Systemic inflammation and stroke: aetiology, pathology and targets for therapy

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Abstract
There is growing evidence that systemic inflammation is involved in multiple aspects of stroke aetiology and pathology. In the present review, we provide an overview of these roles and, in particular, outline recent evidence that the underlying systemic inflammatory profile can critically alter the response to ischaemic brain injury. We also highlight the need for stroke models to more adequately account for the involvement of underlying systemic inflammation.

Systemic inflammation and stroke susceptibility
Most stroke patients present with co-morbidities, such as atherosclerosis, hypertension, diabetes or infection, all of which may be actively involved in the development of stroke [1]. A common feature of these conditions is their association with an elevated systemic inflammatory status. Indices of the extent of systemic inflammation, such as raised circulating levels of CRP (C-reactive protein) and elevated leucocyte count, are predictive of stroke risk and, although not proof of causality, do support a general link between systemic inflammation and stroke susceptibility [2].

Atherothrombosis is the leading cause of stroke [3] and it is now recognized that inflammation is central to the initiation, development and rupture of atherosclerotic plaques [4]. The recruitment of immune cells, such as macrophages and T-cells, to plaques leads to the secretion of multiple inflammatory mediators, including pro-inflammatory cytokines, free radicals and proteases, that ultimately promote plaque rupture and thrombosis [4].

In addition to underlying vascular disease, there is compelling evidence that non-vascular peripheral inflammatory events can modify stroke susceptibility and perhaps trigger a cerebrovascular event. Acute bacterial infection, mostly affecting the respiratory or urinary tracts, significantly increases the risk of stroke [5], particularly in the first few days after infection [6]. Chronic infectious diseases, such as periodontitis, that result in a chronic ‘low-grade’ systemic inflammation are also emerging as predisposing factors for stroke [7]. Systemic infection may enhance stroke risk or act as a trigger via pro-atherogenic and prothrombotic mechanisms. Studies in murine models of atherosclerosis support this interaction. Bacterial or viral infections accelerate disease progression in mice but the effects are attenuated in mice in which components of the innate immune response have been genetically inactivated [8,9]. However, the prevalence of infection in paediatric stroke, where atherosclerosis is absent, also suggests that infection can act as a direct trigger of thrombosis independently of vascular effects [10].

Induction of systemic inflammation after stroke
Ischaemic brain damage stimulates the mobilization and migration of peripheral immune cells, particularly neutrophils (early) and macrophages (delayed), into the brain [11]. The rapid extravasation of neutrophils, which produces an array of toxic mediators, into the ischaemic brain is consistent with a role in the exacerbation of acute damage. However, the signals/mechanisms by which the brain conveys and peripheral components of inflammatory pathways detect ischaemic brain damage in order to mount an inflammatory response are poorly understood. For example, it is unclear how mature immune cells are mobilized from bone marrow stores after cerebral ischaemia. Systemic levels of various inflammatory mediators including acute-phase proteins, cytokines and chemokines are elevated after stroke and correlate with long-term outcome in patients [10]. Leakage of some of these molecules through the disrupted BBB (blood–brain barrier) may be one route of communication from ischaemic brain to the periphery [12], although the extremely low levels of most of these mediators in brain compared with the circulation suggest other sources and modes of signalling. We recently discovered that experimental stroke triggers a massive and rapid hepatic production of the neutrophil-selective CXC chemokine, KC (keratinocyte chemoattractant), implicating the liver as an important intermediary in post-ischaemic brain–immune interactions (K. Chapman, N.J. Rothwell, S.M. Allan and B.W. McColl, unpublished work). The liver receives an abundant autonomic innervation, indicating that a neural pathway may be a possible route for transmitting information conveying brain damage to the periphery. This is supported by recent evidence that sympathetic activity mediates the
lymphocyte-targeted immunosuppression that may occur in parallel and/or subsequently to acute inflammation [13].

Underlying systemic inflammation and impact on stroke outcome

Pre-existing or concurrent systemic inflammation may also modulate the response to stroke. Antecedent infection is associated with less favourable clinical outcome in stroke patients [14], an effect that may relate to an aggravated systemic inflammatory reaction [15]. Multiple inflammatory indices, including leucocyte count, plasma CRP and IL (interleukin)-6 concentration, are elevated after stroke in patients with prior infection, and correlations with these markers and long-term functional outcome have been reported extensively [2].

Results from recent studies using experimental models of cerebral ischaemia are in accordance with these clinical findings and have highlighted potential mechanisms. Peripheral challenge with the bacterial endotoxin, LPS (lipopolysaccharide), or IL-1 markedly exacerbates brain damage in a model of focal cerebral ischaemia (Figure 1) [16]. This effect was critically dependent on neutrophils and suggested that convergence between inflammatory pathways activated by both stroke and infection may result in synergistic amplification of the peripheral innate immune response when infection and stroke are co-incident [16]. The neurovascular unit, comprising neurons, glia and cerebrovascular endothelial cells, is a key structural and functional interface between the periphery and the brain and is disrupted by inflammation during ischaemic brain injury. We have recent evidence indicating that aggravation of stroke-induced neurovascular injury by enhanced matrix metalloproteinase activity is an important consequence of systemic inflammation (B.W. McColl, S.M. Allan and N.J. Rothwell, unpublished work). A similar exacerbation of neuronal injury by systemic LPS challenge was demonstrated in a model of global cerebral ischaemia and was independent of body temperature and local microglial activation and cytokine production in the brain, perhaps implicating neurovascular mechanisms in this paradigm also [17]. Systemic inflammatory challenges also exacerbate neonatal hemorrhagic and hypoxic brain injury [18,19]. Furthermore, the impact of systemic inflammation on cerebral ischaemia parallels its disease-accelerating effects in neurodegenerative conditions, suggesting a fundamental role for immune–brain interactions in neurological dysfunction [20–23].

Implications for the utility of experimental stroke models and stroke therapy

An extensive list of putative neuroprotective agents failed to show effectiveness in clinical trials despite preclinical efficacy. Numerous explanations have been proposed. One factor commonly cited is the appropriateness of animal models to recapitulate the complex aetiology of stroke, in particular the presence of co-morbid disease [24]. It is clear that most stroke patients present with underlying complications, most of which are associated with systemic inflammation. Despite this, only a minority of studies have utilized animal models with co-morbidities. In view of the emerging evidence that systemic inflammation can aggravate the post-ischaemic inflammatory reaction and exacerbate brain damage (see above), it is apparent that the involvement of systemic inflammation should be better accounted for in experimental stroke studies. An important issue to address is whether putative neuroprotectants retain their efficacy in the context of a more fulminant and accelerated systemic inflammatory response that could diminish the volume and/or hasten the dissolution of the penumbra.

Apart from improving the applicability of animal models to human stroke, elucidating how systemic inflammatory pathways interact with other mechanisms to modify stroke...
susceptibility and outcome may uncover novel targets for therapy. Peripheral signalling pathways and inflammatory mediators that may indirectly impact on ischaemic brain damage (for example, via effects on leucocyte trafficking) could represent accessible targets since brain penetration across the BBB is not necessary. Systemic inflammatory mediators are also likely to be good candidates as biomarkers due to their sensitivity to injury and ease of measurement. Notably, the CXC chemokine, IL-8, has shown promise as an early marker of prognosis in traumatic brain injury [25].

Concluding remarks
The accumulating evidence that systemic inflammation is a key component of stroke underlines the need for a fuller understanding of the mechanisms involved. This is likely to produce benefits in multiple areas including stroke prediction, treatment, prophylaxis and modelling (Figure 2).

References
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