Catecholamines, Steroids and Immune Alterations in Ischemic Stroke and Other Acute Diseases

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[Received December 21, 2013; Revised May 9, 2014; Accepted May 27, 2014]

ABSTRACT: The outcome of stroke patients is not only determined by the extent and localization of the ischemic lesion, but also by stroke-associated infections. Stroke-induced immune alterations, which are related to stroke-associated infections, have been described over the last decade. Here we review the evidence that catecholamines and steroids induced by stroke result in stroke-induced immune alterations. In addition, we compare the immune alterations observed in other acute diseases such as myocardial infarction, brain trauma, and surgical trauma with the changes seen in stroke-induced immune alterations.

Key words: ischemic stroke, immune, aging, catecholamines, steroids

Cerebrovascular diseases, including ischemic stroke, are the second most common cause of death worldwide after ischemic heart disease; stroke is the third leading cause of death in the USA [1, 2]. Stroke-related disability ranks third when disability-adjusted life-years are assessed [3]. The clinical outcome of stroke patients is not solely determined by the infarct size and localization, but is also altered by subsequent infections. Stroke-associated infections (SAIs), of which pneumonia is the most common, impair outcome and increase mortality [4, 5]. The frequency of SAIs ranges from 15%–42% depending on the inclusion criteria of the respective study [4, 5]. In recent years it has become evident that increased susceptibility to infections is related to stroke-induced alterations in the immune system. Loss of lymphocytes, lymphocyte dysfunction, and monocyte deactivation following stroke have been observed in both experimental stroke models and in stroke patients [6-8].

If the mechanisms by which stroke induces these immune alterations became known, these pathways could be targeted in future therapeutic trials. The central nervous system, the parasympathetic nervous system, and the hypothalamic-pituitary-adrenal (HPA) axis [9]. These pathways can be triggered through the nervous system by the brain itself or as a response to afferent vagus stimulation. In addition, the immune system can induce a stress response through inflammatory cytokines, which may be locally produced or may reach the central nervous system via the blood stream. Ischemic brain injury has been shown to affect several of these pathways [9].

Catecholamine effects and receptors on immune cells

To alter immune responses, catecholamines must be present in the microenvironment of the leukocytes, and the cells must express a receptor to detect these hormones [10]. Direct sympathetic innervation is found in both primary and secondary lymphoid organs, where norepinephrine and epinephrine are released from the sympathetic nerve endings and immune cells express α- and β-adrenoreceptors that transduce the signal into the cell (Table 1) [10]. Expression levels differ due to epigenetic regulation by histones and DNA methylation [11-13].

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ISSN: 2152-5250
Table 1. Expression of adrenoreceptors on immune cells.

| Immune Cell Type                                      | Adrenoreceptors                  |
|-------------------------------------------------------|----------------------------------|
| Most innate immune cells                              | Both αAR and βAR families        |
| Bone marrow-derived dendritic cells                   | α1AR α2AR                        |
| Monocytes/macrophages                                 | β1AR β2AR                        |
| Natural killer cells                                  | β2AR                             |
| Resting and activated B cells                         | α1AR α2AR                        |
| Naïve T cells and Th1 cells, but not Th2 cells        | No data available                |
| Regulatory T cells and Th17 cells                     | No data available                |

Reviewed in [14]. AR, adrenoreceptor.

Since lymphocytes are primed in lymphoid organs, and catecholamine concentrations within the spleen and lymph nodes are likely to exceed plasma concentrations due to direct sympathetic innervations, sympathetic activation can effectively alter immune responses [15]. Furthermore, catecholamines are not only released from nerve terminals and the adrenal medulla, but can also be actively produced, stored, and secreted by immune cells themselves [16]. Catecholamines released from immune cells serve as auto/paracrine regulators of lymphocyte activity, for example through the suppression of lymphocyte proliferation, cytokine production, and the induction of apoptosis [17, 18]. The biological relevance of immune cell-derived catecholamines versus the catecholamines released by the sympathetic response is not known [19].

Catecholamine release leads to a quick two-phased mobilization: initial lymphocytosis is succeeded by granulocytosis and reduced lymphocytes in the peripheral blood. Lymphocyte recruitment seems to mainly be mediated by β2-adrenoreceptors (β2AR) and originates from the marginal pool and the spleen, whereas granulocytes are predominantly recruited from the marginal pool and the lung via α-adrenoreceptor stimulation [20]. While this biphasic response of lymphocytes to β2AR engagement is well described the underlying mechanisms are only partly resolved. The effect depends on the time of receptor engagement in relation to the activation and differentiation state of the cell, the involved molecular signaling pathway, and the cytokine microenvironment (Table 2) (for reviews see [21-23]). In addition, high concentrations of catecholamines are known to induce lymphocyte apoptosis [17].

Glucocorticoid effects and receptors on immune cells

Another effective pathway for the interaction of the central nervous system and the immune system is the HPA axis. Activation of the HPA axis starts with the release of corticotropin-releasing hormone from the hypothalamus, which induces the secretion of adrenocorticotropic hormone, which leads to the secretion of glucocorticoids from the adrenal gland [10]. Glucocorticoids have long been known to exert anti-inflammatory and immunosuppressive effects, and are broadly used as an anti-inflammatory treatment. In the absence of ligands, the glucocorticoid receptor (GCR) resides in the cytoplasm in a complex with heat shock proteins and immunophilins [24]. The GCR is constitutively expressed in virtually all cell types, but different tissue-specific expression patterns lead to tissue-specific outcomes in different diseases [25].

When binding its ligand in the cytoplasm, the GCR can interact with signaling pathways of the T-cell receptor signaling complex and thus modulate pro-inflammatory gene expression [26]. The primary actions of the GCR are evident in the nucleus. Upon ligand binding, chaperone complex remodeling exposes nuclear localization sequences on the GCR, leading to its nuclear translocation [27]. The GCR has two ways of modulating gene expression. As a dimer, GCR binds the glucocorticoid response element, when undimerized, GCR binds pro-inflammatory transcription factors such as AP-1, NF-kB, IRF-3, STAT, CREB, NFAT, T-beta, and GATA-3, leading to their inhibition [27]. Further details are reviewed in [28]. Cellular effects of stress hormones are summarized in Table 2.
Table 2. Cellular effects of stress hormones in immune cells

|                      | Glucorticoids                                                                 | Catecholamines                                                                 |
|----------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| **DC**               | • induce apoptosis in immature DCs [29]                                      | • enhanced surface expression of MHCII, CD80 and CD86 [36]                     |
|                      | • reduction of MHCII, costimulatory molecules and cytokine expression [30, 31]| • control cell migration via α1bAR [37] and induction of an anti-inflammatory cytokine profile [38] |
|                      | • inhibition of migration in vivo and in vitro [32]; [33] by downregulation of CCR7 [34]| • enhancement of IL-33 production thus promoting Th2 responses [39] inhibited the lipopolysaccharide (LPS)-stimulated production of interleukin (IL)-23, IL-12 p40, tumor necrosis factor (TNF)-alpha and IL-6 [40] |
|                      | • induction of a tolerogenic DC phenotype that induces T cell anergy, suppression of T cells and generates Tregs [35] |                                                |
|                      | • enhanced surface expression of MHCII, CD80 and CD86 [36]                     |                                                |
|                      | • control cell migration via α1bAR [37] and induction of an anti-inflammatory cytokine profile [38] |                                                |
|                      | • enhancement of IL-33 production thus promoting Th2 responses [39]           |                                                |
|                      | • inhibited the lipopolysaccharide (LPS)-stimulated production of interleukin (IL)-23, IL-12 p40, tumor necrosis factor (TNF)-alpha and IL-6 [40] |                                                |
| Macrophages/monocytes| • suppressed activation by IL-10 induction and inhibition of upregulation of pro-inflammatory CD163 [41] | • cAMP/PKA dependent stimulation of IL-10 promoter/enhancer [43] |
|                      | • development of myeloid suppressor cell like phenotype [42]                  | • upregulate L-selectin in vitro [44]                                           |
|                      | • increased surface expression of MHCII, CD80 and CD86 [36]                   | • inhibit IL-6 secretion via αAR [45] but                                     |
|                      | • inhibition of cell migration in vivo and in vitro [32]; [33] by downregulation of CCR7 [34] | • induce secretion of IL-6 (in the presence of GC) via βAR [46] |
|                      | • increased surface expression of MHCII, CD80 and CD86 [36]                   |                                                |
|                      | • control cell migration via α1bAR [37] and induction of an anti-inflammatory cytokine profile [38] |                                                |
|                      | • enhancement of IL-33 production thus promoting Th2 responses [39]           |                                                |
|                      | • inhibited the lipopolysaccharide (LPS)-stimulated production of interleukin (IL)-23, IL-12 p40, tumor necrosis factor (TNF)-alpha and IL-6 [40] |                                                |
| **Neutrophils**      | • suppression of adhesion molecule expression inhibits rolling, adhesion and transmigration [47] | • increase the total circulating neutrophil pool for a few hours [50] |
|                      | • increase of BM-derived neutrophils in blood [48]                           | • increase expression and release of Hsp72 [51]                              |
|                      | • promote neutrophil recruitment [48]                                         | • suppression of CD11b and inhibition of suppression of CD62L (L-selectin) [52] |
|                      | • increased surface expression of MHCII, CD80 and CD86 [36]                   | • increased phagocytosis of zymosan in vitro [53]                            |
| **B cells**          | • reduction of splenic and LN B cell numbers                                  | • state of B cell activation decisive about effect of CA:                    |
|                      | • inhibit B cell progenitor proliferation                                      | - enhanced IgG1 production and IgE on NE exposure during antigen processing or after Th2 coculture [56] |
|                      | • enhance IgE, suppressed IgG production [54, 55]                             | - increase in costimulatory capacity (CD86 upregulation) [57]                |
|                      | • state of B cell activation decisive about effect of CA:                    | - β2AR engagement in presence of IL-4 enhances IgE [58]                     |
|                      | • state of B cell activation decisive about effect of CA:                    |                                                |
| **T cells**          | • affect thymocyte maturation by inducing apoptosis in thymocytes; more sensitive than Teff than Treg cells [59, 60] | • β2AR engagement enhances IFNγ production in TH1 cells the presence of IL-12 in pre activated TH1 cells [67] |
|                      | • physiological doses: shift from Th1 response to Th2 [61]                   | • inhibit IFN-γ in resting TH1 cells [13]                                     |
|                      | • pharmacological doses induce anti-inflammation:                           |                                                |
|                      | - reduce RORγt in Th17 cells [62]                                            |                                                |
|                      | - inhibit TH1 function by direct inhibition of STAT4 and T-bet [63, 64]      |                                                |
|                      | • β2AR engagement enhances IFNγ production in TH1 cells the presence of IL-12 in pre activated TH1 cells [67] |                                                |
|                      | • suppress STAT6 function in Th2 by interfering with GATA [65, 66]           |                                                |
| **NK cells**         | • impaired NK cell function via histone deacetylation and transrepression [68] | • inhibit NK cytotoxic functions by:                                        |
|                      | • inhibit NK cytotoxic functions by:                                         | - reduced TNF-α, IFN-γ, and GM-CSF                                           |
|                      | • β2AR engagement enhances IFNγ production in TH1 cells the presence of IL-12 in pre activated TH1 cells [67] | - impaired, target binding [69]                                             |

DC dendritic cells; CCR C-C chemokine receptor; NK natural killer cells; Treg regulatory T cells; Teff effector T cells; BM bone marrow; LN Lymph node; NE norepinephrine; CA Catecholamine.
Stress responses have been described in stroke; the pathways delineated above have been implicated in stroke-induced immune alterations (SIIAs). In this article, we review the clinical and experimental evidence that stress hormones are indeed the mediators linking ischemic brain injury with SIIA. Other acute diseases such as myocardial infarction (MI), surgical trauma, and trauma-related injury also induce a stress response. We will summarize what is known with respect to immunological changes in patients with these diseases (section 4.1), and discuss whether changes observed in SIIA that enhance the risk for SAIs are unique to ischemic brain injury or extend to other diseases. This review will not address the role of the immune system and SIIAs in secondary immune-mediated organ damage, which has been described in experimental stroke and traumatic brain injury (TBI) [70-73].

**Stress hormones in stroke**

Alterations induced by catecholamines and steroids in specific organs are summarized in Figure 1. Here we will focus on cell type specific alterations and clinical consequences.

**Stroke: catecholamines and clinical outcome**

Several studies of stroke patients have investigated whether epinephrine, norepinephrine, or its metabolites metanephrine and normetanephrine can be used as markers for the extent of SIIA and whether these molecules correlate with patient outcome and the occurrence of SAIs. Metanephrine and normetanephrine, which lack biological activity but are relatively stable, can be determined in urinary samples [74]. Data across different stroke patient populations and research groups consistently indicate that catecholamines are associated with an increased risk of post-stroke infections. Higher levels of metanephrine and normetanephrine on admission and on day 1 enhance the risk of developing SAIs [4, 75, 76]. In agreement with these findings, mortality at 3 months was associated with higher levels of...
normetanephrine on admission and day 1, at least in one study [75].

Furthermore, the cellular changes observed in SIIA, including lymphocytopenia and reduced monocytic HLA-DR expression that leads to impaired immune function, have been linked to catecholamine levels in stroke patients in the ESPIAS and PANTHERIS studies [4, 75]. This observation may be due to the biphasic effect of catecholamines on immune cells, including the autocrine, apoptosis-inducing regulation that was described earlier. However, the observation that lymphocytes remaining in the circulation of stroke patients are primed towards proinflammation [76] is not in line with the earlier report that Th2 cells lack the β2AR [13], and therefore T cells with an anti-inflammatory phenotype should escape catecholamine-induced apoptosis. This scenario suggests that additional mediators are involved in regulating T-cell responses in stroke patients.

The phenotypic findings in human stroke-induced SIIA are very similar to the observations made in experimental stroke: lymphocyte apoptosis in the spleen and thymus, lymphocytopenia in the periphery, and a defective interferon (IFN)-γ response in monocytes predispose patients to post-stroke infections, with bacteremia and spontaneous pneumonia in experimental stroke [77]. Thus, the animal model appears well suited to investigate the underlying pathophysiology of SIIA.

Selective inhibition of the effects of sympathetic nervous-system activation at an early time point, but not the blockage of the effects of HPA axis activation, prevented systemic infections and improved survival in stroked mice [77, 79]. These findings suggest that catecholamines, but not glucocorticoids, are causally related to SAI. Moreover, adoptive transfer of splenocytes, especially T and natural killer cells from control mice into stroked animals, restored the recipient’s defense against pathogens [77]. Both the loss of lymphocytes due to apoptosis and the functional impairment of lymphocytes can be explained by the known β2AR-mediated effects of catecholamines. Additionally, adrenoreceptor antagonism has been demonstrated to inhibit splenic atrophy, reduce the infarct volume, and modulate cytokine expression in the spleen following experimental stroke, but did not affect a specific lymphocyte population within the splenocyte fraction [80]. Thus converging evidence from animal models and human studies support the role of β-adrenergic stimulation in SIIA.

**Stroke: glucocorticoids and clinical outcome**

The stress hormone cortisol is also transiently elevated following stroke [81-83]. However, the data for the kinetics of cortisol in plasma concentrations as well as the relationship of cortisol with SAI remain contradictory. The increase of plasma cortisol levels has been reported to persist through day 5 post-stroke [81], while others observed elevated plasma levels on admission that normalized within 24 h [84, 85].

The correlation of cortisol levels with stroke severity, infarct volumes, unfavorable outcome, and even higher mortality has been repeatedly demonstrated [86-90]. However, the association of cortisol levels with markers of SIIA and post-stroke infections remains poorly understood. Whereas our own data support an association of plasma cortisol levels on day 1 with SAI [76], other studies detected no association of plasma cortisol levels with SAI or with monocyte function [4, 84]. Another study linked interleukin (IL)-6 levels to cortisol levels; in stroke patients, IL-6 levels correlated significantly with cortisol levels, and morning serum IL-6 levels independently predicted evening/night cortisol levels, which has been interpreted as evidence for cytokine-induced HPA axis activation following stroke [91].

In experimental stroke, a three-fold increase in serum corticosterone levels (the primary glucocorticoid in rodents) compared to naïve animals was observed at 4 h after stroke; only 24 h after sham/permanent middle cerebral artery occlusion surgery, corticosterone levels in stroked animals returned nearly to the levels of naïve animals [92].

While several studies have addressed the role of glucocorticoids in brain-lesion development in stroke, there is a surprising paucity of data investigating the effects of glucocorticoids on immune function and infection in experimental stroke. The seminal study by Prass et al. has long been the only investigation of GCR antagonism with respect to SIIA and SAI. They reported that glucocorticoid inhibition reduced apoptosis of splenocytes and lymphopenia following stroke [77]. However, in contrast to β-adrenergic inhibition, GCR antagonism did not prevent pneumonia. A very recent study now reported similar findings demonstrating in experimental stroke that the inhibition of glucocorticoid effects reversed lymphocytopenia while inhibition of β2AR restored interferon release in lymphocytes [78].

**Do stress hormones mimic SIIA in vitro?**

As reviewed in the preceding sections, clinical data and animal models suggest that catecholamines are the major mediator of SIIA. However, it is difficult to prove causality due to the complex pathways activated in whole animals and in patients. In vitro studies could provide complementary evidence if the effects observed in vivo could be replicated in vitro.
Table 3. Immune alterations immediately after disease onset.

|                          | Ischemic stroke (IS) | Traumatic brain injury (TBI) | Myocardial infarction (MI) | (Surgical) trauma (ST/T) |
|--------------------------|----------------------|-----------------------------|---------------------------|-------------------------|
|                          | animal               | human                       | animal                    | human                   | animal               | human               |
| **innate immune system** |                      |                             |                           |                         |                       |                     |
| White blood cell         | ↑[98, 100]           | ↑[101]                      | ↑[102]                    | ↑[98, 103]               | ↓[105, 106]          | ↓[106, 107]        |
| monocytic HLA-DR         | ↓[98, 100, 104]      |                             |                           |                         |                       |                     |
| monocytic LPS activatability | ↑[98, 104]       |                             |                           |                         |                       |                     |
| **cytokines**            |                      |                             |                           |                         |                       |                     |
| IL-10                    | ↑[104, 109]          | ↑[110]                      | ↑[94]                     | ↑[43]                   | ↑[111]               |
| TNF-α                    | ↑[100]               | ↑[110]                      | ↑[94]                     | ↑[98]                   | ↑[112]               |
| IL-6                     | ↑[98, 109]           | ↑[110]                      | ↑[101, 113]               | ↑[98, 102]              | ↑[112]               | ↑[111]             |
| HMGB-1                   | ↑[76, 99]            | ↑[114]                      | ↑[99]                     | ↑[95]                   | ↑[95, 115]           |
| **adaptive immune system** |                      |                             |                           |                         |                       |                     |
| circulatory lymphocyte number | ↑[77]               | ↑[110]                      | ↑[113]                    | ↑[98]                   | ↑[105, 106]          | ↑[107]             |
| T lymphocyte activation  | ↑[116]               | ↑[76]                       | ↓[113]                    | ↑[118]                  |                       |                     |
| IgG, IgM                  | ↑[117]               | ↑[110]                      | ↓[119, 120]               | ↑[112]                  |                       |                     |
| T-cell proliferation to mitogen | ↑[117]               | ↑[76]                       | ↓[113]                    | ↑[118]                  |                       |                     |
| **hormones**             |                      |                             |                           |                         |                       |                     |
| catecholamines           | ↑[77]                | ↑[4, 75, 76, 109]            | ↑[94]                     | ↑[96, 97]               | ↑[95]                |
| cortisol/corticosterone  | ↑[77]                | ↑[100, 104]                 | ↑[94]                     | ↑[98]                   | ↑[106]               |

LPS, lipopolysaccharide; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon.

In peripheral blood mononuclear cells activated through the T-cell receptor in vitro, non-toxic concentrations of norepinephrine induce pro- and anti-inflammatory cytokine expression [93], while the synthetic glucocorticoid dexamethasone reduces cellular activation, lowering the number of cytokine-producing lymphocytes and inhibiting both Th1- and Th2-type cytokines [93]. In this setting, which included the combined in vitro application of dexamethasone and norepinephrine, the dexamethasone-induced alteration dominated [93]. Exposure to norepinephrine or terbutaline, a β2AR agonist, before T-cell receptor stimulation inhibits IFNγ production, as evident in the defective IFNγ response after stroke [12]. However, when peripheral blood mononuclear cells are not activated via the T-cell receptor but through the Toll-like receptors, application of dexamethasone and norepinephrine in vitro did not alter cytokine secretion (A. Kasprik, A. Dressel unpublished observations). These findings suggest that stress hormones may alter immune responses in a manner that is dependent on the activation pathway. We have observed that the in vitro application of catecholamines results in defunct upregulation of CTLA-4 expression on CD4+ T cells upon activation, mimicking observations made in stroke patients [76]. Whether this impaired regulation of CTLA-4 is functionally relevant in stroke patients is not known.

**Mechanisms of immunosuppression in various diseases**

The preceding sections have summarized the currently available evidence on stress hormones and SIIA. Taken together, these data suggest that catecholamines and glucocorticoids are key factors inducing immunosuppression in cerebral ischemia, enhancing susceptibility to SIA. If this emerging pathophysiological concept is correct, the immunological alterations seen in SIIA may not be unique to ischemic stroke, but may extend to other diseases that also induce an acute release of catecholamines and glucocorticoids. A rapid increase in the plasma levels of catecholamines and steroids has long been described in TBI, MI, and surgical trauma and trauma (ST/T), among others [94-97]. Furthermore, a relationship between clinical outcome and initial catecholamine levels has been described for ST/T, similar to the relationship detected in stroke [4, 75, 76, 95]. To the best of our knowledge only two studies have compared...
immune alterations in stroke and MI [98, 99]. We therefore reviewed publications addressing immunosuppressive mechanisms in TBI, MI, or ST/T. Cross-study comparisons have limited validity, as patient characteristics, timing points of sample acquisition, assays used to determine the activation status, and measured cytokines differ between studies. Despite these limitations, there is a striking consistency in the pattern of immune alterations observed within 48 h after disease onset. These patterns are summarized in Table 3 and detailed in section 4.1 and 4.3.

**Immune response and cytokines**

ST/T, MI, and TBI induce increased white blood cell counts and reduced monocyic HLA-DR, similar to findings in cerebral ischemia [7, 94, 95, 98, 101, 103, 106]. Monocyic TNF-α production upon lipopolysaccharide challenge is diminished in ischemic stroke as well as in TBI. The proinflammatory cytokine IL-6 is upregulated in ischemic stroke, TBI, and MI, as is the antiinflammatory cytokine IL-10 [98, 101, 110, 111]. Furthermore HMGB1 which has been shown to be a strong proinflammatory mediator is also elevated in TBI, ST/T, and ischemic stroke [76, 95, 115, 121, 122].

The reduced number of circulating T lymphocytes (CD4+, CD8+) is an overall phenomenon observed in ischemic stroke, TBI, MI, and ST/T. While proliferation in response to mitogenic stimuli is impaired in TBI [113] and surgery [123], it is indistinguishable from controls in ischemic stroke, where T cells are prone to proinflammation [76] or reported to be also impaired [117]. In TBI, even B cells are unable to mount normal IgM or IgG responses [119, 120].

**Gut barrier**

TBI was reported to lead to secondary infections in up to 75% of affected comatose patients [120]. One possible shared source of bacterial infections is endogenous bacteria, Escherichia coli translocated from the patient’s own gut. Increased permeability was reported in experimental ischemic stroke, in TBI [124], in intracerebral hemorrhage [125], and in patients who underwent surgical trauma [126-128]. Vagal nerve stimulation was found to inhibit bacterial translocation in TBI [129].

**Hormones**

Increased catecholamine or cortisol/corticosterone levels are present very early after disease onset in all of the reviewed diseases (ischemic stroke, TBI, MI, ST/T) [4, 75, 76, 94-98, 100, 104, 106, 109]. The blockade of catecholamine effects through the administration of propranolol was beneficial in ischemic stroke and in TBI [77, 94]. For TBI, beta blockade therapy is also suggested to be beneficial [130]. However, the effect of beta-blockade premedication in ischemic stroke patients is still not well enough investigated to draw conclusions. The levels of catecholamines 1 h post trauma (controls 0.3 ng/mL vs. TBI 3.27 ng/mL) correlate with mortality [95], while the results for TBI are contradictory [131, 132].

**Summary and conclusion**

Stress hormones are important regulators of immune cell function via adrenoreceptors and GCR. Lymphoid organs are directly innervated and nerve terminals release catecholamines. Moreover immune cells can actively secrete hormones. There is strong evidence that the increase of stress hormones early after stroke is a marker for the extent of SIIA that can be expected to develop. Surprisingly, the experimental evidence suggests that catecholamine-triggered pathways, but not well-known immunosuppressive glucocorticoid-induced alterations, are causally related to SAI. However, which immune alterations induced by catecholamines mediate the enhanced susceptibility to infection in stroke patients remains to be determined. A recent observation from our laboratory provides evidence that catecholamine induced immune alterations are not limited to lymphocytes and monocytes but may extend to granulocyte function. The ability of monocytes and granulocytes to generate oxygen radicals (oxidative burst) was impaired in stroke patients compared to healthy controls. In vitro data suggest that catecholamines and glucocorticoids can both reduce oxidative burst [133].

In stroke and TBI, the brain injury itself is thought to trigger rapid activation of the stress pathways. MI patients suffer from thoracic pain and possibly respiratory distress, triggering a stress response in the absence of brain damage; similarly, patients with trauma also experience acute stress due to the trauma and to the resulting injury. Cross-study comparisons of ischemic stroke and TBI with ST/T and MI suggest that these diseases lead to similar induction of immunosuppression and subsequent infection through common activation of the stress response independently of direct central nervous system involvement (Figure 1).

Due to the similarities observed in alterations to the immune system in these very different diseases, we propose that SIIAs constitute a common response of the immune system to acute stress. SIIAs, which currently refer to “stroke-induced immune alterations”, may therefore be better termed as “stress-induced immune alterations.” Direct comparisons of the stress-induced immune alterations in various diseases are required to test
this hypothesis, which would offer a common therapeutic target to prevent infection and improve patient outcome across a wide spectrum of acute diseases.

Competing Interests

The authors declare that no competing interests exist.

Acknowledgement

We thank the German Research Foundation, Research Training Group 840 and the EU grant EnVision (FP7-REGPOT-2010, Grant-No 264143) for supporting our research.

The funders had no role in the decision to publish or the preparation of the review.

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Juliane Schulze et al

Stress hormone induced immune alterations

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Aging and Disease • Volume 5, Number 5, October 2014
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