CENTRAL NERVOUS SYSTEM INJURY-INDUCED IMMUNE DEFICIENCY SYNDROME

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Abstract | Infections are a leading cause of morbidity and mortality in patients with acute CNS injury. It has recently become clear that CNS injury significantly increases susceptibility to infection by brain-specific mechanisms: CNS injury induces a disturbance of the normally well balanced interplay between the immune system and the CNS. As a result, CNS injury leads to secondary immunodeficiency — CNS injury-induced immunodepression (CIDS) — and infection. CIDS might serve as a model for the study of the mechanisms and mediators of brain control over immunity. More importantly, understanding CIDS will allow us to work on developing effective therapeutic strategies, with which the outcome after CNS damage by a host of diseases could be improved by eliminating a major determinant of poor recovery.

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Infections are a leading cause of death in patients with acute CNS injury, such as stroke, traumatic brain injury (TBI) and spinal cord injury (SCI). In affected patients, infections impede neurological recovery and increase morbidity as well as mortality. Infections after CNS injury may be attributed to exposure of these patients to invasive medical procedures and hospitalization, dysphagia and aspiration, bladder dysfunction, and so on. However, it has become clear that CNS injury is an independent risk factor, which, through specific mechanisms, significantly increases susceptibility to infection. It has only recently been realized that CNS injury induces a disturbance of the normally well balanced interplay between the immune system and the CNS, and that this is the mechanism by which CNS injury leads to secondary immunodeficiency (CNS injury-induced immunodepression, CIDS) and infection.

The CNS senses inflammation in the body through the autonomic nervous system, and mounts a strong counter-regulatory response in case of systemic infection or injury. This response is anti-inflammatory and immunodepressant in nature, and can be considered adaptive, as it helps to contain infection- and injury-induced inflammation when they occur in the periphery. Brain or spinal cord injury can lead to the production of inflammatory mediators in the CNS, or disruption of signalling in the control circuitry of neural–immune interactions, both of which may also lead to systemic downregulation of INNATE AND ADAPTIVE IMMUNITY. However, in the absence of immune stimulation by peripheral inflammation this leads to profound deficiencies of the body's defence systems, which leaves the host vulnerable to invading microorganisms.

In this article, we review the clinical and experimental evidence for CIDS after CNS injury, and compare it with other medical conditions in which the brain modulates the immune system, such as during systemic inflammation or trauma. We focus on stroke, TBI and SCI, as CIDS induced by these prototypical acute CNS disorders is best understood. As CIDS is an important contributor to the negative outcome for patients with brain injury, there is an urgent need to raise the awareness of CIDS in physicians treating patients with acute CNS injury, to understand its mechanisms and to devise therapeutic countermeasures.

Infection as a result of CNS injury

There is overwhelming clinical evidence that infection is a highly relevant complication in three major injury conditions of the CNS: TBI, stroke and SCI.

Stroke. The prognosis of STROKE patients is mainly dependent on the occurrence of medical complications[1]. In a prospective study, up to 85% of stroke patients experienced complicating events during acute care[2]. The most frequently occurring medical complications of stroke are fever and pneumonia[3]. The association between stroke and fever had already been recognized more than 160 years ago[4]. Fever occurs in up to 61% of all stroke patients during the acute phase[5] and has a negative effect on stroke outcome[6,7]. The main cause of fever in stroke patients is infection[8], in particular pneumonia and urinary tract infections[1,9]. Pneumonia is the most common serious medical complication in stroke care[9,10], occurring in up to 22% of all stroke patients. Stroke-associated pneumonia increases acute and long-term mortality 2.5-fold, and is the most frequent cause of death in the post-acute phase[11–14]. In many patients, stroke-associated pneumonia is an early complication (58% of pneumonias develop within 48 h)[1,2,5,15]. The high incidence of infection abides over time, with a cumulative incidence of about 50% during the rehabilitation phase[10].

The incidence of pneumonia correlates with stroke severity[16], infarct location[15], impairment of protective reflexes[17], dysphagia and mechanical ventilation[15], as well as neurological deficit. However, although aspiration is the commonly cited explanation for stroke-induced pneumonia, aspiration alone is not sufficient to induce pneumonia: approximately half of all healthy adults aspirate during sleep without developing pneumonia[18,19]. In addition, not only severely affected patients are at risk: even silent cerebral infarcts are related to a higher incidence of pneumonia[20].

Traumatic brain injury (TBI). NOSOCOMIAL infections are common extracranial complications in patients with head injuries[21,22]. The frequent need for mechanical ventilation places patients with severe traumatic brain injuries at particular risk of developing ventilator-associated pneumonia (VAP). The overall incidence of VAP in patients receiving mechanical ventilation ranges from 8% to 28%[23], but can reach 60% in patients with neurotrauma, which shows the high susceptibility to infections of this particular pathology[21,24–26]. Risk factors for VAP include trauma severity, aspiration and nasal carriage of *Staphyloccocus aureus* on admission[24,27,28]. In addition, the use of high dose barbiturates and treatment with hypothermia for the management of intracranial hypertension after brain injury may increase susceptibility to infections[24,29,30]. Although ventilated intensive care unit patients with VAP seem to have a higher risk of death compared with patients without pneumonia[21], whether VAP independently contributes to mortality

in patients with TBI is controversial. Some investigators have reported pneumonia, particularly late onset pneumonia due to certain pathogens (for example, *Pseudomonas aeruginosa* and *Acinetobacter spp*), to be an independent risk factor for mortality after TBI, whereas other studies found no excess mortality attributable to pneumonia in these patients[21,22,25,31,32]. However, pneumonia is associated with fever, HYPOXAEMIA, arterial hypotension and intracranial hypertension, which are known to worsen the neurological outcome of patients with brain injuries[24].

Spinal cord injury (SCI). Infectious complications, predominantly pulmonary and urinary tract infections, occur frequently within the first days after SCI[33,34]. Although early mortality is due to direct complications of other organ systems, infections are the leading cause of death in the post-acute phase following SCI[35,36]. The incidence of pneumonia is higher in patients with complete tetraplegia (38%) than in those with complete paraplegia (15%).

It is of note that the incidence of pneumonia in patients not undergoing surgery (spine-stabilization or other) has been shown to be similar to that in those undergoing surgery, which suggests that surgery-induced 'post-aggression syndrome' is of minor relevance, with injury of the spinal cord being the determining factor[37]. This view is further supported by the fact that patients develop drastic immunodepression after SCI, whereas patients undergoing lower limb surgery show no or only minor immunosuppression. Furthermore, despite its well known immunodepressant effects, iatrogenic application of high dose methylprednisolone, a common treatment after SCI, is not the determining factor of post-SCI immunodepression, as rats with or without high dose methylprednisolone treatment develop similar immune deficiency after experimental SCI (T. Riegger, S. Conrad, H. J. Schluesener, H.-P. Kaps, C. Baron, J. Gerstein, K. Dietz, M. Adibzahdeh, R. Meyermann and J.M.S., unpublished observations).

Almost 50% of the deaths that occur subsequent to SCI are due to infections, such as pneumonia or septicaemia. Reines and Harris[38] reported an attributed mortality rate of 11% for patients with SCI due to pulmonary complications. Pneumonia was the leading cause of death during a period of 12 years after injury[35]. Pneumonia occurs more frequently in patients with extensive SCI than in patients with milder injury.

Surprisingly, pneumonia was diagnosed late, at an average of 25 days following injury[33]. In addition, recent evidence shows that infections and associated hyperthermia are linked with worse neurological outcomes after CNS injury[39,40]. Therefore, current evidence suggests that clinically relevant infections are common after SCI, and that they have an important impact on outcome after SCI.

As reviewed above, there is ample evidence that CNS injury is associated with a high risk of infection, and that the consequences of these infections for outcome are profound (TABLE 1). This holds true not only for

INNATE AND ADAPTIVE IMMUNITY
The early phases of the host response to a pathogen depend on innate resistance mechanisms. The activation of innate effector mechanisms induces the clonal expansion of antigen-specific lymphocytes and initiates adaptive immune responses, including the development of immunological memory.

STROKE
There are two main types of stroke: ischaemic (caused by blockage in an artery that supplies blood to the brain) and haemorrhagic (caused by the bleeding of ruptured blood vessels in the brain).

NOSOCOMIAL
A disease acquired in hospital.

HYPOXAEMIA
Describes critically decreased arterial oxygen levels.

Table 1 | **Clinical features and effects of CNS injury-associated infections**

Injury	Incidence (per million)	Rate of infection	Attributed mortality	Typical infections
Stroke	2,000—3,500	16–23 %	> 30% (acute)	Pneumonia, urinary tract infections
Traumatic brain injury	1,600	21–60%	up to 6.7%	Pneumonia, septicaemia, urinary tract infections
Spinal cord injury	30–60	28–38 %	4.4–16.7 %	Cystitis, pneumonia, pancreatitis, wound infections

the acute phase but also for the chronic phase. Even in patients with chronic CNS injury, peripheral infection or inflammation exacerbates CNS symptoms. But why are patients with CNS injury at such a high risk of infection? They often have complicating peripheral injury (polytrauma), undergo invasive medical treatment (such as surgery, catheterization and mechanical ventilation), may be immobilized and exposed to various multiple-drug-resistant bacteria, and may have CNS lesions that specifically impair their ability to swallow — leading to aspiration — and/or cause retention of urine. These factors, alone or in combination, seem sufficient to explain the high incidence of infection. Below, we review evidence that CNS injury can directly induce immunodepression, and that this may explain the high risk of infection in patients with CNS injury. We show that CIDS results in profound deficiencies of the body's defence systems, which leaves the host susceptible to infection at a time when efficient immunity is desperately needed.

Cell-mediated immune responses

A host of studies have demonstrated immune dysfunction after CNS injury[41–45]. Although the initial local response to brain damage is pro-inflammatory and accompanied by a systemic response comprising features of the SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS), patients with injuries of the CNS also show signs of systemic immunosuppression[28,46]. Commonly reported defects in immune function in patients after stroke, TBI or SCI include reduced peripheral blood lymphocyte counts and impaired T- and natural killer (NK)-cell activity. There is evidence that peripheral blood T-lymphocytes obtained from patients with CNS injury show reduced mitogen-induced cytokine production and proliferation *in vitro*[41,42,47,48]. The response rate of patients with brain trauma to the anergic delayed-type hypersensitivity (DTH) skin test was found to correlate with trauma severity[48,49]. Similarly, decreased natural killer (NK) cell counts and cytotoxic activity was observed in these patients[41,50,51]. In contrast to impaired T- and NK-cell functions, HUMORAL immune responses seem less affected after CNS injury[47,50,52]. Trauma-induced immunosuppression is also reflected by impaired phagocytotic activity of granulocytes and by monocyte deactivation[45,53,54].

Circulating monocytes from patients with acute brain injury have decreased expression of major histocompatibility complex (MHC) class II and a profoundly reduced capacity to produce pro-inflammatory cytokines in response to *ex vivo* stimulation with ENDOTOXIN[45,54]. Impaired monocyte functions result in insufficient antigen-presentation and decreased expression of secreted or membrane-bound co-stimulatory molecules and may, therefore, contribute to reduced lymphocyte responses[55].

In general, changes in cellular immune responses correlate with the severity of brain injury. They occur rapidly — within hours after the injurious insult — and can last for up to several weeks[41–43]. In addition, the extent and duration of impaired cell-mediated immune responses in patients with CNS injuries often correlate with an increased risk of infection and poor outcome[45,56,57]. The importance of impaired cellular immune responses for the increased susceptibility to infection after CNS injury was recently shown by Prass *et al.*[58] in a mouse model of cerebral ischaemia. Stroke induced a rapid and extensive apoptotic loss of lymphocytes in lymphoid organs and peripheral blood, which was observed as early as 12 h after cerebral ischaemia. Cellular dysfunction was evident by the decreased production of lymphocytic interferon-γ (IFNγ) and monocytic tumour necrosis factor-α (TNFα). Immune dysfunctions were observed for up to 6 weeks after stroke. Importantly, mice spontaneously developed systemic bacterial infections 1–3 days after cerebral ischaemia, well after first signs of immunosuppression were observed. Immune reconstitution by adoptive transfer of IFNγ-producing lymphocytes (that is, T and NK, but not B cells) from healthy littermates or treatment with recombinant IFNγ greatly diminished bacterial burden, demonstrating a causative link between suppression of cell-mediated immune responses and increased susceptibility to bacterial infections.

In summary, substantial clinical and experimental evidence points towards a major role of impaired cell-mediated immune responses in the high incidence of infectious complications after CNS injury. Brain injury leads to a characteristic immunological phenotype, which is immunodepressant. To understand how and why CNS injury induces immunodepression, we have to explore the mechanisms by which the immune system and CNS interact.

SYSTEMIC INFLAMMATORY
RESPONSE SYNDROME
(SIRS). This describes the host response to a critical illness of either infectious or noninfectious aetiology. The response is mediated by a cascade of pro-inflammatory mediators, such as inflammatory cytokines (for example, TNFα), activated complement factors and lipid mediators.

HUMORAL
Derived from the blood.

ENDOTOXINS
Inflammatory bacterial cell wall products that can cause sepsis.
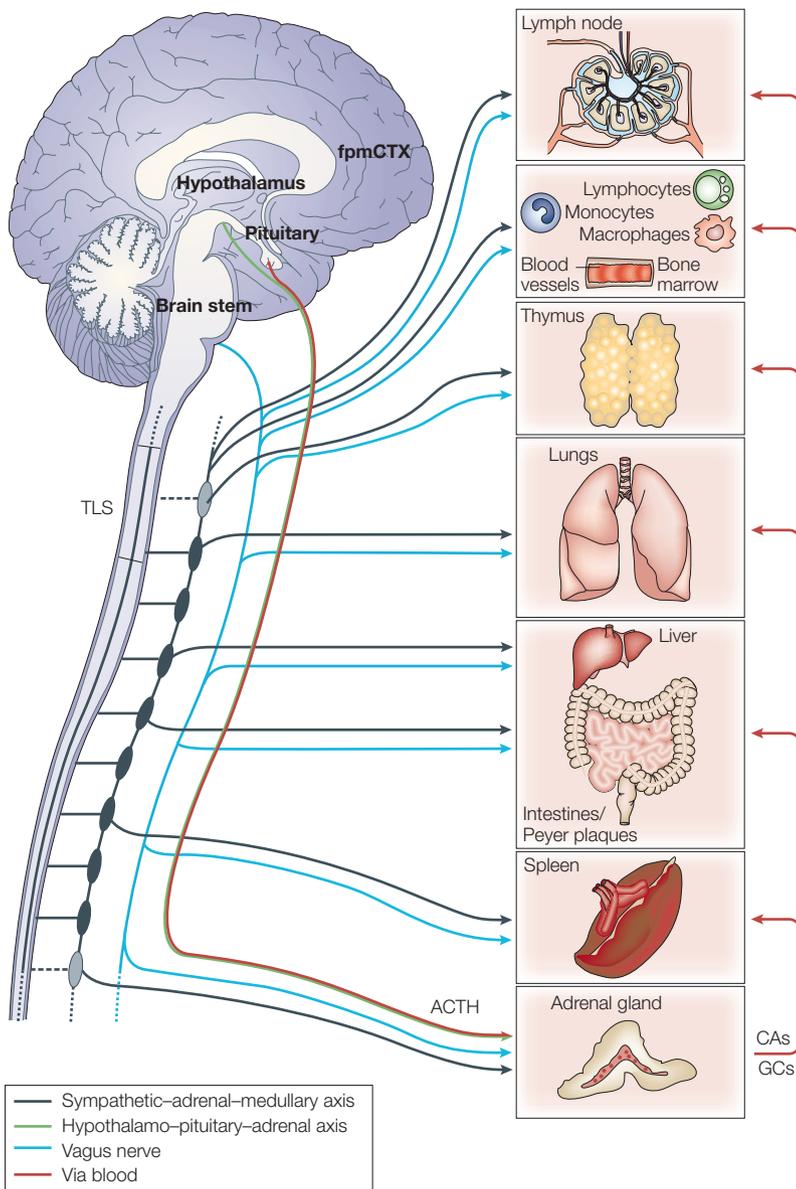
Figure 1 | **The nervous and immune systems are engaged in bidirectional communication.** Sensors within the central and peripheral autonomic nervous systems relay information about the status of the immune system. This input is processed by the CNS, in particular the frontal premotor cortex (fpmCTX), the hypothalamus, the pituitary and the brain stem. This processing results in homeostatic signals being sent to various sites in the body via three major pathways of neuroimmunomodulation: the hypothalamo—pituitary—adrenal (HPA) axis, the sympathetic–adrenal–medullary (SAM) axis and the parasympathetic nervous system (vagus nerve). Activation of the HPA and the SAM axes results in production of glucocorticoid hormones (GCs) and catecholamines (CAs). ACTH, adrenocorticotropic hormone; TLS, thoraco–lumbar system.

CNS modulation of the immune system

To respond to challenges from within the body and from the outside world, the nervous and immune systems are engaged in intense bidirectional communication. Sensors in the central and peripheral autonomic nervous systems relay information about the status of the immune system. This input is processed by the CNS and results in homeostatic signals via three main pathways of neuroimmunomodulation:

the hypothalamo–pituitary–adrenal (HPA) axis, the sympathetic nervous system (SNS) and the parasympathetic nervous system[59–61]. FIGURE 1 and TABLE 2 give an overview of the relevant anatomical pathways and structures, which are reviewed below in more detail.

Sensing of inflammation by the CNS. Today, we know of at least two pathways by which the brain senses inflammation: a neural (mainly by the vagus nerve) and a humoral pathway (for reviews, see REFS 62,63). Inflammation leads to the production of cytokines (for example, TNF, interleukin-1β (IL-1β) and IL-6), which can either engage with their cognate receptors outside the CNS — on local afferent fibres of the vagal nerve[64] — or after entry from the bloodstream into the brain, with receptors in the CNS. Passage into the brain of these large molecules may occur actively, through carrier-mediated mechanisms[65], or passively, through the capillary endothelium of circumventricular organs that lack blood–brain barrier properties[66]. The circumventricular organs include the pineal gland, the subfornical organ, the median eminence, the neural lobe of the pituitary, the subcommissural organ and, importantly, the organum vasculosum of the lamina terminalis[67]. The circumventricular organs are central relays of neuroendocrine and neuroimmune signalling, through which information about the immune status is fed into sympathetic and parasympathetic processing. Alternatively to direct brain access, cytokines in the blood stream may act at intact sites of the blood–brain barrier through receptors on brain endothelial cells, where they induce the abluminal release of diffusible mediators, such as nitric oxide and prostaglandin E2.

Cytokines arising from injury-induced inflammation in the CNS may access control centres of neural–immune interaction directly, via diffusion in the extracellular space and cerebrospinal fluid, or indirectly, via the bloodstream. In general, cytokine receptors relevant for CNS–immune communication in the brain are preferentially located in the circumventricular organs and the medial preoptic area, from which the signal is relayed to the paraventricular nucleus (PVN) of the hypothalamus through neural projections[68].

The hypothalamus. Besides that from the preoptic area, the hypothalamus receives input from many other CNS regions, including the nucleus tractus solitarius –(NTS), formatio reticularis, the retina and the insular cortex, all of which modulate its activity and output. Through the release of corticotropin-releasing factor (CRF) from its PVN, the hypothalamus modulates the HPA axis and the SNS. Descending projections to brain stem centres (for example, the NTS) affect vagal output. In addition, CRF neurons in the hypothalamus can respond directly, to cytokines, as well as to autonomic input. For example, vagal input is connected to the hypothalamus directly, via the NTS, and indirectly, via the locus coeruleus.

Table 2 | **Mechanisms of brain–immune interaction during CARS and CIDS**

Variable	SNS	HPA axis	N. Vagus
Triggers (CIDS only)	Neurogenic (Disinhibition or excitation of autonomic nervous system through lesion) Inflammatory cytokines (locally produced)	Neurogenic (Disinhibition or excitation of autonomic nervous system through lesion) Inflammatory cytokines (locally produced)	Neurogenic (Disinhibition or excitation of autonomic nervous system through lesion) Inflammatory cytokines (locally produced)
Triggers (CARS and CIDS)	Inflammatory cytokines (through blood stream/afferent vagus nerve)	Inflammatory cytokines (through blood stream/afferent vagus nerve)	Inflammatory cytokines (through blood stream/afferent vagus nerve)
Sensors	Chemoreceptive areas of the midbrain	Chemoreceptive areas of the midbrain	Chemoreceptive areas of the midbrain
Mediated through	Tracts and fibres of the SNS	ACTH in blood stream	Efferents of vagus nerve
Effectors	Catecholamines	Glucocorticoids	Acetylcholine
Targets in immune system	Lymphocytes, monocytes/macrophages, granulocytes	Lymphocytes, monocytes/macrophages, granulocytes	Tissue macrophages

ACTH, adrenocorticotropic hormone; CARS, compensatory anti-inflammatory response syndrome; CIDS, CNS injury-induced immunodepression; HPA axis, hypothalamo–pituitary–adrenal axis; SNS, sympathetic nervous system.

The sympathetic nervous system. The SNS innervates both primary and secondary lymphoid organs, including the thymus, bone marrow, spleen, lymph nodes and mucosa-associated lymphoid tissues (for a review, see REF. 69). The extensive sympathetic innervation of immune organs and the presence of adrenergic receptors on almost all leukocytes indicate that immune function is strongly influenced by the level of sympathetic activity. Activation of the SNS causes the release of catecholamines (CAs) from sympathetic nerve terminals and from the adrenal medulla.

CAs induce a rapid, but transient, increase in blood lymphocyte counts and granulocytes. They appear to increase circulating leukocyte numbers by mobilizing cells from the marginal pool and peripheral reservoirs such as the spleen and lungs[70]. However, prolonged exposure to CAs decreases circulating lymphocyte numbers. CAs seem to selectively inhibit IFNγ and IL-2 production by TYPE 1 T-HELPER T CELLS (Th1), but do not affect or even enhance TYPE 2 T-HELPER T CELL (Th2) cytokine production[71,72]. It is of note that β_2-adrenoreceptor (β_2AR) expression has been found on Th1 but not on Th2 cells, providing a molecular explanation for the observed differential effects of CAs on T-helper cell subsets[72]. As well as exerting direct inhibitory effects on Th1 cells, CAs suppress the capacity of antigen-presenting cells to induce Th1 cell responses, and β_2AR activation inhibits the differentiation of naive CD4+ T cells to Th1 cells in an IL-12-dependent manner[73]. Several studies have shown that noradrenaline and adrenaline decrease the production of TNFα, IL-1β and IL-12 by lipopolysaccharide (LPS)-stimulated monocytes, dendritic cells and human whole blood[73–75]. In addition, NK-cell activity, including cytotoxic activity and the production of effector molecules, is suppressed by CAs[76–78].

In contrast to the inhibition of pro-inflammatory cytokines, CAs and β_2AR agonists increase the production of the anti-inflammatory cytokine IL-10 by LPS-stimulated monocytes and dendritic cells, and may even stimulate the release of preformed IL-10 from unstimulated monocytes[45,74,75]. In turn, increased IL-10 concentrations potently inhibit the pro-inflammatory and antigen-presenting capacity of monocytes/macrophages and dendritic cells, impairing their ability to initiate Th1 cell immune responses.

The parasympathetic nervous system. Recently, a novel bidirectional communication pathway between the nervous and immune systems was uncovered: the vagal 'cholinergic anti-inflammatory pathway', which results in a fast (real-time) and localized modulation of immune function (for reviews, see REFS 63,79). In response to acetylcholine, activated macrophages swiftly decrease the production of pro-inflammatory cytokines such as TNFα, IL-1β and IL-18, but not the anti-inflammatory cytokine IL-10 (REF. 80). Very recently, the α-7 nicotinic acetylcholine receptor, which is expressed on macrophages, was identified as the key target of cholinergic anti-inflammatory signalling[81].

The hypothalmic–pituitary–adrenal axis. The end products of the HPA axis — glucocorticoids — have well known anti-inflammatory and immunosuppressive effects. They prevent inflammation by suppressing the production of many pro-inflammatory mediators, including cytokines (such as IL-1β and TNFα), chemokines (IL-8), prostaglandins and nitric oxide[82–84]. By contrast, they may enhance the release of the anti-inflammatory mediators IL-10 and transforming growth factor-β (TGFβ)[85–87]. Glucocorticoids also have strong anti-proliferative properties and induce apoptosis in eosinophils, and in immature and mature T lymphocytes, as well as in leukaemic cells[88–91]. Glucocorticoids enhance the resolution of inflammation by stimulating the production of acute phase reactants and by promoting antigen uptake by phagocytes[84,92–94]. On one hand,

TYPE 1 T-HELPER T CELLS (Th1). T-helper cells can be divided on the basis of their cytokine expression pattern. Th1 cells produce mostly IFNγ and mediate delayed-type hypersensitivity and protection against intracellular pathogens.

TYPE 2 T-HELPER T CELLS (Th2). Th2 cells produce mainly IL-4 and IL-5, and have been implicated in humoral and allergic immune responses.
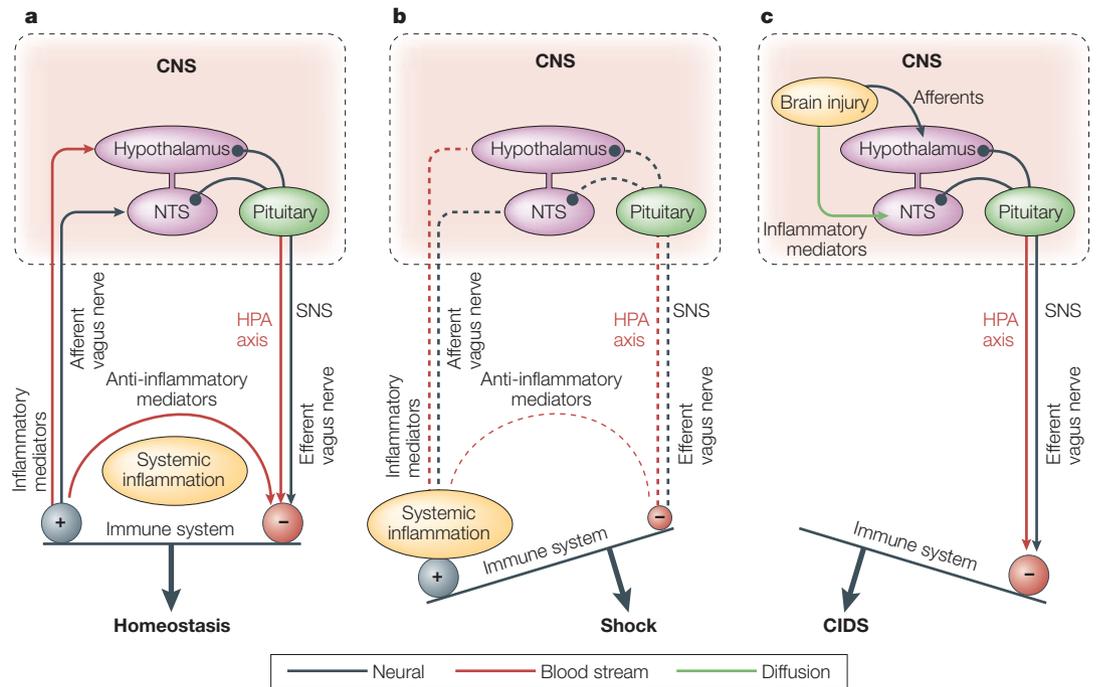
Figure 2 | **Interactions between the central nervous system and the immune system. a** | Systemic inflammation, as a result of bacterial infection or injury, is a potent stimulus of anti-inflammatory signalling by the CNS. Pro-inflammatory cytokines released during inflammation have a central role in wound healing and bacterial defence. To control inflammation, the CNS mounts a homeostatic, counter-regulatory anti-inflammatory response and brain–immune interaction helps to maintain homeostasis. **b** | Systemic infections or disturbed brain–immune interaction may result in overwhelming systemic inflammation: severe stresses such as sepsis can so strongly induce the systemic inflammatory response that there is an imbalanced anti-inflammatory counter-regulation, and both responses contribute significantly to morbidity and mortality (from septic shock), as a result of either systemic inflammation or impaired antimicrobial defences. **c** | CNS inflammation without systemic inflammation may lead to active depression of peripheral immunity by the brain. When triggered in the absence of systemic inflammation, for example, by local diffusion of inflammatory cytokines after brain injury, an anti-inflammatory response may be triggered that is detrimental because it shuts down defence mechanisms, rendering the organism susceptible to infection. Under these conditions the immunodepression exerted by the brain is not balanced by general immunostimulation. CIDS, CNS injury-induced immunodepression; HPA axis, hypothalamo–pituitary–adrenal axis; NTS, nucleus tractus solitarius; SNS, sympathetic nervous system.

glucocorticoids decrease the capacity of monocytes/macrophages and dendritic cells to present antigen to T lymphocytes and to elicit immune responses by downregulating the expression of MHC class II and co-stimulatory molecules (for example, CD86)[95,96]. In particular, glucocorticoids block differentiation of naive T cells to Th1 lymphocytes through the inhibition of monocytes/macrophages, dendritic cell-derived IL-12 secretion and IL-12 responsiveness of T cells[97,98]. On the other hand, glucocorticoids may promote differentiation of Th2 cells and give rise to the development of regulatory, IL-10-producing T cells[86,99].

Secretion of factors from brain to blood after CNS injury. In addition to the neural and neurohumoral communication channels from the brain to the peripheral immune system, there is a third option for neuroimmunomodulation, which may be of particular relevance in CNS injury: the brain to blood transfer of cytokines and other immunomodulatory macromolecules. In contrast to the highly selective control of entry of substances from blood to brain through the blood–brain barrier, the exit of substances from the brain is nonselective and relatively rapid. From studies of brain tumours it is known that

such tumours may induce immunosuppressive effects through the production of the pleiotrophic growth factor TGFβ[100], and the anergic state of patients with glioblastoma is attributed to the brain-blood transfer of this cytokine[101]. TGFβ is also produced by astrocytes after brain trauma, ischaemia and/or increased intracranial pressure. After TBI[102] and stroke[103], increased serum levels of TGFβ have been measured. However, brain-derived IL-1β, IL-6 and IL-10, as well as other cytokines, have also been found to reach the systemic circulation after injury to the human brain[28,104–109]. The functional consequences of the secretion of immunomodulatory mediators from brain to blood after CNS injury remain to be established.

Other chemical mediators of neuroimmunomodulation. We have focused our discussion on a few prototypical cytokines (such as IL-1β, TNFα and IL-6) and amines (such as adrenaline/epinephrine and noradrenaline), which have been called the common language of CNS–immune system communication. It should be noted, however, that this 'language' has a much more complex syntax and grammar, and includes the sensory neuropeptides calcitonin gene-related peptide (CGRP),

Why do organisms react to CNS injury with such an apparently maladaptive response? Although compensatory anti-inflammatory response syndrome (CARS) may have evolved as a protective mechanism against excessive inflammation after infection or trauma, CNS injury-induced immunodepression (CIDS) could be viewed as its dysregulated, pathophysiological counterpart.

Alternatively, CIDS may have evolved as a protective response. During CNS injury self epitopes, which are normally shielded from the systemic immune system by a number of mechanisms, may become exposed to adaptive immunity. This may 'educate' the immune system to react to self antigens in the CNS, and, ultimately, lead to autoimmunity or autoaggression. According to this concept, by globally downregulating innate and adaptive immunity, CIDS may help to prevent post-injury autoaggression. Indeed, after stroke and brain trauma brain-specific antigens can be measured in the blood plasma[145], and T cells invade the brain[146,147]. At present, there is no epidemiological evidence that patients with stroke or brain trauma have an increased incidence of autoimmune CNS disorders (such as multiple sclerosis). This might point to effective control of autoimmunity under injury conditions, which would come at the price of an increased susceptibility to infection.

However, the interpretation of CIDS 'function' is complicated by the fact that a certain degree of autoimmunity may be needed for repair and regeneration after CNS injury ('protective autoimmunity'). According to this concept, injury of the CNS evokes a purposeful T-cell-mediated autoimmune response that reduces the injury-induced degeneration in the CNS[113]. Whether and how CIDS might relate to protective autoimmunity is completely unknown.

substance P, neuropeptide Y (NPY) and vasoactive intestinal peptide (VIP), preproenkephaline products, melatonin and lipid derived mediators, among others. Each of these is produced by CNS cells as well as immune cells, which both carry their receptors. However, much less is known about whether and to what degree these latter mediators are involved as signals or effectors in neuroimmunomodulation after systemic injury, and almost nothing is known about their role after CNS injury.

Immunodepression as a result of CNS injury

Systemic inflammation resulting from bacterial infection or injury is a potent stimulus for anti-inflammatory signalling by the CNS: pro-inflammatory cytokines released during inflammation have a central role in wound healing and bacterial defence. However, excessive production of pro-inflammatory cytokines can lead to an overwhelming systemic inflammatory response (SIRS), which may result in shock and multiple organ failure. To control inflammation, the CNS, in addition to autoregulatory mechanisms of immune cells, mounts a homeostatic counter-regulatory anti-inflammatory response (COMPENSATORY ANTI-INFLAMMATORY RESPONSE SYNDROME, CARS)[110,111] (FIG. 2a).

Ideally, inflammatory and anti-inflammatory responses to stress are balanced to allow containment of pathogens and wound healing, while preventing hyper-inflammation or severe immunodepression. However, severe stresses such as sepsis[112] can so strongly induce the systemic inflammatory response with an imbalanced anti-inflammatory counter-regulation that both contribute significantly to morbidity and mortality (septic shock), as a result of either systemic inflammation

COMPENSATORY ANTI-INFLAMMATORY RESPONSE SYNDROME (CARS). The systemic inflammatory response induces, and is then balanced by, counter-regulatory processes, known as CARS. This includes the release of anti-inflammatory molecules (for example, IL-10) and activation of neuroendocrine pathways (for example, the HPA axis).

or impaired antimicrobial defences (FIG. 2b). A well balanced anti-inflammatory action of the nervous system appears to be beneficial in the presence of systemic inflammation. When triggered in the absence of systemic inflammation, however, this response may be detrimental, shutting down defence mechanisms and rendering the organism susceptible to infection (FIG. 2c). Under these conditions the immunodepression induced by the brain is not balanced by general immunostimulation. BOX 1 discusses whether CIDS may have evolved as an adaptive response to prevent the exposure of CNS epitopes to the immune system when the barrier between blood and the brain is severely disturbed. At present, it remains an open question as to whether CIDS is advantageous for the CNS, or whether its negative effects for the CNS (such as impairment of protective autoreactive immune responses[113]) should be added to the list of harmful consequences of immunodepression after CNS injury.

CIDS induction by humoral signalling?

The mechanisms by which CNS injury triggers the systemic anti-inflammatory response remain to be elucidated. Several lines of clinical and experimental evidence indicate that pro-inflammatory cytokines produced in the damaged brain tissue can directly induce HPA axis and SNS activation. Increased levels of cytokines such as IL-1β, TNFα and IL-6 in brain parenchyma and cerebrospinal fluid have been found in various brain disorders, including trauma, subarachnoid haemorrhage and ischaemia[114]. In patients with brain injury or stroke, elevated levels of IL-6 released into the cerebrospinal fluid and plasma have been shown to correlate with increased plasma adrenocorticotropic hormone (ACTH) and cortisol concentrations[28,115,116]. In addition to central cytokine-mediated stimulation of the HPA axis, plasma IL-6 may increase cortisol secretion directly by augmenting adrenal function[115,117]. Furthermore, intracerebroventricular infusion of IL-1β in rats and primates results in rapid increases in plasma ACTH, glucocorticoid and catecholamine levels[118–120]. Finally, administration of IL-1β into the brain suppresses various cellular immune responses, including NK-cell activity, mitogen-induced T-cell proliferation and cytokine production, as well as monocyte/macrophage functions[118,119,121,122]. The involvement of HPA axis and SNS activation in brain IL-1β-induced systemic immunosuppressive/immunosuppressant effects can be shown by either partial or total prevention of IL-1β-induced changes by adrenalectomy, hypophysectomy or β_2AR antagonists[118,121,122]. Although these findings confirm the ability of raised intracerebral pro-inflammatory cytokine levels to activate the SNS and HPA axis, there is, so far, no formal proof that pro-inflammatory cytokines are the primary trigger of CIDS after CNS injury.
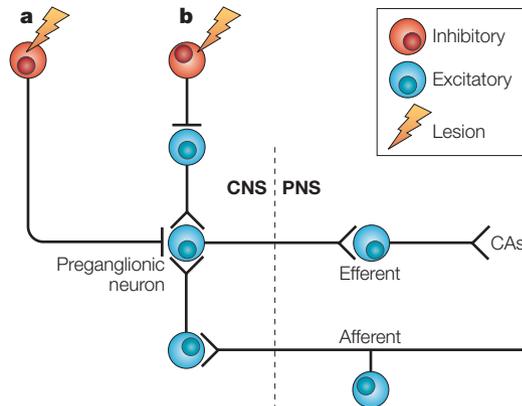
CIDS induction by 'neurogenic' mechanisms?

As outlined above, the release of pro-inflammatory cytokines in the CNS after injury may result in CIDS. Therefore, the possible mechanisms for triggering CIDS considered so far are similar to those responsible for

NEUROGENIC
Caused by a primarily neuronal mechanism through either blockade or stimulation of trans-synaptic nerve conduction.

Figure 3 | **Most types of CNS injury can lead to direct damage to sympathetic CNS structures involved in vegetative neuroimmunomodulation.** Because the autonomic system of the CNS is 'hard wired' with secondary lymphoid organs, interruption of these circuits by lesions can result in immune dysfunction. The scheme shows how a preganglionic lesion may increase sympathetic output (tonic as well as reflex). The lesion may be at the level of the cortex, midbrain or spinal cord. **a** | Denotes the most simple case, in which a lesion of an inhibitory pathway increases the tone within the sympathetic reflex arch. **b** | Demonstrates that the same effect may ensue from lesions that do not project directly onto the preganglionic neuron . CAs, catecholamines.

triggering anti-inflammation when injury occurs outside the CNS (CARS). In contrast to CARS, however, there may be additional, alternative pathways by which anti-inflammation and immunodepression are induced after the CNS has been injured, pathways that do not rely on cytokine signalling. Damage to sites in the nervous system that control neural–immune interactions (for example, the hypothalamus) can lead to NEUROGENIC

anti-inflammatory signals, without initial involvement of immune mechanisms. Although highly plausible, surprisingly little attention has been focused on such mechanisms, clinically or experimentally.

As the autonomic system of the CNS is 'hard wired' with secondary lymphoid organs, it comes as no surprise that interruption of these circuits can result in immune dysfunction. Most types of CNS injury can lead to direct damage of sympathetic CNS structures involved in vegetative neuroimmunomodulation. These are located in the brain (frontal pre-motor cortex, thalamus, hypothalamus, formatio reticularis, hippocampus, cerebellum and brain stem) and spinal cord (columna lateralis and nucleus intermediolateralis). Sympathetic neurons in the spinal cord innervate the adrenal medulla, thymus, spleen and lymph nodes[123]. A straightforward example of how damage to vegetative control centres may directly affect immunity can be seen in injury to the SNS of the spinal cord (FIG. 3). After SCI the peripheral vegetative nervous system may escape supraspinal control and display segmental sympathetic autonomy. This results in a 'sympathetic reflex-like condition', which, for example, may give rise to hypertensive episodes, headache or even cardiac arrest[124]. These symptoms of autonomic dysfunction result from stimulation of the SNS below the level of injury and are a consequence of preganglionic injury, resulting in deafferentation of the CNS from the peripheral vegetative nervous system[124]. As sympathetic nervous stimulation leads to downregulation of innate and adaptive immunity, autonomic dysfunction may be accompanied by immunodepression. Therefore, disruption of preganglionic sympathetic pathways may cause 'reflex-like' sympathetic outflow to the lymphatic organs, resulting in immunodepression. This does not only apply to SCI, as autonomic dysfunction also occurs by similar mechanisms following stroke or TBI, when brainstem or midbrain structures of sympathetic control are affected[125,126]. For example, because the direct neural connection from the medial preoptic area to the paraventricular nucleus is inhibitory[127], a lesion of the preoptic area or its fibres is predicted to trigger release of corticotropin-releasing factor from the paraventricular nucleus, with resultant SNS and HPA axis activation and reduction in cellular immunity.

Besides causing chronic autonomic dysfunction, trauma to sympathetic preganglionic neurons or synaptic deafferentation is accompanied acutely by a massive release of noradrenaline into sympathetic targets, including secondary lymphoid organs[128,129]. In the later stages after SCI, there is chronic depletion of noradrenaline release from sympathetic terminals, which is thought to induce alpha receptor hyper-responsiveness[124,128].

Further support for the concept of an at least partially neurogenic nature of CIDS comes from studies on the lateralization of the autonomic nervous system in the brain. Lateralization of the structures of the vegetative nervous system[130,131] might also serve to explain some localization-dependent effects of neural-immune interactions subsequent to a brain lesion[132]. For example, the severity of the immune deficit after a stroke is localization

Table 3 | **Potential targets for the prevention and therapy of CIDS**

Therapeutic agent	Remarks
Central sensors of inflammation	
COX inhibitors, indomethacin, interleukin-1 receptor antagonist	Timing of treatment? Do these agents have negative systemic immunomodulatory effects?
β_2-adrenoreceptor antagonists, nicotinic acetylcholine receptor α-7 subunit antagonists	Potential side effects (for example asthma and hypotension)
Microsomal prostaglandin E synthase-1 (mPGES-1) inhibitors	mPGES-1 is a central switch during immune-induced pyrexia
Immunomodulators	
Interferon-γ, G-CSF, GM-CSF, immunoglobulins	Timing of treatment? Risk of worsening inflammation? CNS effects?
Thymomimetic drugs (such as thymulin and thymopentin)	Have been shown to restore lymphocyte proliferative responses after open heart surgery
Glucan (active component of zymosan)	Stimulates macrophage activity, has been tested in patients undergoing abdominal surgery
Anti-infectives	
Antibiotics	Currently given when infection is already clinically apparent. Preventive treatment?

CIDS, CNS injury-induced immunodepression; COX, cyclooxygenase; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte–macrophage colony-stimulating factor.
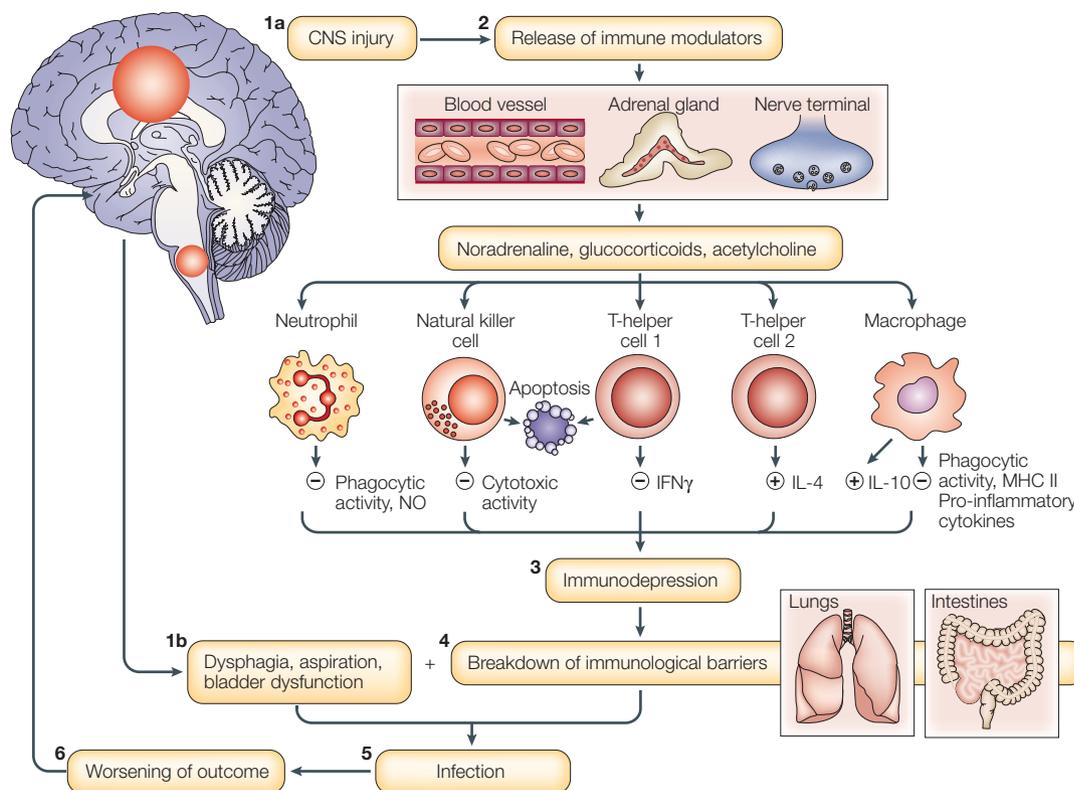
Figure 4 | **Scheme summarizing the pathophysiological events that lead from CNS injury to infection and worsening of patient outcome.** CNS injury (1a) induces a disturbance of the normally well balanced interplay between the immune system and the CNS. By inducing the local release of immune modulators (2), such as interleukins, CNS injury activates the hypothalamo–pituitary–adrenal axis, and the sympathetic and parasympathetic nervous systems. Through the release of noradrenaline, glucocorticoids and acetylcholine, a systemic anti-inflammatory response is mounted that negatively affects the function and composition of the innate and adaptive immune systems. As a consequence of the resulting immunodepression (3) and breakdown of immunological barriers (4), infection develops (5). The risk of infection is further increased because these patients are hospitalized under intensive care conditions and the CNS lesion itself may lead to dysphagia, aspiration, bladder dysfunction and so on (1b). Systemic infection increases morbidity and mortality in patients with CNS injury, and leads to worsening of outcome (6). IFNγ, interferon-γ; IL-4/10, interleukin-4/10; MHC II, major histocompatibility complex class II; NO, nitric oxide.

dependent. Cutaneous T-lymphocyte activity ipsilateral to the affected brain hemisphere has been shown to be significantly diminished in patients with right-sided hemiparesis compared with left-sided hemiparesis, which suggests that stronger immunosuppression occurs when the right side is involved[133]. Furthermore, lateralization is also reflected in vegetative dysfunction following stroke[134,135]. Interestingly, post-injury activation of the SNS was most pronounced when the insular cortex of the right hemisphere was affected[126]. The insular cortex receives projections from the nucleus tractus solitarius of the dorsal vagal complex in the medulla oblongata and projects to the amygdala and lateral hypothalamus. The insular cortex thereby has an important role in the higher control of the autonomic nervous system[136]. Therefore, localization (for example, insular infarction) and, to a lesser extent, size of infarct may differentially affect the degree and type of autonomic dysfunction in stroke patients[137].

Similarly, following SCI, the extent of vegetative dysfunction and corresponding immunodeficiency, which depends on lesion level, is correlated with the extent of sympathetic outflow deafferentation[124,138].

SCI above thoracic level 6 results in marked reduction of intact sympathetic fibres and supraspinal control of the spleen, as well as the vasculature of the lower extremities[124]. With regard to the immune system, complete tetraplegics, who are injured above the level of sympathetic outflow tracts, show a pronounced reduction in lymphocyte proliferation, responsiveness and NK-cell function. Moreover, the degree of immune dysfunction in SCI patients correlated well with the extent of deafferentation of the sympathetic outflow, with higher injuries inducing more severe immune dysfunction[53].

Only a few studies have directly addressed the issue of the neurogenic mechanisms by which CNS lesions affect immune function. However, the evidence so far suggests that damage to vegetative control structures in the CNS plays an important part in the induction of CIDS.

Therapeutic implications

Patients with brain injury are at high risk of developing immunodepression and bacterial infections, which are major causes of morbidity and mortality in this patient population. It is therefore important for clinicians to

Box 2 | **Open issues**

Although great progress has been made during recent decades in understanding the physiological interactions between the CNS and the immune system, little is known about the pathophysiology of the interaction of the two 'supersystems'. It has been clearly established that CNS injury is associated with an increased risk of infection, and it is well known that infection and its consequences are important contributors to outcome after CNS injury. It is also recognized that suppression of immune responses due to humoral and neurogenic signals after CNS injury at least partially underlies the increased susceptibility to infection. However, numerous questions remain to be answered, some of which are included below.

• Does the parasympathetic nervous system contribute to CNS injury-induced immunodepression (CIDS)? How does the CNS sense that it is injured? Which mediators, receptors, anatomical structures and pathways are involved?

• What is the differential relevance of neurogenic versus humoral mechanisms of CIDS?

• How does localization of brain injury affect the severity and characteristics of CIDS? Can brain imaging be used to predict the risk of developing CIDS?

• Does CIDS protect the CNS against autoaggression by invading immune cells? Does CIDS impede protective autoimmunity?

• Which parameters are useful for monitoring the immune status of patients with CNS injury? Can these parameters guide specific therapy?

• Should CIDS be treated by immunomodulation? If so, how and when should CIDS be treated?

Elevated intracranial pressure (ICP) is a common complication of brain injury. Increases in ICP induce sympathetic activation[142,143], and may lead to the release of TGFβ and other cytokines from the brain into the blood (see above). To preserve cerebral perfusion pressure and avoid cardiovascular as well as pulmonary complications, monitoring and control of ICP is a a primary goal in patients with CNS injury. We propose that avoidance of SNS activation-induced immunosuppression should be added to the list of negative consequences of intracranial hypertension.

At present, it is unclear whether direct intervention against CIDS is possible, and whether it would be effective in improving outcome. TABLE 3 lists potential targets for therapeutic modulation of CIDS. It should be noted that, besides immunoglobulins[144], none of these agents have ever been tested in this indication. A number of unwanted side effects may severely restrict the use of several of these agents. In addition, given our ignorance concerning the 'function' of CIDS (BOX 1), it is conceivable that its blockade may foster autoaggressive reactions of the immune system against the CNS. Clearly, further basic research is needed before direct targeting of CIDS by immunomodulation can be clinically tested.

Conclusions and future perspectives

Although the study of neural–immune interactions during recent decades was biased towards studying the impact of the immune cells invading the CNS and their effectors, understanding the role of modulation of peripheral immune functions by the diseased CNS has received comparatively little attention. We do know that CNS injury, through the release of neuromodulators, downregulates the immune system, which may result in immunodepression, breakdown of immunological barriers and, consequently, infection (FIG. 4). Although it is emerging that brain–immune interactions after CNS injury have serious clinical implications, numerous issues remain to be resolved (BOX 2). CIDS is a prototypical example for pathological brain–immune interactions: CIDS after experimental stroke, TBI or SCI may serve as a model for the study of the mechanisms and mediators of control of brain over immunity during pathophysiological conditions. Even more importantly, understanding CIDS may eventually lead us to effective therapeutic strategies with which the outcome after CNS damage from a host of diseases might be improved by eliminating a major determinant of poor recovery.

realize that patients with acute lesions of the CNS are highly susceptible to infection. Although standard in severely affected patients, close monitoring of immunological and microbiological parameters as well as early intervention against bacterial infection should be advocated even in milder cases of injury when the CNS is affected.

In stroke patients, for example, careful prevention, early detection and consequent treatment of fever and infection are crucial elements of specialized stroke care. Patients in stroke units receive more antipyretics, antibiotics and measures to reduce aspiration than those in general wards, and, consequently, infectious complications are less frequent[139,140]. As a result, during the last decade there was a remarkable improvement in survival rates and outcomes among stroke patients who were treated in specialized stroke units compared with those treated on general medical wards. This beneficial effect of stroke unit care is already significant soon after treatment onset, and is sustained for at least 18 months[141]. To improve long-term survival after stroke, aggressive management of pulmonary infection is as important as secondary stroke prevention[140].

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