

Catecholamine-induced interleukin-10 release: a key mechanism in systemic immunodepression after brain injury

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Background: Infections after severe brain injury or polytrauma are still a problem, and may be the result of a brain-mediated disturbed systemic immunoreactivity. The mechanism that connects initial brain affection and systemic immunodepression, however, is still poorly understood.

Review: In order to analyze the influence of the sympathetic nervous system in the context of brain injury on systemic immune functions, we performed various *in vitro*, *in vivo* and clinical studies. We were able to demonstrate that catecholamines trigger the release of the strong anti-inflammatory cytokine interleukin (IL)-10 from peripheral blood mononuclear cells and monocytes. In animal models we were able to show that increased intracranial pressure as well as intracerebral proinflammatory cytokines (eg IL-1 β) produce a rapid systemic IL-10 release through sympathetic activation. Thus, in both models, the predominant role of catecholamines for this effect was confirmed by the complete prevention of IL-10 increase after β -adrenoreceptor blockade. Moreover, in clinical studies we clearly demonstrated that neurosurgical procedures involving brain-stem manipulation invoke sympathetic activation and a rapid systemic IL-10 release. Remarkably, this was associated with monocytic deactivation – a sign of systemic immunodepression and a high risk of infectious complications. Finally, these data were validated in patients with accidental brain injury, in whom we demonstrated a correlation between the severity of injury, sympathetic activation, IL-10 plasma levels and the incidence of infectious complications.

Conclusion: In summary, we suppose that activation of inhibitory neuroimmune pathways like the sympathetic nervous system, but also the hypothalamic–pituitary–adrenal axis, may trigger a systemic anti-inflammatory response syndrome that leads to systemic immunodepression. In this process the catecholamine-mediated systemic IL-10 release that causes monocytic deactivation may be a key mechanism.

Introduction

Brain injury has been found to be an independent risk factor for infectious complications in polytrauma patients [1]. It has been reported that early pneumonia occurs in 40% of patients with closed head injury [2,3]. Moreover, brain injury is associated with the appearance of different cytokines [e.g. interleukin (IL)-1 β , IL-6, IL-8, IL-10] in the cerebrospinal fluid [4–7]. Interestingly, high levels of proinflammatory cytokines in the brain and an elevated intracranial pressure (ICP) lead to an activation of neuro-immune pathways, such as the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system, which correlates with the severity of injury and an unfavourable prognosis [8–10]. Because monocytes and macrophages are the main targets of the immunomodula-

tory action of both glucocorticoids and catecholamines, alterations of these immunologically important cells should reflect the brain impact on the systemic postinjury immunodepression [11–13]. Indeed, monocytic alterations such as impaired endotoxin-induced cytokine production and a diminished major histocompatibility complex (MHC) class II antigen [human leucocyte antigen (HLA)-DR] expression occurred in patients who developed infectious complications after surgery, major trauma and burn injury [14–18]. An important mediator of monocytic deactivation is the anti-inflammatory cytokine IL-10. This cytokine inhibits the production of proinflammatory cytokines [eg tumour necrosis factor (TNF)- α] and is a major depressor of antigen presentation and specific cellular immunity through the reduction of MHC class II antigen expression

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and IL-12 production [19,20]. Interestingly, enhanced systemic IL-10 levels have been suggested to contribute to postinjury immunodepression by us and others [21–23].

We performed several studies to establish a link between brain-injury triggered sympathetic activation, systemic IL-10 release and immunodepression. *In vitro*, we investigated the impact of catecholamines on monocyte function. Furthermore, we developed two animal models in order to study the importance of proinflammatory brain cytokines and an increased ICP for sympathetic activation, systemic IL-10 release and altered immunoreactivity. Finally, we checked the significance of the *in vitro* and animal data in neurosurgical and accidentally brain-injured patients.

Catecholamines induce interleukin-10 release from monocytes *in vitro*

Monocytes/macrophages play a critical role in immunity as regulators of homeostasis, antigen-presenting cells, and effector cells in infection, tumour surveillance and wounding [9,10,14,15,24–27].

The cytokines secreted by monocytes/macrophages in inflammation fall into three categories. First are those that promote or mediate the acute inflammatory response as well as the type 1 response of lymphocytes. These include TNF- α , IL-1, IL-6, the IL-12 heterodimer (p70) and a range of chemotactic proteins such as IL-8 [28–32]. A second category of cytokines are those that inhibit inflammation. Included are IL-10, transforming growth factor- β and IL-1 receptor antagonist [24,33–36]. Finally, monocytes/macrophages have been shown to release cytokines that promote tissue repair and homeostasis after or during inflammation, such as platelet-derived and fibroblast growth factors [29]. Consequently, monocytes/macrophages regulate the inflammatory and immune response through both suppressive and enhancing signals.

Furthermore, monocytes/macrophages themselves can be activated and deactivated [24]. Recently, we showed that monocytic deactivation is associated with a much higher risk of infection and with a high mortality in established sepsis [25,37,38]. Deactivated monocytes are characterized by markedly reduced HLA-DR expression, diminished antigen-presenting and respiratory burst capacities, and a profoundly decreased ability to produce proinflammatory cytokines like TNF- α after *ex vivo* endotoxin stimulation [25,38,39]. An important mediator of monocytic deactivation is IL-10 [19,28,40,41].

In addition to direct immunoregulatory loops (eg IL-10 induction in monocytes by TNF- α [42]), monocytic deactivation or switch of these immune cells into an anti-inflammatory action can be triggered by neuroimmune pathways. Thus, monocytes/macrophages express glucocorticoid and β -adrenergic receptors [24,43]. Catechol-

amines act on their target cells through binding to cell-surface adrenergic receptors. These adrenoreceptors are divided into two classes – α and β – from which the latter are more widely expressed on immune cells [43]. β -adrenoreceptors are coupled intracellularly to the guanosine triphosphate-binding protein of the adenylate cyclase complex, resulting in a rise in intracellular cyclic adenosine monophosphate (AMP) levels and protein kinase A activation upon stimulation. In this way, catecholamines or other cyclic AMP-elevating drugs can regulate cytokine production in monocytes [12,42,44,45] (Fig. 1).

In order to establish a link between sympathetic activation and monocytic deactivation and anti-inflammatory function, we tested whether catecholamines can trigger IL-10 release from peripheral blood mononuclear cells and purified monocytes *in vitro* [8]. Indeed, both catecholamines (adrenaline and noradrenaline) and their second messenger (dibutyryl-cyclic AMP) induced a marked IL-10 release in otherwise unstimulated peripheral blood mononuclear cells from healthy donors within 15 min. Separation experiments revealed that monocytes were responsible for this effect. The adrenaline- and noradrenaline-triggered IL-10 induction was dose-dependently inhibited by preincubation with the β_2 -adrenoreceptor antagonist propranolol. The protein kinase A inhibitor H89 blocked IL-10 secretion in response to both catecholamines and dibutyryl-cyclic AMP [8].

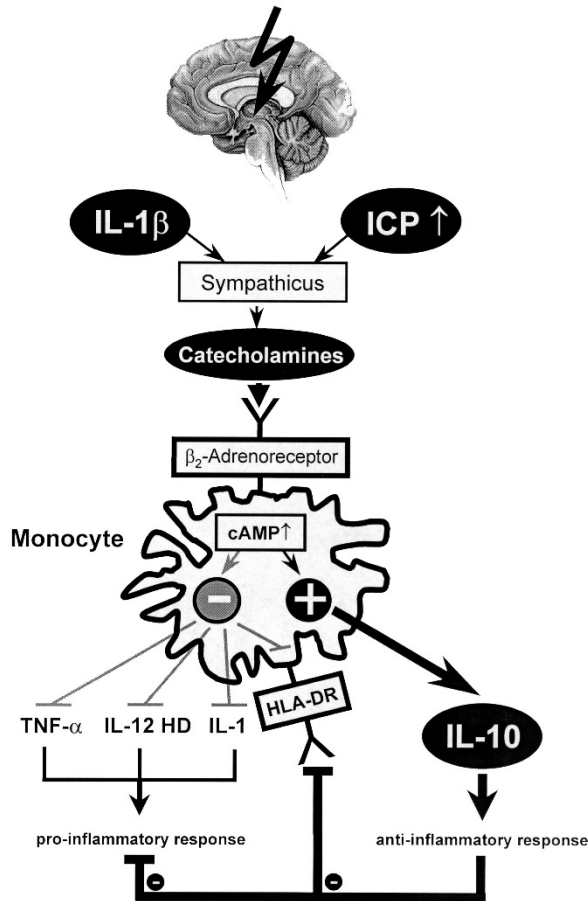
Our *in vitro* data confirmed other studies [43] that demonstrated that catecholamines and adrenergic agonists can modulate various aspects of the immune response (initial, proliferative and effector phases), altering such functions as cytokine production, lymphocyte proliferation and antibody secretion. Thus, it has been shown that catecholamines inhibit the monocytic production of TNF- α after endotoxin stimulation [11,45]. Furthermore, van der Poll *et al* [12] demonstrated that pre-exposure of mononuclear cells to adrenaline or noradrenaline not only inhibits endotoxin-induced TNF- α production but also increases the endotoxin-induced IL-10 release. These findings were also proved *in vivo* using catecholamine infusions in healthy volunteers [12].

In summary, catecholamines may cause a switch of monocytes/macrophages into an anti-inflammatory action and may act to dampen excessive proinflammatory effects of the cytokine network during early phases of systemic insults.

Brain IL-1 β and increased ICP induce systemic IL-10 release through stimulation of the sympathetic nervous system *in vivo*

Interestingly, in recent investigations an anatomical link between the autonomic nervous system and the immune system was established. Primary and secondary lymphoid organs are thus innervated extensively by noradrenergic

Figure 1



Mechanism of the brain injury-induced interleukin (IL)-10 release that leads to systemic immunodepression. Proinflammatory cytokines are produced in the brain after infection, injury and ischaemia. Microglia, astrocytes and blood-derived immune cells are the main sources for this cytokine production. These brain cytokines (especially IL-1 β) and/or an increased intracranial pressure (ICP) may activate inhibitory neuroimmune pathways, such as the sympathetic nervous system. This leads to high catecholamine levels in plasma. Immune cells, especially monocytes, carry β -adrenoreceptors on their surface that mediate the catecholamine-induced increase of intracellular levels of cyclic adenosine monophosphate (cAMP) as second messenger for the regulation of monocytic cytokine production. Thus, catecholamines and cyclic AMP-elevating drugs can inhibit the production of IL-1 β , IL-12 heterodimer and tumour necrosis factor (TNF)- α and increase the synthesis of the potent anti-inflammatory and immunosuppressive cytokine IL-10, resulting in the downregulation of monocytic proinflammatory and accessory functions. By this mechanism, catecholamines may switch the monocytes/macrophages to a predominant anti-inflammatory action. HLA, human leukocyte antigen.

sympathetic nerve fibres [43,46]. Additionally, mediators of the immune system (especially IL-1 β) can enhance splenic sympathetic nerve activity and increase noradrenaline turnover in the spleen, lung, diaphragm and pancreas [47–49]. Taken together, the *in vivo* situation seems to be

characterized by a close mutual regulation of the immune and the sympathetic nervous systems.

Considering brain injury, cytokines produced in the brain after trauma as well as an increased ICP can enhance sympathetic nerve activity. Therefore, we investigated the role of brain cytokines and increased ICP in the systemic IL-10 release via the catecholamine- β_2 -adrenoreceptor pathway using different animal models.

First, we tested the consequences of an acutely increased ICP for the IL-10 plasma levels [8]. In rats, an elevation of ICP to 60 mmHg was achieved by inflation of a subdurally placed Forgarty catheter. Furthermore, one animal group was additionally treated with the β_2 -adrenoreceptor antagonist propranolol by intravenous infusion during the whole observation period. Using this approach we showed that 30 min after ongoing elevated ICP, IL-10 plasma levels were significantly raised. Moreover, the systemic IL-10 increase was completely prevented by parallel infusion of the β_2 -adrenoreceptor antagonist propranolol, demonstrating the pivotal role of catecholamines for this effect [8].

In order 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 [23]. Using this model, we were able to demonstrate that continuous intracerebroventricular infusion of IL-1 β (but not TNF- α) at 10 ng/h significantly diminished the endotoxin-induced TNF- α secretion capacity in whole-blood cell cultures, whereas the IL-10 production was increased 4 h after initiation of the infusion [50]. Remarkably, the brain IL-1 β -induced early IL-10 peak was prevented by the β_2 -adrenoreceptor antagonist propranolol [50]. Furthermore, intracerebroventricular bolus injections of IL-1 β (100 ng) also caused a rapid systemic IL-10 after 30 min, which was comparable to the IL-10 release after ICP increase (unpublished data). Finally, intravenous infusion of catecholamines produced the same effect, with increase in IL-10 plasma levels within minutes (unpublished data).

Interestingly, we showed that brain cytokines and sympathetic activation may also participate in the changes in blood immune cell numbers after brain injury [51]; intracerebroventricular infusion of IL-1 β but not TNF- α dramatically increased neutrophil counts, whereas lymphocyte numbers dropped. Remarkably, administration of the β -adrenoreceptor antagonist propranolol prevented the decrease in lymphocytes and diminished the neutrophilia after intracerebroventricular infusion of IL-1 β .

In conclusion, our *in vivo* data in rats completely confirmed the *in vitro* results of a catecholamine-triggered rapid IL-10 release. Moreover, they gave strong evidence

for the involvement of this mechanism in brain-mediated immunodepression. Thus, in both models of brain injury (ICP increase and intracerebral IL-1 β infusion) a rapid systemic IL-10 release was found, which was mediated through the activation of the sympathetic nervous system.

Sympathetic activation is involved in systemic immunodepression after neurosurgery and accidental brain injury

In several clinical studies we demonstrated that neurosurgical procedures are associated with a postoperative cytokine release into the cerebrospinal fluid and a decreased monocytic HLA-DR expression – a sign of systemic immunodepression. If the percentage of monocytes that express HLA-DR molecules was lower than 30% during the first 3 days after neurosurgery, this was closely related to the development of infectious complications (predictive value 0.9) [8–10,52]. This monocytic deactivation was linked to a brain cytokine-induced stimulation of the HPA axis [10,53].

Our studies also revealed that stimulation of the HPA axis is not the only mechanism involved in monocytic deactivation after brain surgery/injury, however. We found a strong effect of tumour location on the postoperative immunological changes after elective neurosurgery [8]. Almost exclusively, patients with infratentorial tumours with brain-stem compression showed a marked systemic release of the anti-inflammatory cytokine IL-10 4–8h after neurosurgery. These patients, however, also had strong intraoperative signs of sympathetic activation, such as increases in systolic blood pressure. Therefore, we assumed that sympathetic activation, probably induced by brain IL-1 β or brain-stem irritation/compression (manipulation, increased ICP), could be of major importance for the IL-10 release and immunodepression in neurosurgical patients.

To further study the effect of brain-stem compression on the IL-10 plasma levels and the monocytic HLA-DR expression we analyzed patients with an ICP greater than 20mmHg after selective head injury, or intracerebral haemorrhage or infarction [8]. We showed 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 expression on monocytes – signs of systemic immunodepression.

Finally, it should be emphasized again that IL-10 not only downregulates monocytic MHC class II expression and antigen-presenting capacity. It also inhibits monocytic production of proinflammatory and the specific cellular immune response-stimulating cytokines, including IL-1 β , IL-12 heterodimer and TNF- α , while inducing secretion of IL-1 receptor antagonist that competitively inhibits IL-1 activity (Fig. 1) [22,33,35,36,54]. Thus, the rapid catecholamine-mediated systemic release of the immuno-

inhibitory cytokine IL-10 might be a key mechanism in brain injury-induced systemic immunodepression.

It also has to be considered, however, that increased intracellular cyclic AMP levels, as induced by catecholamines, have been demonstrated to have marked IL-10-independent immunosuppressive effects in monocytes (Fig. 1) [42]. Lastly, other immune-inhibitory cytokines such as transforming growth factor- β can be triggered by catecholamines and may further enhance their immunosuppressive action [55].

Conclusion

In summary, our data regarding brain injury suggest that brain-derived cytokines as well as direct brain-stem irritation can trigger strong sympathetic activation leading to a systemic IL-10 release and monocytic deactivation which, as a sign of severe systemic immunodepression, is associated with a high risk of infectious complications. The likely pathophysiological role of this neuroimmunological pathway of immune suppression is further underlined by the fact that, apart from brain injury, ‘sympathetic storm’ with elevated plasma catecholamine concentrations can also result from other stressful events, such as myocardial infarction, sepsis and stressful episodes [56–61].

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