ROLE OF THE SYMPATHETIC NERVOUS SYSTEM AND THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS IN BRAIN-MEDIATED COMPENSATORY ANTIINFLAMMATORY RESPONSE

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Local infection or trauma induce a local inflammatory response. The release of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β), and IL-6 activates an inflammatory cascade improving wound healing and antimicrobial defence. Overwhelming response, however, can result in systemic inflammatory response syndrome (SIRS) and septic shock. In order to control the potentially harmful inflammatory response, the immune system can release several antiinflammatory mediators like IL-10, IL-1 receptor antagonist (ra), and soluble TNF-α receptors. TNF-α, IL-1β and prostaglandins by themselves are powerful inducers of the compensatory antiinflammatory response syndrome (CARS). However, there are evidences that in addition to the autoregulatory pathways of the immune cells the delicate balance between pro- and antiinflammatory response is controlled by central mechanisms. Hence, a bidirectional communication between the immune and central nervous system (CNS) exists and is most evident in the increase in secretion of different neuromodulators and neurohormones that follows systemic inflammation. Moreover, in vitro *studies demonstrate that these neuromediators, especially glucocorticoids and catecholamines, predominantly decrease the secretion of proinflammatory cytokines (IL-1, IL-6 and TNF-α) and increase the release of antiinflammatory mediators like IL-10 and transforming growth factor-beta. Consequently, the activation of the neuroimmune pathways reduces the intensity of the immune response and prevents an overwhelming inflammatory immune reaction. If the immunoinhibitory CNS pathways are activated without systemic inflammation, however, a brain-mediated immunodepression can develop. This activation can result from the production of cytokines in the brain following infection, injury, and ischemia or in response to different stressors (life events, depression, anxiety etc) or directly from brain stem irritation. In summary, mediators of the CNS are implicated in the regulation of immune functions and play a role in both conditioning the host's response to endogenous or exogenous stimuli and generating a brain-mediated immunodepression.*
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INTRODUCTION

An overpowering inflammatory immune response can result in systemic inflammation, septic shock, and multiorgan dysfunction. In order to prevent the excessive and deleterious action of proinflammatory cytokines after they have produced their initial, beneficial effects, the immune system can release several antiinflammatory mediators like interleukin (IL)-10, IL-1 receptor antagonist (ra), and soluble tumor necrosis factor (TNF)-α receptors. These either inhibit the production

(IL-10), neutralise [soluble TNF-α receptors 1 (p55) and 2 (p75)], or competitively antagonise (IL-1ra) proinflammatory mediators (1-3). However, *in vivo* the delicate balance between pro- and antiinflammatory responses is additionally controlled by the central nervous system (CNS).

We will focus on the following questions: What are the main routes on those the immune system and the nervous system communicate together? How do the signals go from the immune system to the brain and *vice versa*? What do neurotransmitters and neurohormones on immune cells, and, conversely, what do cytokines on neurones? Finally, an important question is what happens in case the neuroimmune pathways are activated without a systemic inflammation? This can result from production of cytokines in the brain following infection, injury, ischemia or in response to different stressors (life events, depression, anxiety etc) or directly from brain stem irritation.

The present overview highlights the most significant neuro-immune pathways, the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). We discuss the routs of communication between the CNS and the immune system, and describe the known mechanisms how mediators of the immune system act on neurones and how neuromodulators influence different immune functions.

HOW DO THE IMMUNE SYSTEM AND THE BRAIN COMMUNICATE TOGETHER?

There is evidence now that immune mediators, peptide hormones and neurotransmitters, as well as their receptors, are all inherent to the brain, endocrine and immune systems. Here, we discuss how these shared ligands and receptors are used as a common chemical language for communication within and between the immune system and CNS (Fig. 1). Such communication suggests an immunoregulatory role for the brain and a sensory function for the immune system. A clearer understanding of this circuitry could dramatically alter our understanding of integrative physiology and may profoundly affect the treatment of human disease. Glucocorticoids, catecholamines and cytokines are major players in this scenario (4).

Glucocorticoids are well known for their antiinflammatory and immunosuppressive properties. They restrain the production of proinflammatory cytokines (IL-1,TNF-α) and enhance the release of transforming growth factor-beta (TGF-β), a major antiinflammatory cytokine (5-8). Moreover, *in vivo* they augment the secretion of the antiinflammatory cytokine IL-10 in response to injury (9). Furthermore, glucocorticoids suppress the expression of MHC class II molecules like HLA-DR on antigen-presenting cells and inhibit various lymphocyte functions (10-12). However, glucocorticoids not only suppress but also enhance immune

reactions. They shift the T-cell cytokine production towards a T helper 2-like profile, which includes IL-4 (5,13, 14). Moreover, there are some reports documenting that glucocorticoids can promote the production of acute phase proteins (5). Finally, glucocorticoids stimulate the release of the proinflammatory mediator macrophage migration inhibitory factor (MIF) which has the capacity to directly counterregulate the inhibitory effects of glucocorticoids on the immune system (15). Thus glucocorticoids appear to be crucial in controlling the individual repertoire of immunological responses, including the direction and magnitude of immune reactions. With their potent antiinflammatory activity glucocorticoids represent one arm of the brain-mediated antiinflammatory response ["central" compensatory antiinflammatory response syndrome (CARS)] (Fig. 2).

There are further endogenous neuropeptides that can modulate the immune response. Recent investigations suggest antiinflammatory activities of alpha-melanocyte-stimulating hormone (α-MSH), an proopiomelanocortin-derived peptide. α-MSH antagonizes the effects of proinflammatory cytokines such as IL-1, IL-6, and TNF-α and enhances the plasma levels of PGE_2 and IL-10 (16-18). Furthermore, *in vivo* studies have consistently indicated an immune suppressive action for β-endorphin (19). There are also descriptions of an immune regulatory role of substance P, somatostatin, prolactin (16), vasoactive intestinal polypeptide (VIP) (19a), and nerve growth factor (19b).

Catecholamines act on their target cells through binding to cell surface adrenergic receptors. These adrenoceptors are divided into two classes, α and β, from which the latter are more widely expressed on immune cells (20,21). β-adrenoceptors are coupled intracellularly to the GTP-binding protein of the adenylate cyclase complex, resulting in rise of intracellular cyclic AMP (cAMP) levels and protein kinase A activation upon stimulation. By this way, catecholamines or other cAMP-elevating drugs can regulate cytokine production in monocytes (22-25).

In order to establish a link between sympathetic activation and antiinflammatory response, we tested whether catecholamines can trigger IL-10 release from peripheral blood mononuclear cells (PBMC) and purified monocytes *in vitro* (26). Indeed, both catecholamines (epinephrine and norepinephrine) as well as their second messenger dibutyryl (db)-cAMP induced a marked IL-10 release in otherwise unstimulated PBMC from healthy donors within 15 minutes. Separation experiments revealed that monocytes were responsible for this effect. The epinephrine- and norepinephrine-triggered IL-10 induction was dose-dependently inhibited by preincubation with the β-adrenoceptor antagonist propranolol but not by solely β1-receptor blockade. The protein kinase A inhibitor H89 blocked IL-10 secretion in response to both catecholamines and db-cAMP (26).
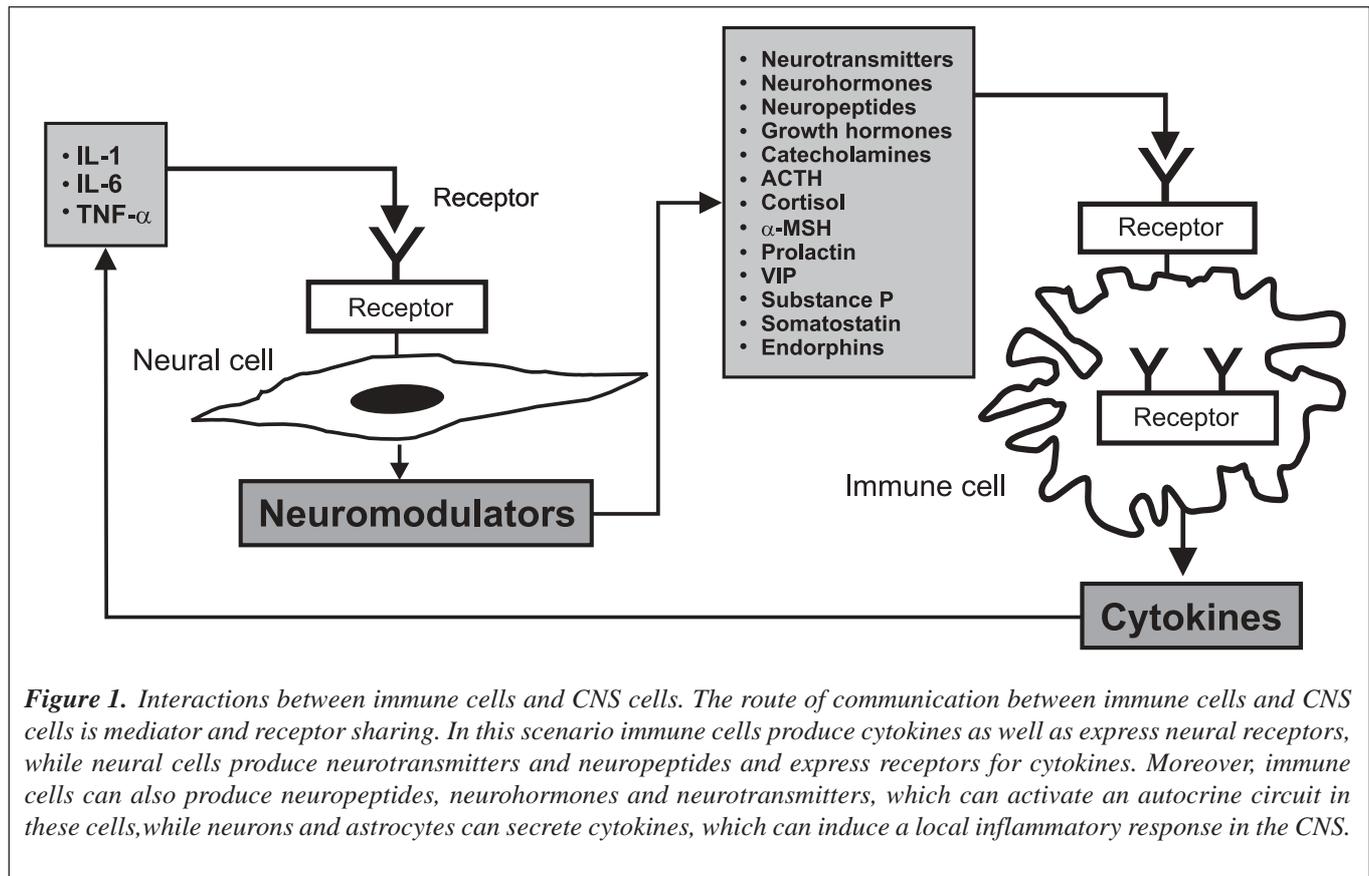
Figure 1. Interactions between immune cells and CNS cells. The route of communication between immune cells and CNS cells is mediator and receptor sharing. In this scenario immune cells produce cytokines as well as express neural receptors, while neural cells produce neurotransmitters and neuropeptides and express receptors for cytokines. Moreover, immune cells can also produce neuropeptides, neurohormones and neurotransmitters, which can activate an autocrine circuit in these cells,while neurons and astrocytes can secrete cytokines, which can induce a local inflammatory response in the CNS.
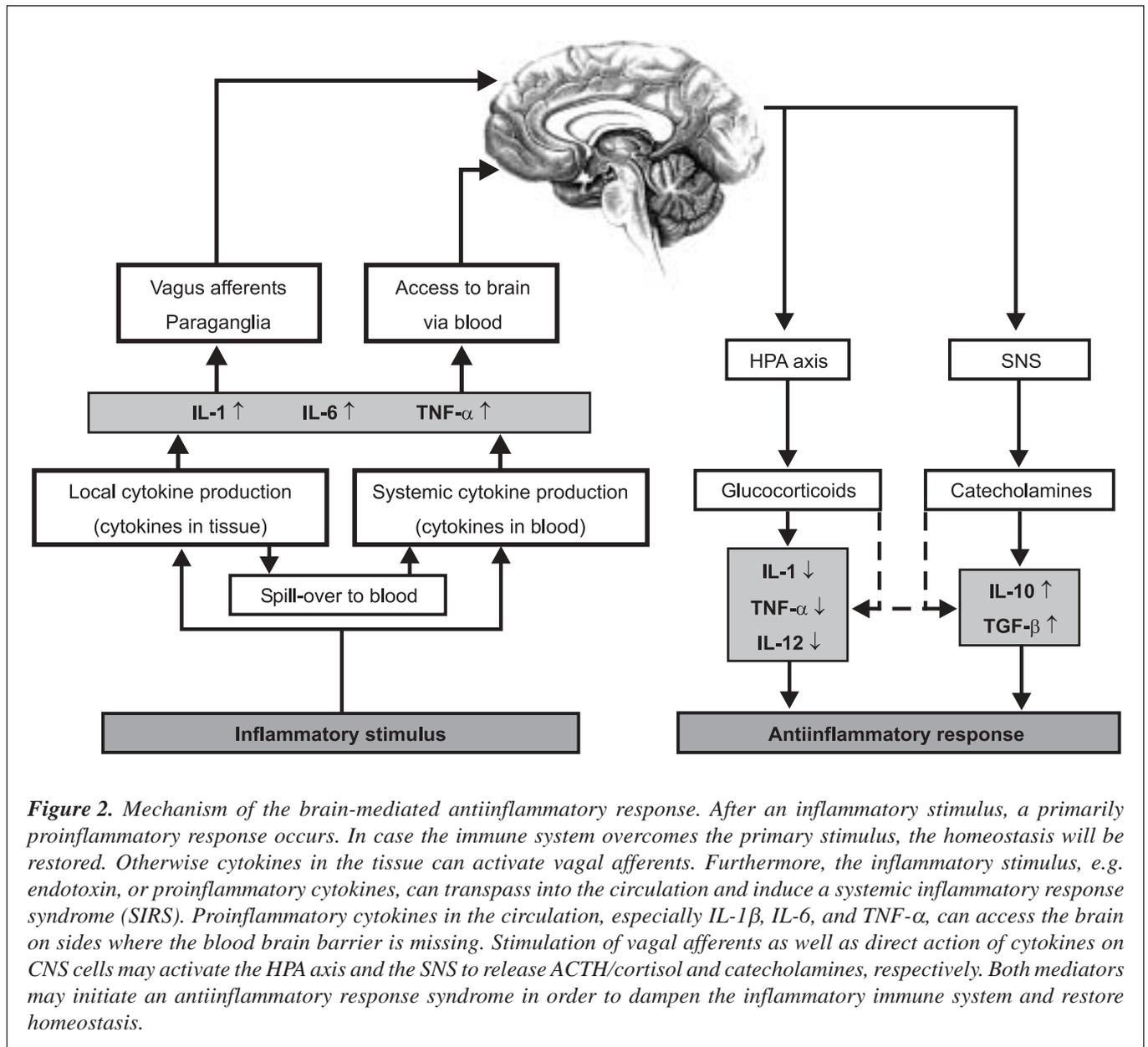
Our *in vitro* data confirmed other studies which demonstrated that catecholamines and adrenergic agonists can modulate various aspects of the immune response (initial, proliferative, and effector phases), altering such functions as cytokine production, lymphocyte proliferation, and antibody secretion (20). It has been shown that catecholamines inhibit the monocytic production of TNF-α after endotoxin stimulation (27,28). Furthermore, van der Poll *et al* (1996) demonstrated that preexposure of mononuclear cells to epinephrine or norepinephrine not only inhibits endotoxin-induced TNF-α production but also increases the endotoxin-induced IL-10 release (24). These findings were also proven *in vivo* using catecholamine infusions in healthy volunteers (24). In effect, catecholamines may cause a switch of immune cells into an antiinflammatory action and may act to dampen excessive proinflammatory effects of the cytokine network during early phases of systemic insults. Therefore, the stimulation of the sympathetic nervous system may represent the second arm of brain-mediated antiinflammatory response (Fig. 2).

Cytokines are soluble mediators involved in cell-cell regulations in the immunological and the hematopoietic system which can also act as neurotransmitters in the CNS. Brain cytokines are involved in growth-promoting activity, neuromodulatory action, fever induction, sleep and decreased food intake. In addition, cytokines participate in an intricate interrelationship to contribute to the development and maintenance of brain homeostasis (29,29a).

Clinical studies for a long time suggested that the immune system can directly activate the HPA axis and provide a shortcut by which immune recognition of an infectious challenge rapidly induces the secretion of glucocorticoids. Besedovsky *et al* (30) were the first, however, who demonstrated the existence of an immunoregulatory feedback circuit in which proinflammatory cytokines, especially IL-1β, act as afferent and glucocorticoids as efferent signal vectors (30). Interestingly, various sites of IL-1 injection, either intraperitoneal (ip) (30, 31), intravenous (iv) (32), or intra-cerebroventricular (icv) (33), provoked dose-related increases in adrenocorticotropic hormone (ACTH) and corticosterone plasma concentrations in rats. Furthermore, proinflammatory cytokines, especially IL-1β, can enhance splenic sympathetic nerve activity and increase norepinephrine turnover in the spleen, lung, diaphragm, and pancreas (34-36).

Moreover, immune cells can also produce neuropeptides, neurohormones and neurotransmitters, which can activate an

Figure 2. *Mechanism of the brain-mediated antiinflammatory response. After an inflammatory stimulus, a primarily proinflammatory response occurs. In case the immune system overcomes the primary stimulus, the homeostasis will be restored. Otherwise cytokines in the tissue can activate vagal afferents. Furthermore, the inflammatory stimulus, e.g. endotoxin, or proinflammatory cytokines, can transpass into the circulation and induce a systemic inflammatory response syndrome (SIRS). Proinflammatory cytokines in the circulation, especially IL-1β, IL-6, and TNF-α, can access the brain on sides where the blood brain barrier is missing. Stimulation of vagal afferents as well as direct action of cytokines on CNS cells may activate the HPA axis and the SNS to release ACTH/cortisol and catecholamines, respectively. Both mediators may initiate an antiinflammatory response syndrome in order to dampen the inflammatory immune system and restore homeostasis.*

autocrine circuit in the cells, and neurons and astrocytes can secrete cytokines (37,38). These cytokines with a regulatory role in immune function may also mediate inflammation associated with brain injury and repair processes resulting from head injury, hypoxia or infection (39).

HOW DO THE SIGNALS GO FROM THE IMMUNE SYSTEM TO THE BRAIN AND *VICE VERSA*?

Numerous studies investigated the mechanisms by which inflammatory mediators, especially IL-1, increase the blood

levels of neuroendocrine hormones. Most research groups proved that the main part of the neuroendocrine response mediated by IL-1β is through the induction of corticotropin releasing factor (CRF) rather than by direct action of the cytokine at the median eminence or pituitary gland (32,33,40,41). The mechanisms, however, how IL-1 releases CRF, are still speculative. There are reports suggesting a substantial role for the organum vasculosum laminae terminalis (OVLT), which lacks blood-brain barrier, as a possible site of entry of **blood-borne IL-1β** into the brain and for the preoptic area (POA), which may contain the

neurones required for the neuroendocrine response (41). An involvement of prostaglandin E$_2$ (PGE$_2$) in the OVLT and POA are also discussed (33,41). Being small and lipophilic, PGs would rapidly penetrate the tight junctions separating the OVLT from the brain. The PGs are then argued to reach and activate noradrenergic neurones in the POA that project to the paraventricular nucleus of the hypothalamus (PVH) and release CRF (40). Furthermore, using *in vivo* microdialysis, Linthorst *et al* (42) demonstrated that endotoxic challenge results in norepinephrine rise in the POA in parallel with a marked increase in corticosterone levels. The authors postulated that the profound increase in preoptic noradrenergic neurotransmission may be related to the LPS-evoked activation of the HPA axis (42,43).

There are also other hypotheses how cytokines may activate the HPA axis (40). Some authors proposed a neural route of cytokine to brain communication. By such a mechanism, local increases in **tissue levels of cytokines** would be sufficient to signal the brain, increases in blood levels would not need to occur (Fig. 2). The authors have provided evidence that activation of subdiaphragmatic vagal afferents mediate a wide range of illness responses produced by ip application of endotoxin, IL-1β, and TNF-α (26,40,44-46).

However, the transfer of cytokines from tissue into blood is a key mechanism for the induction of systemic inflammatory response syndrome (SIRS) representing the involvement of the whole organism in the inflammatory process. In this scenario, the cytokine-mediated activation of the HPA axis has the critical function to modulate and dampen the immune system and to prevent more severe and excessive catabolic effects including the ultimate deleterious consequence, death (Fig. 2) (47). Therefore, for the protective role of the HPA axis against lethality produced by immune, infectious, and inflammatory stress, the presentation of cytokines in the circulation seems to be crucial (47). Additionally to IL-1β, IL-6 and TNF-α are major cytokines involved in the induction of SIRS, and these cytokines act also centrally to stimulate hypothalamic CRF release and subsequent ACTH and glucocorticoid secretion (Fig. 1) (48-53).

The activation of the HPA axis has long been considered to be the key mechanism of the brain-mediated and stress-induced modulation of immunity and related disease processes (54). However, Keller *et al* (1983) described a corticosteroid-independent mechanism in the stress-induced suppression of lymphocyte functions. It was suggested that a variety of hormonal and neurosecretory systems may be involved in the adrenal-independent neuroimmunomodulation including α-MSH and β-endorphin (16-19,54,55).

Interestingly, in recent investigations an anatomical link between the autonomic nervous system and the immune system was established. For instance, primary and secondary lymphoid organs are innervated extensively by noradrenergic sympathetic nerve fibres (20,21). Also, nerve-mast cell links are increasingly documented (21a). Moreover, brain injection of IL-1β causes dose-related increases in plasma epinephrine and norepinephrine levels (56). The mechanisms mediating brain-IL-1-induced stimulation of the SNS remain to be elucidated. A possible role of CRF is discussed, which is released by IL-1 and known to act within the brain to stimulate both catecholamines and glucocorticoids (56). This hypothesis is supported by the observation that brain-IL-1β-induced impairment of T-cell proliferation and natural killer cell activity in adrenalectomized rats can be prevented by application of neutralising anti-CRF antibodies (57, 58). Thus it seems likely that CRF plays a key role for the brain-IL-1β-triggered activation of the SNS (34,36,58,59).

In order to investigate the role of sympathetic activation for the systemic immune response we performed various experimental studies using different animal models. In particular, we were interested in the consequences of a "sympathetic storm" after severe brain injury for the brain-mediated antiinflammatory response syndrome. Therefore, we tested the effects of an acutely increased intracranial pressure (ICP) for the IL-10 plasma levels. In rats, an elevation of ICP to 60 mm of Mercury was achieved by inflation of a subdurally placed Forgarty-catheter. Furthermore, one animal group was additionally treated with the β-adrenoceptor antagonist propranolol by iv infusion during the whole observation period. Using this approach we could show that thirty minutes after ongoing enhanced ICP, IL-10 plasma levels were already significantly raised. Moreover, the systemic IL-10 increase was completely prevented by parallel infusion of the β2-adrenoceptor antagonist propranolol demonstrating the pivotal role of catecholamines for this effect (26).

As to study the importance of brain cytokines for the systemic immune alterations, an animal model of chronic intracerebral infusion of different proinflammatory cytokines was established (60). So, we could demonstrate that continuous icv infusion of IL-1β (but not TNF-α) at 10 ng/hour significantly diminished the endotoxin-induced TNF-α secretion capacity in whole blood cell cultures whereas the IL-10 production was increased 4 hours after initiation of the infusion (61). Remarkably, the brain-IL-1β induced early IL-10 peak was prevented by the β-adrenoceptor antagonist propranolol (61). Furthermore, icv bolus injections of IL-1β at the dose of 100 ng also caused a rapid systemic rise of IL-10 after 30 min comparable to the IL-10 release after ICP increase (unpublished data). Finally, iv infusion of catecholamines produced the same effect with increase of IL-10 plasma levels within minutes (unpublished data).

Furthermore, we could show that brain cytokines and sympathetic activation may also participate in the changes of blood immune cell numbers after brain injury. We demonstrated that icv infusion of IL-1β but not TNF-α dramatically

increased neutrophile counts, whereas lymphocyte numbers dropped. Remarkably, application of the β-adrenoceptor antagonist propranolol prevented the decrease of lymphocytes and diminished the neutrophilia after IL-1β icv infusion (62).

CLINICAL CONSEQUENCES OF A BRAIN-MEDIATED ANTIINFLAMMATORY RESPONSE SYNDROME WITHOUT SYSTEMIC INFLAMMATION

Above we described the mechanisms how mediators of the immune system, e.g. IL-1β, IL-6, TNF-α, may activate neuro-immune pathways in order to protect the organism from the consequences of an uncontrolled systemic inflammatory response (Fig. 2). We called this phenomenon "central" CARS in order to demarcate it from the CARS inaugurated by Bone (63) that describes the mechanisms of systemic autoregulation of the inflammatory cascade.

The neuroimmune inhibitory pathways can also be activated, however, by cytokines released into the brain or by other stressors without a preexisting "adequate" SIRS. This may lead to systemic immunodepression and enhance the risk of infections. Natural killer cell activity, response to phyto-hemagglutinin stimulation, and IL-2 production are markedly depressed in lymphocytes isolated from blood and spleen after infusion of IL-1β into the lateral ventricle in animal experiments (57,58,64-66). Moreover, numerous studies have demonstrated that peripheral blood lymphocytes obtained from patients with malignant brain tumors respond poorly to mitogens and antigens. The production of T-helper cell cytokines [IL-2, interferon (IFN)-gamma, granulocyte/monocyte colony-stimulating factor (GM-CSF)] and the expression of IL-2 receptors (IL-2R) after mitogenic stimulation were significantly lower than those from T-cells obtained from normal individuals (67-70). Furthermore, we were able to show for the first time that in glioblastoma patients not only the function of lymphocytes but also that of monocytes is impaired. Our data demonstrated a decreased monocytic HLA-DR expression and *ex vivo* secretion capacity for pro-inflammatory cytokines. Monocyte deactivation in glio-blastoma patients could partially be restored by tumor extirpation (71). Interestingly, brain tumors produce an immense diversity of pro- and antiinflammatory cytokines (72-75). In summary, the data suggest that the described immune alterations on lymphocyte and monocyte level in brain tumor patients are caused at least in part by the brain tumor itself, probably due to local cytokine production and activation of neuroimmune pathways.

Furthermore, in several clinical studies we could demonst-rate that neurosurgical procedures were associated with a postoperative cytokine release into the cerebrospinal fluid and a decreased monocytic HLA-DR expression as sign of systemic immunodepression. If the percentage of monocytes expressing HLA-DR molecules was lower than 30 % in our assay during the first three days after neurosurgery, this was closely related to the development of infectious complications (predictive value 0.9) (26,76-78). This monocytic deactivation was linked to a brain cytokine-induced stimulation of the HPA axis (77,79).

However, our studies revealed also that stimulation of the HPA axis is not the unique mechanism involved in monocytic deactivation following brain surgery/injury. We found that intraoperative brain stem irritation induced a marked systemic release of the antiinflammatory cytokine IL-10 four to eight hours after the surgery. These patients had also strong intraoperative signs of sympathetic activation like increases in systolic blood pressure. Therefore, we assumed that sympathetic activation, likely induced by brain stem irritation/compression (manipulation, increased intracranial pressure) could be of major importance for the IL-10 release and immunodepression in selected neurosurgical patients.

To further study the effect of brain stem compression on the IL-10 plasma levels and the monocytic HLA-DR expression as marker of immunocompetence, we analysed patients with an ICP > 20 mm Hg following selective head injury, intracerebral hemorrhage or infarction. We could show that an elevated ICP in patients with brain insults was regularly associated with massive sympathetic activation, increased IL-10 plasma levels, and a severely decreased HLA-DR expres-sion on monocytes as sign for systemic immunodepression (26).

Finally, it should be emphasised again that IL-10 not only downregulates monocytic MHC class II expression and antigen-presenting capacity but also inhibits monocytic production of proinflammatory and the specific cellular immune response-stimulating cytokines, including IL-1β, IL-12 heterodimer, and TNF-α while inducing the secretion of IL-1ra that competitively inhibits IL-1 (80-84). Therefore, the rapid catecholamine-mediated systemic release of the immunoinhibitory cytokine IL-10 may be a key mechanism in the brain injury-induced systemic immunodepression. Additionally it has to be considered, however, that increased intracellular cAMP levels, as induced by catecholamines, has been demonstrated to exhibit also marked IL-10-independent immunosuppressive effects in monocytes (22). Lastly, other immune inhibitory cytokines like TGF-β can be triggered by catecholamines and may further enhance their immuno-suppressive action (85).

In summary, our data suggest that brain-derived cytokines as well as direct brain stem irritation can trigger strong activation of the HPA axis and the SNS leading to glucocorti-coid and IL-10 release inducing a severe systemic immuno-depression (26,61,76-78,86,87).

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