhibitor injection vs. transgenic animals, should not be dismissed lightly. Transgenic animals which are deficient of IL-1 activity in the brain throughout their development may compensate by employ alternative cytokine-CNS connections such that other cytokines, e.g., IL-6 may play a more prominent role in LPS-induced fever. Thus, it is likely that the CNS role of any given cytokine is a dynamic one, i.e., the deficiency of one cytokine may engender its functional replacement by another. In this sense, the CNS actions of cytokines should not be evaluated only in transgenic animals. Combining evidence from both cytokine inhibitor studies and transgenic studies, it appears that IL-1, IL-6, TNF and INF are the major centrally active cytokines, although the predominant cytokine may differ during different types of infection, e.g., local vs. systemic, and bacterial vs. viral.

Pathways via which cytokine signals are related across the blood-brain barrier (BBB)

Regardless which cytokine is the mediator of a given CNS effect, the BBB presents a physical barrier to cytokine-CNS interaction. Five pathways via which cytokine signals may be relayed across the BBB have been studied. 1) Cytokines are actively transported across the BBB, 2) cytokines activate peripheral vagus nerves, which in turn, activate targets in the CNS, 3) cytokines leak across the BBB at circumventricular organs (CVOs), and activates CNS targets in the vicinity of CVOs, 4) cytokines induce the production of cytokines from cells of the BBB, which then secrete cytokines into the brain parenchyma, and 5) cytokines may be carried across the BBB by infiltrating leukocytes.

Banks' group is the major proponent for the mechanism of active transport of various cytokines across the BBB (Banks et al., 1995b). Over the last 10 years, they have provided ample evidence that several cytokines (IL-1, TNF, IL-2) appear to be transported across the BBB (Banks et al., 1989, 1995a; Waguespack et al., 1994). The method used in these studies was the measurement of the amounts of radiolabeled cytokines

that entered brain tissue after intravenous injection of these cytokines. In one study, they injected recombinant human IL-1 (rhIL-1) into mouse and measured the presence of rhIL-1 and murine IL-1 (mIL-1) in the brain (Banks and Kastin, 1997). They found that in the brain, the majority of IL-1 was rhIL-1 instead of mIL-1 and that the amounts of hIL-1 were higher in the brain than in the blood. It was concluded that the main source of IL-1 for its appearance in the brain after peripheral IL-1 injection was the injected hIL-1 that was actively transported across the BBB, rather than the newly synthesized IL-1 by cells within the brain. These experiments suggest that active transport plays a significant role in getting cytokines across the BBB. One caveat, however, is that the absorption of labeled cytokines into the brain tissue may reflect the binding of cytokines to the BBB, but not transporting of cytokines across the BBB. This question was addressed by Maness et al. who showed that i.v. infused radio-labeled IL-1 was present in the brain parenchyma, although majority of the radioactivity was found on brain endothelial cells (Maness et al., 1998). Similarly, Hashimoto et al. showed by electron microscopy that i.v. injected gold-labeled IL-1 was localized to the surface and pinocytotic vesicles of the brain endothelia shortly after injection (Hashimoto et al., 1991).

The second pathway for cytokines to engage the CNS is the vagus nerve. Interesting, when the role of vagus was first evaluated by Pitterman et al., no alteration in peripheral LPS-induced responses was found after abdominal vagotomy (Pitterman et al., 1983). Eleven years later, Watkins et al. found that peripheral LPS induced hyperalgesia can be blocked by vagotomy, and suggested that afferent vagal pathway innervating specific regions of brain as a key connection between peripheral cytokines and the CNS. Since then, numerous studies have been published demonstrating the involvement of vagus nerve in peripheral cytokine-induced CNS responses. These responses include fever (Sehic and Blatteis, 1996), activation of HPA axis, depletion of norepinephrine in the hypothalamus (Fleshner et al., 1995), prolonged slow-wave sleep (Opp and Toth, 1998), and depression of food-motivated behavior (Bret-Dibat et al., 1995). The discrepancy found in the literature may be attributable to the dose and route of LPS administration. It is now clear that vagal afferents are important for conveying signals generated from i.p. injection of low doses of LPS. On the other hand, CNS effects induced by i.p. injection of high doses of LPS or by i.v. injection of LPS are not altered by vagotomy (Romanovsky et al., 1997; Konsman et al., 2000; Hansen et al., 2000, 2001). In addition, the hepatic branch of the vagus nerve appears to the major nerve tract that relays the information of abdominal inflammation to the brain (Watkins et al., 1994; Simons et al., 1998).

Several mechanisms have been postulated to describe the complete circuitry by which cytokines stimulate vagal afferents and how stimulated vagal

afferents might trigger specific actions in the CNS. Goehler et al. found specific binding sites for IL-1ra in cells near vagal terminals (Goehler et al., 1997). In addition, IL-1 β immunoreactivity was induced in immune cells associated with the abdominal vagus nerve after i.p. LPS injection (Goehler et al., 1999). It was suggested that the IL-1 binding cells together with the vagal terminals form transducer units that monitor the levels of abdominal inflammation. Whether this type of transducer unit exist for other cytokines remains to be determined. Next, two studies showed that vagotomy can blocked the induction of IL-1 in the hypothalamus after peripheral injection of IL-1 (Hansen et al., 1998) or LPS (Laye et al., 1995). It was suggested that the activated vagus may stimulate CNS synthesis of IL-1. One caveat, however, is that most of in situ hybridization studies have localized IL-1 expression in the hypothalamus only in non-neuronal cells (Yabuuchi et al., 1993; Nakamori et al., 1994; Buttini and Boddeke, 1995; Quan et al., 1998a). Therefore, a remaining difficulty is to explain how ascending vagal afferents stimulate non-neuronal cells in the hypothalamus to produce IL-1. Nonetheless, Hosoi et al. showed by RT-PCR and ELISA that electrical stimulation of the vagal afferents can indeed induce the expression of IL-1 in the hypothalamus and hippocampus (Hosoi et al., 2000).

The third pathway is that cytokines may affect the CNS at the CVOs, which possess leaky BBB. An early proponent of this theory is Clark Blatteis who showed that lesions of organum vasculosum laminae terminalis (OVLT), a CVO close to the hypothalamic thermoregulatory center, suppressed i.p. LPS-induced fever (Blatteis et al., 1983, 1987). On the other hand, a report by Stitt found that ablation of the OVLT results in enhanced febrile response (Stitt, 1985). Similarly, controversial results were generated concerning another CVO, area postrema (AP). Whereas Lee et al. showed that removal of AP, a CVO close to the nucleus of the solitary tract (NTS), blocked IL-1-induced c-fos expression in the hypothalamic paraventricular nucleus (PVN) (Lee et al., 1998), Ericsson et al. found no change in PVN c-fos expression after AP lesion (Ericsson et al., 1997). The discrepant results may be attributable to the extent of the lesion and the different doses of LPS and IL-1 used in these studies. It appears that low doses LPS and IL-1 may specifically affect the CVOs and high doses of LPS and IL-1 may gain access to CNS at other sites.

The fourth pathway is that peripheral immune stimuli may induce the production of cytokines by cells of the BBB, which then secret cytokines into the brain parenchyma. Brady et al. were the first to note that peripheral injection of IL-1 induced intense transcriptional activity in cells of the BBB (Brady et al., 1994). Later, in situ hybridization studies showed that the cells of the BBB respond to peripheral immune stimulation by producing IL-1 (Quan et al., 1998a), IL-6 (Vallieres and Rivest, 1997), and TNF α (Nadeau and Rivest, 1999). In addition, after high dose peripheral

LPS injection, the expression of the cytokine responsive immediate early gene I B was induced mostly in cells of the BBB throughout the entire brain (Quan et al., 1997). Thus, during systemic immune challenge, production of cytokines by cells of the BBB may result in widespread cytokine activity in the entire CNS. This is consistent with our report the IL-1 bioactivity can be found in all brain regions after high-dose peripheral LPS injection (Quan et al., 1994).

The most under-appreciated pathway is that cytokines may enter the brain via infiltrating leukocytes. It is long known that leukocytes may enter the brain under both normal and pathological conditions (Oehmichen et al., 1982). In normal brain, scattered and random crossing of the BBB by leukocytes provide immune surveillance for the CNS (Hickey, 1991). The infiltrating leukocytes under normal condition do not express inflammatory cytokines because no detectable leukocyte cytokine expression has been found in the normal brain parenchyma (Quan, 1998). Under pathological conditions, e.g., bacterial meningitis (Frei et al., 1993) and ischemic brain damage (Gregersen et al., 2000), activated leukocytes expressing inflammatory cytokines may infiltrate the brain (Del Maschio et al., 1999). Interestingly, i.c.v. injection of IL-1 can cause widespread infiltration of leukocytes into the brain (our unpublished observation). Therefore, CNS action of IL-1 may weaken the BBB, resulting in infiltration of cytokine producing leukocytes. One can envision a vicious cycle by which cytokines in the CNS act to induce the infiltration of cytokine-expressing leukocytes, which in turn, release cytokines inside the brain to further weaken the BBB, leading to significant neuropathology.

It should be noted that all of the above-mentioned pathways represent novel mechanisms in physiology. Transporting molecules as large as cytokines across the BBB, for example, has never been described before. At molecular level, the presumed transporter molecule will have to bind to cytokines, move through the cytoplasm or move on the cell membrane from one side of the cell to the other, and then release the intact cytokines. Such a feat is not yet known from other transporter systems. Likewise, vagal transmission of immune signals to the CNS represents a novel sensory pathway via which immune status may be monitored. How the vagus nerve differentially relay immune vs. non-immune signals to the CNS remains a fascinating problem. Upon first examination, the pathway that cytokines may reach CNS via the leaky CVOs appears a simple one. But Maness et al. showed that even though cytokines can be found in the extracellular space in the CVOs, they rarely enter the brain parenchyma probably due to the glia limitans surrounding the CVOs. Therefore, action of cytokines at CVOs will have to be transmitted into the brain, either by movement of the cytokines or highly diffusible transduced molecules to the neighboring structures or by signals generated in CVO projection neurons (Mark and Farmer, 1984). How such transduction events take place

in the CVOs remains to be defined. Finally, production of cytokines by cells of the BBB represents a novel function of the BBB such that the immune signals are relayed across the BBB. We have shown that whereas sub-septic doses of LPS only induced cytokine expression at the BBB structures, septic doses of LPS induces the expression of cytokines inside the BBB (Quan et al., 1999a). Thus, widespread expression of cytokines by cells of the BBB may be particularly relevant to systemic immune stimulation.

The proposed pathways should not be viewed only as competing hypotheses. The CVOs, e.g., are known to receive vagal afferents (Kalia and Sullivan, 1982; Shapiro and Miselis, 1985). Therefore, vagotomy may affect signal transduction processes in the CVOs, and lesions of CVOs may attenuate vagal-mediated effects. Likewise, whereas cytokines may be transported across the BBB, binding of cytokines to brain endothelial cells can also induce the production of cytokines (Reyes et al., 1999). Thus, these pathways may operate simultaneously or separately under different conditions. The dose and route of cytokine administration can dictate the pathway and CNS outcome, as described. In addition, the status of the BBB may play a role, especially in inflammation and injury states. Finally, combinations of cytokines may have interactive effects.

Activation of specific neural circuits by cytokines

Defining the specific neural circuits involved in cytokine-mediated CNS responses presents another daunting challenge. From the foregoing, it is clear that cytokines may induce many CNS-mediated effects. These effects, however, are controlled by different neural circuits. Feeding behavior, e.g., involves the balanced activity of ventromedial hypothalamic nucleus (VMH) and lateral hypothalamic area (LHA) (Oomura, 1988). Fever production, on the other hand, is critically associated with neurons in the anterior pre-optic area (APO) (Blatteis et al., 1984). Activation of the HPA axis obviously involves the PVN. The precise neuroanatomical loci for cytokines to induce changes in sleep patterns are not yet known. There are two types of thinking behind the search for the connections between cytokines and these neural circuits. The first type assumes that cytokines are able to reach any brain sites and the action of cytokines at the specific sites of the brain determines their activity. The second type assumes that there is sequential activation of different brain sites such that cytokine actions at some critical sites trigger chain reactions to engage distant neural circuits.

Direct cytokine actions on neurons at specific brain regions have been examined by electrophysiological methods. In APO, there are temperature sensitive neurons that increase their firing rate in response to increase (warm-sensitive) or decrease (cold-sensitive) in body temperature (Boulant, 1998). These neurons appear to control the "set point" of body temperature. Microelectrostatic application of IL-1 into APO

decreased the activity of warm-sensitive neurons and increased the activity of cold-sensitive neurons (Hori et al., 1988). These results have been replicated *in vitro* in hypothalamic slice preparations containing the APO (Shibata and Blatteis, 1991). Such IL-1-induced alterations are consistent with the view that IL-1 acting at APO to shift the set point of body temperature to a higher level, thereby producing fever. In another system, Hori et al. showed that local actions of IL-1 on glucose-sensitive neurons in the VMH are consistent with the induction of anorexia by IL-1 (Hori et al., 1992). Thus, if cytokines do reach these brain sites, they would induce the appropriate responses via their direct local actions.

Alternatively, cytokines may act at a distance, triggering synaptic neurotransmission to reach a target neural structure. Adrian Dunn was the first to show that peripheral injection of IL-1 stimulates norepinephrine metabolism in the brain (Dunn, 1988). Later, it was found that peripheral immune challenge also alters the metabolism of 5-HT (Dunn and Welch, 1991; MohanKumar et al., 1998) and dopamine in the brain (Dunn, 1992; Song et al., 1999). These data suggest that cytokines may affect the CNS via noradrenergic, serotonergic, or dopaminergic pathways. Elegant work from Ericsson et al. showed that activation of PVN neurons by iv injected IL-1 can be attenuated by cutting the nerve fibers connecting the medullary noradrenergic neurons to the PVN (Ericsson et al., 1994). In addition, they showed that IL-1-induced activation of PVN can be blocked with indomethacin, a prostaglandin synthesis inhibitor (Ericsson et al., 1997). Finally, injection of prostaglandin E2 directly into the rostral ventrolateral medulla, the region containing the noradrenergic neurons that project to PVN, mimicked activation of the PVN induced by peripheral injection of IL-1 (Ericsson et al., 1997). Taken together, it was concluded that circulating IL-1 may induce the synthesis of prostaglandins in the medulla, which in turn, stimulate noradrenergic neurons in the area to activate PVN.

It should be pointed out that the two modalities of cytokine signaling described above are not mutually exclusive. For example, peripheral injection of IL-1 (Komaki et al., 1992) and LPS (Van Dam et al., 1993) can induce the synthesis of prostaglandins in the PVN itself. Experiments using hypothalamic slice preparations containing PVN have shown that local action of IL-1 and prostaglandins can also stimulate CRF synthesis (Sandi and Guaza, 1995).

Another approach to look for where cytokines might act in the CNS is to localize cytokines and/or their receptors in the CNS. Breder et al. were the first to localize IL-1 β immunoreactivity (IL-1 β -ir) in the hypothalamic nerve fibers (Breder et al., 1988). These results were later partially substantiated by three other studies that showed IL-1 β -ir in the hypothalamus of several species (Lechan et al., 1990; Molenaar et al., 1993; Huitinga et al., 2000). Huitinga et al. further defined these IL-1 β containing neurons as the oxytocin neurons. The functions of IL-1 β found in these neurons

remain mysterious because the levels of this neuronal IL-1 do not change in parallel to any known stimulation, and constitutive expression of IL-1 β mRNA in hypothalamic neurons has not been found by *in situ* hybridization histochemistry. On the other hand, after peripheral immune challenge, IL-1 β is induced primarily in the microglia and endothelial cells (Van Dam et al., 1992, 1995; Buttini and Boddeke, 1995; Quan et al., 1998a), not in neurons. Similarly, induction of TNF- α , and IL-6 were all found in non-neuronal cells in the brain (Vallieres and Rivest, 1997; Laflamme and Rivest, 1999). Thus, non-neuronal cells may be the primary source for cytokines found in the CNS.

As for cytokine receptors, initial studies using radiolabeled IL-1 showed widespread binding of IL-1 throughout the entire brain, concentrating in many neuron-rich sites such as the dentate gyrus, the hypothalamus, and the granular cell layers of the cerebellum (Farrar et al., 1987). Later studies by immunohistochemistry and *in situ* hybridization histochemistry, however, showed that the distribution of IL-1 type 1 receptor (IL-1R1, the functional receptor for IL-1) in the brain was limited largely to the cells of the BBB (Cunningham et al., 1992; Ericsson et al., 1995; Van Dam et al., 1996). Neurons bearing IL-1R1 was found only in a few structures including the basolateral nucleus of the amygdala, the arcuate nucleus of the hypothalamus, the trigeminal and hypoglossal motor nuclei, and the area postrema (Ericsson et al., 1995). Such a limited distribution was not expected for two reasons. First, the promoter for IL-1 receptor gene expression lacks the CAAT and TATA box and shares striking sequence resemblance to the TATA-less promoter of the house-keeping gene terminal deoxynucleotidyltransferase (Ye et al., 1993). Thus, it might be assumed the IL-1R1 will be expressed ubiquitously at low levels. Second, neurons presumably sensitive to IL-1 stimulation such as the neurons in the PVN, APO, and VMH do not appear to possess IL-1R1. Similarly, the receptor for TNF- α was also found primarily in cells of the BBB (Cunningham et al., 1997). Thus, the unexpected conclusion is that local action of cytokines at many brain sites may actually be mediated via the receptors on endothelial cells. We and others have shown strong activation of cyclooxygenase-2 (COX-2, a rate-limiting prostaglandin synthase) after peripheral immune challenge in the endothelial cells throughout the brain (Cao et al., 1996; Matsumura et al., 1998; Quan et al., 1998b). Furthermore, many cytokine-induced CNS effects can be blocked by COX inhibitors (Szekely, 1978; Johnson and von Borell, 1994; Dunn and Swiergiel, 2000). Therefore, contrary to the initial concern that the BBB may prevent cytokines from signaling the CNS, cells of the BBB may provide an essential interface for cytokine-CNS interaction.

As for IL-1R1 bearing neurons in hippocampus and amygdala, recent studies have demonstrated a new type of neural activity for IL-1. Namely, IL-1 may act on these neurons to inhibit long-term potentiation (Katsuki

et al., 1990; Bellinger et al., 1993; Cunningham et al., 1996) and weaken synaptic strength. This new found cytokine activity may be involved in the ability of cytokines to alter the neural processes of learning (Gibertini, 1996), memory (Rachal Pugh et al., 2001), and emotion (Pugh et al., 1999).

What is the role of cytokines in the pathogenesis of neurological diseases?

A key feature of cytokine biology is that inflammatory cytokines are double-edged swords. In peripheral immune system, inflammatory cytokines are essential for the development of appropriate immune responses against infection and cancer. For example, IL-1R1 knockout mice displayed reduced delayed-type hypersensitivity response and were highly susceptible to infection by *Listeria monocytogenes* (Labow et al., 1997). It was also demonstrated that CD8⁺ T cell-mediated killing of lung cancer cells is crippled in mice deficient of the TNF type 1 receptor (TNFR1) (Prevost-Blondel et al., 2000). On the other hand, a lesson learned from cytokine therapy is that cytokines can cause cell death, not only in infected and cancerous cells, but also in normal bystanders (Heaton and Grimm, 1993). Similarly, cytokine-CNS interactions have both physiological and pathological implications. In fact, evidence accumulated from clinical research and from *in vitro* and *in vivo* experiments suggests that the inflammatory cytokines may play significant roles in the pathogenesis of a number of neurological diseases.

Clinical evidence implicating cytokines in the pathogenesis of human neurodegenerative diseases

IL-1 and TNF- α have long been suspected to play important roles in inflammation related neuronal cell death. An early example implicating these cytokines as contributing factors in neuropathology is bacterial meningitis (reviewed by Frei et al. (1993)). In this disease, there is substantial cortical neuronal cell death, inflammation, and edema in the brain (Mito et al., 1993), resulting in mortality and a high incidence of long-term neurological sequelae in the survivors. The outcome of this disease has been shown to correlate with TNF- α and IL-1 concentrations in the cerebrospinal fluid (CSF) (Mustafa et al., 1989; Arditì et al., 1990). Conversely, increased levels of soluble IL-1 receptor, which inhibits the effects of IL-1, has been observed during the recovery phase of the disease (van Deuren et al., 1997). Furthermore, treatment with antisera against TNF- α has been found to protect against the lethal effects of bacterial endotoxin (Beutler et al., 1985). Therefore, these results suggest a pathogenic role of IL-1 and TNF- α in this disease.

Another example is multiple sclerosis (MS). The central lesion of this disease is immune-mediated CNS damage and myelin destruction (Brosnan and Raine, 1996), although MS often runs a protracted and varied

course. Degeneration of nerve fibers may occur secondary to the demyelination. The involvement of IL-1 and TNF- α in the pathogenesis of this disease is indicated by the facts that 1) in brain lesions of MS patients, TNF- α immunoreactivity has been found associated with astrocytes and macrophages (Hofman et al., 1989); 2) higher-than-control levels of IL-1 and TNF- α have frequently been detected in the CSF of MS patients (Hauser et al., 1990); and 3) a clinically effective therapy for MS is interferon- β (IFN- β) treatment (Munschauer and Stuart, 1997), which inhibits the production of IL-1 and TNF- α and enhances the production of IL-1ra (Coclet-Ninin et al., 1997). These lines of evidence have led to the hypothesis that IL-1 and TNF- α are critically involved in the pathogenesis of MS (Raine, 1994).

More recently, both IL-1 and TNF- α have also been found in the CSF of patients with Parkinson's disease (Mogi et al., 1996). The principal cause of the motor symptomatology of Parkinson's disease is the loss of substantia nigra dopaminergic neurons that project to the striatum (Hirsch and Herrero, 1997). High levels of TNF- α mRNA expression have been found in both striatum (Mogi et al., 1994) and substantia nigra of Parkinson patients (Boka et al., 1994). In addition, activation of transcription factor NF- κ B has been observed in dopaminergic neurons of patients with Parkinson's disease (Hunot et al., 1997). IL-1 and TNF- α are two of the well-known NF- κ B activators (Miyamoto and Verma, 1995). These findings suggest that IL-1 and TNF- α are active at the site of Parkinson lesions. Additionally, the case report of a young girl who had suffered severe inflammatory meningitis and subsequently developed Parkinson-like symptoms (Geddes et al., 1993) also suggests a role of inflammatory cytokines in the pathogenesis of this disease.

Perhaps the most extensive clinical evidence linking inflammatory cytokines to the pathogenesis of neurodegenerative diseases is found in work on Alzheimer's disease (AD) (reviewed by Griffin et al. (1995)). Pathological changes indicative of this disease are the appearance of amyloid deposits, neurofibrillary tangles, and Hirano bodies (Mrak et al., 1997). Both elevated tissue levels of IL-1 and increased numbers of activated, IL-1-immunoreactive (IL-1⁺) microglia have been found in AD patients (Griffin et al., 1989). The IL-1⁺ microglia are found in close proximity of tangle-bearing neurons (Sheng et al., 1994) and amyloid plaques (Griffin et al., 1989). It is also known that IL-1 upregulates the production of S100 β and β -amyloid precursor protein (β -APP) (Sheng et al., 1996)—two important factors implicated in the pathogenesis of AD (Mrak et al., 1996a). In addition, β -APP can stimulate microglial IL-1 production (Araujo and Cotman, 1992). Therefore, over-expression of IL-1 induces increased expression of β -APP, which could, in turn, result in further IL-1 production. Such an IL-1 initiated "cytokine cycle" has been envisioned as a driving force in the

pathogenesis of AD (Sheng et al., 1996). Consistent with this view, increased expression of IL-1 in the brain has been found in conditions that predispose patients to Alzheimer-like lesions such as head injury (Griffin et al., 1994), aging (Mrak et al., 1996b), and epilepsy (Sheng et al., 1994). Further association between inflammatory cytokines and AD comes from epidemiologic studies (reviewed by McGeer (McGeer et al., 1996)) that show that the use of anti-inflammatory drugs is negatively correlated with the prevalence of AD. It has been postulated that anti-inflammatory drugs may interfere with the development of AD, partly due to blocking the effects of IL-1 (Breitner, 1996). TNF- α has also been implicated in the pathogenesis of AD, although so far the evidence for such involvement is not as extensive as it is for IL-1 (Mattson et al., 1997).

Taken together, the above-reviewed examples strongly suggest a pathogenic role of IL-1 and TNF- α in several major neurodegenerative diseases, although the neuropathological changes of these diseases are vastly different from one another. The postulated pathogenic role of IL-1 and TNF- α is the rationale for numerous experimental studies that have attempted to determine the extent to which elevations of IL-1 and TNF- α expression in the brain contribute to neurodegeneration.

In vitro experiments

Direct examination of the neurotoxic effects of IL-1 and TNF- α *in vitro* has produced ambiguous results. Early work by Piani et al. (1992) found that addition of IL-1 and/or TNF- α to cultured cerebellar neurons did not cause neurotoxicity. In contrast, Täuber et al. (1992) found that TNF- α produced toxic effects to the neuronal cell line, NH33.1. More recently, Chao et al. (1995c) found that IL-1 and TNF- α induced neurotoxicity when they were added to a human fetal brain cell culture together, but that neither cytokine alone was toxic. Strijbos and Rothwell (1995) on the other hand, showed that, whereas high concentrations of IL-1 alone were neurotoxic in a rat cortical neuronal culture, low concentrations of IL-1 were neuroprotective against glutamate mediated neurotoxicity. In addition, a report by Westmoreland et al. (1996) showed that TNF- α , but not IL-1, was toxic for human neuronal cell line, NT2N. The discrepant results found in these reports may have arisen from the differences in neural cultures, in doses of IL-1 and TNF- α , and in susceptibility for the induction of neurotoxicity in various cell lines used in these *in vitro* studies (Chao et al., 1995a).

In the case of glial toxicity, Merrill (1991) reported that IL-1 but not TNF- α selectively induced cytotoxicity to isolated oligodendrocytes, the type of glial cell that provides myelin sheath for nerve fibers. On the other hand, Selmaj and Raine (1988) and D'Souza et al. (1996) showed that, in cultures containing both astrocytes and microglia, TNF- α causes myelin damage and toxicity to oligodendrocytes. The observations by Selmaj et al., and D'Souza et al., appear to be more

consistent with *in vivo* observations that suggest that TNF- α contributes to the demyelination process in multiple sclerosis and experimental allergic encephalomyelitis (EAE) (Raine, 1994). The failure of the study by Merrill et al. to show the neurotoxic effects of TNF- α to oligodendrocytes may have been due, in part, to the absence of astrocytes and/or microglia in their culture preparation.

As noted earlier that, with the exception of a few brain regions, both IL-1 and TNF receptors have been localized primarily to non-neuronal cells in the brain. Thus, *in vivo*, IL-1 and TNF- α may exert direct neurotoxic effects on neurons bearing the receptors for these cytokines or, more likely, produce neurotoxicity indirectly via activation of microglia and/or astrocytes (Chao et al., 1996a). Consistent with this notion, IL-1 and TNF- α have been found to stimulate the proliferation of both microglia and astrocytes in tissue culture (Merrill, 1991) and *in vivo* (Giulian et al., 1988; Mizuno et al., 1994; Lee et al., 1995). Activated glial cells have been found to produce an array of potentially neurotoxic substances, such as quinolinic acid (Schwarcz et al., 1983), reactive oxygen intermediates (Chao et al., 1995b), reactive nitrogen intermediates (Chao et al., 1996b), and glutamate (Piani et al., 1991). Therefore, the manifestation of IL-1- and TNF- α -induced neurotoxic effects may require the presence of multiple cell types in the affected brain region, and consequently, investigation of these effects may have to be evaluated in *in vivo* models where multiple cell types are present naturally.

In vivo studies

Both IL-1 and TNF- α have been used in clinical trials for treating certain types of cancer. Neurotoxic effects such as headache, confusion, and seizures have been reported after high dose treatment of either TNF- α (Mittelman et al., 1992) or IL-1 (Redman et al., 1994). The neuropathological correlates of these toxic effects have not been determined.

The most compelling evidence suggesting a neurotoxic role for IL-1 comes from animal models of acute brain injury. Head trauma (Taupin et al., 1993; Shohami et al., 1997), cerebral ischemia (Minami et al., 1992; Wang et al., 1994; Saito et al., 1996), and excitotoxic injury to the CNS (Yabuuchi et al., 1993) rapidly and markedly increase levels of IL-1 mRNA and protein in the brain. Injections of IL-1 β have been shown to exacerbate the damage produced by brain ischemia (Yamasaki et al., 1992; Loddick and Rothwell, 1996). In contrast, injection of IL-1ra, significantly inhibits neuronal damage in all of the above-mentioned models of acute brain injury (Relton and Rothwell, 1992; Garcia et al., 1995; Toulmond and Rothwell, 1995; Loddick and Rothwell, 1996). The same neuroprotective effects can be achieved by over-expressing IL-1ra (Yang et al., 1997), knocking-out IL-1 β converting enzyme (ICE, the only known IL-1 β convertase which catalyzes the

production of active mature IL-1 β from its inactive precursor) (Schielke et al., 1998), or inhibiting ICE activity (Loddick et al., 1996; Hara et al., 1997). All of these effects appear to be due to a reduction in IL-1 activity. Furthermore, neutralizing IL-1ra activity by injection of antibodies against IL-1ra into the brain markedly enhances ischemic brain damage (Loddick and Rothwell, 1996), suggesting that endogenously produced IL-1ra during brain ischemia serves to limit the neurotoxic effects of IL-1. These findings strongly indicate that IL-1 can act as a neurotoxic agent during acute brain injury.

TNF- α expression is also induced concurrently with the induction of IL-1 during acute brain injury (Wang et al., 1994; Saito et al., 1996; Mathiesen et al., 1997; Zhai et al., 1997). Injection of exogenous TNF- α into peripheral nerves induces axonal degeneration and demyelination (Redford et al., 1995; Madigan et al., 1996), which can be blocked by the anti-TNF drug, pentoxifyllin (Petrovich et al., 1997). In addition, demyelination and axonal degeneration induced in experimental autoimmune encephalomyelitis (EAE) can be ameliorated by inhibiting the action of TNF- α (Selmaj et al., 1995), suggesting that endogenously produced TNF- α possesses the same neurotoxic potential as that revealed by exogenously injected TNF- α . Finally, transgenic mice with targeted over-expression of TNF- α in astrocytes have been created (Campbell et al., 1997; Probert et al., 1997). These animals exhibit variable degrees of neurodegeneration, ranging from mild demyelination to substantial destruction of both gray and white matter. These findings suggest that TNF- α possesses neurotoxic potentials *in vivo*. Furthermore, TNF receptor knockout animals exhibit reduced neuropathology and IL-1 receptor knockout animals were completely protected in murine EAE models (Schiffenbauer et al., 2000).

Despite the findings cited above supporting a neurotoxic role of IL-1 and TNF- α , other reports in the literature suggests the opposite. Thus, it is known from *in vitro* studies that IL-1 and/or TNF- α stimulate the synthesis of antioxidant enzymes (Wong and Goeddel, 1988; Visner et al., 1992) and nerve growth factor (Lindholm et al., 1988; Gadiant et al., 1990). Both of these factors have been shown to play significant neuroprotective roles during nerve injury (Chan et al., 1994; Mattson and Scheff, 1994; Wengenack et al., 1997). IL-1 and TNF- α have also been shown to afford neuroprotection against excitotoxic neurodegeneration in *in vitro* preparations (Cheng et al., 1994; Strijbos and Rothwell, 1995). *In vivo*, IL-1 expression induced by a small ischemic insult has been shown to reduce neuronal damage from a subsequent global ischemia (Ohtsuki et al., 1996). Further highlighting such neuroprotective effects is the report that mice lacking TNF receptors incur exacerbated neuronal damage after excitotoxic and ischemic brain injury (Bruce et al., 1996). Therefore, IL-1 and TNF- α may play crucial neuroprotective roles in animal models of brain injury.

Consequently, the important question regarding the role of IL-1 and TNF- α in neurodegenerative diseases now is not whether these cytokines are neurotoxic or neuroprotective but rather what are the specific conditions under which these cytokines become neuroprotective or neurotoxic. Three basic parameters have been considered. The first important parameter is the level of these cytokines. Strijbos and Rothwell (1995) have shown that whereas low concentrations of IL-1 attenuated glutamate-induced neurodegeneration in a neuronal culture system, high concentrations of IL-1 induced neurotoxicity by itself. Similarly, Cheng et al. (1994) reported the TNF- α at 10 ng/ml was neuroprotective against glutamate-induced neuronal death, but Chao and Hu (1994) reported that TNF- α at 20–100 ng/ml potentiated glutamate neurotoxicity. Although different culture systems were used in these two studies, it is possible that disparate results were obtained because different concentrations of TNF- α were used.

Another important parameter is the duration of exposure. Scarim et al (1997) have shown that exposure of rat islets to IL-1 for 18 hours resulted in reversible damage to the islet cells, 36-hour exposure caused irreversible inhibition to the metabolic function of these cells, and 96-hour exposure induced outright islet degeneration. Whether the duration of exposure to IL-1 and/or TNF- α in the brain helps to dictate whether they are neuroprotective or neurotoxic has not been examined.

The third parameter is the site of action. Stroemer and Rothwell (1997) have shown that cortico-striatal projection neurons can be damaged by a neurotoxic level of IL-1 in the striatum, but not in the cortex. Therefore, it is possible that different regions of the brain are differentially susceptible to the neurotoxic effects of IL-1 and/or TNF- α , rendering specific neural structures particularly vulnerable to these cytokines. A survey of brain regions, structures, and cell types in regards to their susceptibility to IL-1 and/or TNF- α induced neurotoxicity, however, is lacking.

Specific neurodegeneration patterns after chronic peripheral infection

From the foregoing, it is clear, that cytokines in the CNS should not be viewed simply as friends or as foes. It is critical to understand the transitional processes by which physiological actions of cytokines in the CNS might change into pathological ones. To this end, we have selected a unique model to investigate the pathophysiology of CNS cytokines. Infection of humans by the trypanosome parasite causes African Sleeping sickness, a severe inflammatory disease with involvement of the brain. In rats infected with the rodent subspecies *Trypanosoma brucei brucei* (*T.b. brucei*), the parasites have been found lodged in the choroid plexus and circumventricular organs of the brain (Schultzberg et al., 1988). Although these parasites rarely penetrate into

the brain parenchyma across the blood-brain barrier (BBB) (Schultzberg et al., 1988), they stimulate the secretion of IL-1 and TNF- α production from peripheral immune cells (Bakhiet et al., 1996). At early stage of the *T. brucei* infection, many CNS-cytokine-mediated physiological responses can be observed. These include fever, sickness behavior, and reduced appetite. At later stage of the infection, many neurological symptoms such as insomnia, depression, loss of memory, cognitive dysfunction, hallucination, manic episodes, and epileptic fits would appear (Dumas and Bouteille, 1996). Correlating the neuropathology and cytokine expression in *T. brucei* infected brain, therefore, might provide a unique opportunity to reveal when and how the expression in the CNS can turn from non-pathological to neurotoxic.

In rats infected with *T. brucei*, we found that chronic cytokine expression was induced in the brain (Quan et al., 1999b). Increased expression of IL-1 β and TNF- α mRNA were first observed on day 22 post-infection (p.i.) and maintained for the duration of the infection (over 25-30 days).

No gross abnormalities in the brains of infected animals were found except for a few cases on day 56 p.i. Scattered apoptotic cells were observed only in non-neuronal cells surrounding the cerebral ventricles.

Severe degenerating nerve fibers, however, were found after day 36 p.i. bilaterally in the vagus nerve, lateral olfactory tract, and in rostral hippocampus. Scattered degenerating fibers were also found in the nerve and nucleus of spinal trigeminal nucleus, the medial edge of the gracile nucleus bordering the area postrema, deep cerebellar nuclei and inferior cerebellar peduncle, lateral thalamus, and in several fiber tracts near the lateral ventricle, including the fimbria, stria terminalis, subcortical white matter/external capsule, and the internal capsule. Degenerating neuronal cell bodies were rare among the degenerating fibers. Thus axonal and terminal degeneration is evident in this model. In addition we found apoptotic non-neuronal cells in these brains.

The observed neurotoxic effects closely associated with the chronic induction of inflammatory cytokines, IL-1 and TNF- α in particular, in the brain. The widespread, often symmetrical, patterns of expression of these molecules suggest that the actions of these molecules should be able to reach the entire brain tissue through extracellular space. Therefore, these findings point to several unique features of the potential neurotoxic effects of inflammatory cytokines. 1) Specific brain structures appeared to be more susceptible. 2) The neurotoxic injury was not confined to neuronal cells, non-neuronal cell degeneration was also present. 3) Injury to the non-neuronal cells might involve apoptotic processes whereas the neuronal injury appeared to be necrotic.

Interestingly, when we treated *T. brucei* infected rats with sodium salicylate (an aspirin derivative), CNS expression of IL-1 and TNF- α was enhanced, the above-

mentioned neurodegeneration greatly exacerbated, and several new patterns of neurodegeneration elicited (Quan et al., 2000).

Taken together, our studies suggest that chronic, but not transient, expression of inflammatory cytokines in the CNS may be neurotoxic, and different expression levels of these cytokines may cause qualitatively different patterns of neurodegeneration. There may also be specific brain structures and cell types that are especially vulnerable to CNS cytokines. We are currently testing these hypotheses in cytokine receptor knockout mice infected with *T. brucei*.

Concluding remarks

The field of cytokine-CNS interaction has matured from asserting that cytokines do communicate with the CNS to defining specific pathways by which these interactions actually take place. Many novel physiological concepts are taking hold to describe the CNS activity of cytokines while inviting further discoveries to fully comprehend these mechanisms. What are the cytokine transporters? How do peripheral vagal afferents code specifically for immune signals? Do cells of the BBB generate unknown molecules that are capable of inducing cytokine expression from parenchymal cells? By what molecular mechanisms inflammatory cytokines might cause glial and axonal degeneration? These questions remain unanswered. Meanwhile, unexpected interfaces between cytokines and CNS are emerging as important conduits. For example, cytokines are most often expressed in cells of the BBB and structures close to the cerebral ventricles. Therefore, the flow of CSF may be a major carrier for CNS produced cytokines and volume transmission may be the key modality for cytokines to reach their targets (Proescholdt et al., 2000). In addition, brain endothelial cells have been found to produce cytokines and are the major cytokine-receptor-bearing cell type in the CNS. Therefore, endothelial products, e.g., prostaglandins, could be the crucial link between cytokines and the CNS.

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