Age-related hypoxia in CNS pathology

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Abstract

Although neuropathological conditions differ in the etiology of the inflammatory response, cellular and molecular mechanisms of neuroinflammation are probably similar in aging, hypertension, depression and cognitive impairment. Moreover, a number of common risk factors such as obesity, hypertension, diabetes and atherosclerosis are increasingly understood to act as “silent contributors” to neuroinflammation and can underlie the development of disorders such as cerebral small vessel disease (cSVD) and subsequent dementia. On the other hand, acute neuroinflammation, such as in response to traumatic or cerebral ischemia, aggravates the acute damage and can lead to a number of pathological such as depression, post-stroke dementia and potentially neurodegeneration. All of those sequelae impair recovery and most of them provide the ground for further cerebrovascular events and a vicious cycle develops. Therefore, understanding the mechanisms associated with vascular dementia, stroke and related complications is of paramount importance in improving current preventive and therapeutic interventions. Likewise, understanding of molecular factors and pathways associated with neuroinflammation will eventually enable the discovery and implementation of new diagnostic and therapeutic strategies indicated in a wide range of neurological conditions.

Keywords: cerebral ischemia, depression, cognition, post-stroke dementia.

Introduction

Worldwide, more than 15 million people have a stroke each year. Therefore, stroke remains one of the main causes of death and adult disability. Population aging will result in a dramatic increase in the burden of stroke. Therefore, it is not surprising that pharmaceutical industry has invested a huge amount of money in the development of pharmacotherapies of acute ischemic stroke. Promising experimental data, however, have almost consistently failed to produce a clinically effective neuroprotective drug [1–5]. Only the intravenous recombinant tissue plasminogen activator (tPA) has been approved for the treatment of acute ischemic stroke.

Co-morbidities are the major determinant in the treatment of ischemic stroke. Modifiable risk factors some of which are more common in women results from lifestyle can be modified with healthcare and medical interventions [6]. Unmodifiable risk factors serve also as markers for high stroke risk. Interestingly, the recent evidence shows that cognitive decline below dementia threshold [7] or depression [8] is associated with incidence of stroke.

The failure to consider the complexity and heterogeneity of human diseases and co-morbidities may contribute to fact that neuroprotective drugs does not work in clinical practice but do so in experimental models of stroke. Several committees (STEPS, 2009) have proposed a design framework aimed to improve the quality of preclinical stroke studies by including animals with co-morbidities.

It is highly recommended that prior clinic, positive results obtained in experimental studies in young animals should be confirmed in additional studies done in aged animals and young animals models with comorbidities such as neuroinflammation, metabolic inflammation, hypertension, and hypercholesterolemia [9].

Aging, atherosclerosis, chronic inflammation and perfusion deficits

Atherosclerosis, a major risk factor for stroke and central nervous system (CNS) tissue destruction, is a disease of arteries characterized by vascular inflammation caused primarily by infiltrated monocytes into the injured vascular wall.

Several studies have suggested that inflammation may be important for accelerated progression of atherosclerosis. In a study investigating the association between inflammatory biomarkers and progression of intracranial large artery stenosis after ischemic stroke it found that in addition to traditional risk factors, circulating levels of interleukin (IL)-6 after stroke are associated with future intracranial large artery stenosis progression [10, 11]. Currently, it is widely accepted that in addition to other established cardiovascular risk factors, markers of inflammation such as C-reactive protein (CRP) is a strong predictor of subclinical and clinical atherosclerosis [12, 13] and progression of hemorrhagic stroke [14–16]. Thus, in patients with hypertension, elevated CRP levels predicted clinical events. These patients also showed a significant
relationship between clinical events and quintiles of CRP levels [12, 17, 18].

Other studies have reported on pathological vicious cycles related to CRP and atherosclerosis. For example, elevated circulating levels of CRP independently predict the development of new plaques in older persons with carotid arteries free from atherosclerotic lesions [19, 20].

However, CRP represents the strongest evidence that (neuro)inflammation is of paramount importance in a neurological syndrome such as stroke.

Virtually, all drug interventions that have been successful pre-clinically in experimental stroke have failed to demonstrate positive results in stroke patients. Our research as well as group’s studies indicate that ignoring the molecular characteristics of ageing and the associated co-factors present in clinical stroke results in disappointing results in clinical trials [3, 21–23].

Studies conducted on aged rats have demonstrated that neurological impairment is more severe and functional recovery less successful than in young rats [24–26]. In addition, elderly individuals recover less well from stroke than young individuals [27, 28].

**Stroke, obesity and neuroinflammation**

Age represents the most important risk factor for stroke. Virtually, all drug interventions that have been successful pre-clinically in experimental stroke have failed to demonstrate positive results in stroke patients.

Our research as well as studies done in other laboratories indicate that ignoring ageing and the associated co-morbidities may lead to failure in clinical trials [3, 21–23].

Epidemiological studies have revealed an age-dependent increase of stroke susceptibility in men and women, with half of all strokes occurring in people over 75 years, and one third of cases in people over 85 years [29, 30]. Studies conducted on aged rats have demonstrated that neurological impairment is more severe and functional recovery delayed and often less successful than in young rats [24–26]. In addition, elderly individuals recover less well from stroke than young individuals [27, 28].

Stroke patients are at highest risk of death in the first weeks after the event, and between 20% to 50% die within the first month depending on type, severity, age, comorbidity and effectiveness of treatment of associated complications. Considerable spontaneous recovery occurs up to about six months. Few of the patients who survive may be left with no disability or with mild, moderate or severe disability [31, 32]. However, patients with a history of stroke are at high risk of a subsequent event, about 10% in the first year and 5% per year thereafter [33].

The obesity paradox has been reported in many articles as an inverse relationship between the body mass index (BMI) and mortality in stroke patients. However, the relationship between BMI and functional recovery in post-stroke patients has not been well described [34–39].

A cohort study from the China National Stroke Registry analyzed the relationship between the BMI, mortality and post-stroke functional recovery at three months after the event. This study enrolled and analyzed 10,905 eligible patients with acute ischemic stroke. Favorable behavioral recovery was seen in 52.4% of underweight (BMI 18.5 kg/m²), 55% of normal weight (BMI 18.5–22.9 kg/m²), 61% of overweight (BMI 23–27.4 kg/m²), 59.2% of obese (27.5–32.4 kg/m²) and 60.3% of severe obese (BMI >32.5 kg/m²) stroke survivors. The overweight acute ischemic stroke survivors had a better three-month functional recovery. Remarkably, patients with obesity (BMI <32.5 kg/m²) showed a positive outcome. However, severe obesity was associated with higher mortality while an overweight status was not a protective factor of survival at three months after stroke [40, 41].

Another study evaluating the effect of BMI on stroke rehabilitation conducted in 819 patients revealed that overweight patients had better functional progression than non-obese patients [4, 42].

Likewise, a large retrospective cohort study from the Danish Stroke Register enrolling 53,812 patients has assessed the obesity paradox by analyzing the BMI, age, gender, civil status, stroke severity, stroke subtype, a pre-defined cardiovascular profile, and the socio-economic status. There was no evidence of an obesity paradox in patients with reported stroke. However, stroke occurred at a significantly younger age in patients with higher BMI [42].

Adipose tissue dysfunction in obesity contributes to chronic, low-grade inflammation that predisposes to type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) [43]. In obese mice, the adipose tissue is characterized by a lower interstitial oxygen partial pressure (PO2) [44, 45]. Quite interestingly, obese patients have a lower PO2 in the subcutaneous adipose tissue of the lateral upper arm compared with non-obese patients [46]. Furthermore, abdominal subcutaneous adipose tissue PO2 is slightly lower in overweight/obese compared with lean subjects [47].

In conclusion, obesity could determine a worse outcome in stroke patients, yet it is not known the exact molecular pathways [4, 41, 48]. However, since obesity represents a state of chronic inflammation it is likely that this factor plays a crucial role in the general evolution of post-stroke patients.

**Diabetes mellitus and metabolic inflammation**

Diabetes mellitus (DM) is a great challenge for the healthcare system accounting for ~6% of global mortality in industrialized countries. Half of DM-associated deaths are attributed to cardiovascular (macro- and micro-vascular) complications.

Neuropathic complications are also frequent, occurring in about 60% of people with DM, and often overlap with, and worsen the consequences of vascular disease. Sensory neuropathy is a typical form of peripheral neuropathy characterized by an altered perception of noxious stimuli or ischemic pain. This promotes the foot ulcers caused by pressure or traumas and abrogates warning symptoms during a heart attack.

It is becoming well established that lifestyle, especially dietary habits, greatly affect metabolic health. Bad nutritional habits can lead to metabolic disorders, triggered by a system-wide chronic inflammation, also called inflammation, metabolic inflammation [49, 50]. A metabolic inflammation state can lead to a series of disorders and diseases, including hypertension, metabolic syndrome,
CVD, stroke, insulin resistance and T2DM. It is postulated that lipid hormones including sphingolipids and eicosanoids in concert with cytokines and adipokines play an important role in this process by inducing adverse regulatory responses in target cells such as macrophages. The role of genetics in driving metabolic disease development is strongly indicated by the higher concordance rate of T2DM in monozygotic than in dizygotic twins. It has been estimated that 30% to 70% of T2DM risk can be attributed to genetics [51, 52]. The investigation of gene-environment interactions through large collaborative efforts holds promise in furthering our understanding of the interplay between genetic and environmental factors [52, 53].

Since the availability of whole human genome single nucleotide polymorphisms (SNP) assays, genome-wide analysis of correlations between genetic variants (SNPs) and phenotypes has become an important approach to find disease-causative genes. Genome wide SNP typing is often performed in very large groups of human individuals (cohorts), and a large number of loci underlying disease have now been catalogued (http://www.genome.gov/gwa studies/), including variants that increase susceptibility to T2DM. However, these loci confer effects of only modest size and do not add to the clinical prediction of diabetes beyond that of traditional risk factors, such as obesity, physical inactivity, family history of diabetes, and certain clinical parameter. Furthermore, recent studies led to the identification of new genetic loci linking adipocyte and insulin biology to body fat distribution [53, 54]. The combination of genome-wide association study (GWAS) with metabolomics is breaking new grounds, as it allows making associations between SNPs and so-called intermediate phenotypes [55–57].

Metabolomics facilitates the exact quantitative measurement of large sets of lipid molecules and other metabolites, and GWAS has allowed the mapping of numerous metabolic phenotypes on the genome, as demonstrated by the discovery of substantial numbers of loci with relative strong effects [58–63]. Therefore, we could speculate diabetes mellitus is characterized by a state of increased general inflammation including at the CNS level, which might impair recovery and outcome in a wide range of neurological conditions.

Aging and neuroinflammation

Normal aging is characterized by a chronic low-grade, proinflammatory state [64, 65], with an overexpression of systemic inflammatory factors, including proinflammatory cytokines [66–68]. Age-associated inflammation in the brain manifests primarily by the chronic activation of perivascular and parenchymal macrophages/microglia expressing proinflammatory cytokines and an increased number of astrocytes [45, 69]. Given the potential role of inflammation in psychopathology, it is possible that chronically activated inflammatory signals in aging may contribute to increased vulnerability to neuropsychiatric disorders [3, 70, 71]. Inflammation in obese women is associated with increased concentrations of inflammatory markers (IL-6, CRP and adipokines) that correlated with increased symptoms of depression and anxiety [72, 73]. Conversely, removal of fat tissue surgically was associated with reduced inflammation [74, 75].

The prevalence of depression and cognitive dysfunction is particularly elevated in the elderly and obese subjects. Patients with major depression have an increased onset risk of aging-related diseases affecting the cardiovascular, cerebrovascular, endocrine, metabolic, and immune systems [76–80]. Depression can thus significantly compromise successful aging defined subjectively as freedom from chronic disease and disability, along with high physical and cognitive functioning and social engagement [81, 82].

Perfusion deficits in the elderly, inflammation and depression

Recent data suggest that perfusion deficits in the elderly can trigger microglial activation and subsequent neuroinflammation [83, 84] ultimately resulting in demyelination and neurodegeneration [22, 84].

Previous studies in rodents indicate that aging and neurodegenerative diseases promote a proinflammatory state in older individuals and leads to the development of an activated population of microglia [85–93]. Further, immune activation can be a characteristic of depression [94–96] and precipitate depressive symptoms [3, 96]. This was particularly evident in middle-aged rodents as compared to the young counterparts [97].

In the elderly, perfusion deficits can trigger microglial activation and shifts the CNS into a proinflammatory state [82–84, 90]. Recent research suggests that the inflammatory process is potentially intricately linked with multiple neurodegenerative pathways and depression and plays a central role in the pathophysiology of both depression and dementia [95, 98–104]. There is strong evidence that in human vascular disease, vascular \( \beta \)-amyloid (A\( \beta \)) deposition in the brain promotes development of depression and increases the risk of dementia by causing rigidity of arterioles and leading to infarction in the territory of their branching vessels in the temporal cortex of patients with cerebral amyloid angiopathy (CAA). This is associated with marked vascular and perivascular infiltration of inflammatory cells, a condition mimicked in mice subjected to chronic cerebral hypoperfusion [105–107].

Aging, neuroinflammation and depression

Major depressive disorder (MDD) is a severe psychiatric illness that is associated with significant morbidity and mortality. In addition to mortality associated with suicide [108, 109], depressed patients are more likely to develop dementia, coronary artery disease and type 2 diabetes [110, 111]. Depression also complicates the prognosis of other chronic diseases [111–113]. However, biological mechanisms underlying depression remains poorly understood.

Despite advances in the treatment of major depression, one-third of depressed patients fail to respond to conventional antidepressant medication [114, 115]. One pathological mechanism hypothesized to contribute to treatment resistance in depression is inflammation. Depression and dementia by a number of putative mechanisms involving neuroinflammation, oxidative stress, endothelial nitric oxide synthase uncoupling, and hyperglutamatergia, as well as neurovascular dysfunction in MDD [116, 117].
Recent evidence has shown that resistance to conventional antidepressants in major depression is associated with increased levels of inflammatory markers in the periphery including inflammatory cytokines, acute phase proteins, chemokines, and adhesion molecules [118–121]. Indeed, patients treated with cytokines for various illnesses are at increased risk of developing major depressive illness [122]. A recent study reported that treatment-resistant depression (TRD) who has highly increased inflammation [i.e., elevated baseline high-sensitivity (hs)-CRP concentration] responded preferentially to Infliximab while participants with a low level of inflammation treated with Infliximab appeared to do worse than placebo-treated participants [123]. Of note, increased inflammatory markers in depressed patients have also been associated with remitted stages of depression in response to treatment with conventional antidepressant medications [120, 121, 124–126]. On a background of systemic inflammation, proinflammatory cytokines can access the CNS and interfere with serotonin metabolism, and reduce both synaptic plasticity and hippocampal neurogenesis [94, 127]. Behavioral consequences of these effects of the immune system on the brain include depression [94, 127–129].

Cross-sectional [130–132] and prospective [133, 134] epidemiological studies have focused on peripheral inflammatory markers, such as cytokines and acute phase proteins have investigated the hypothesis that peripheral inflammatory markers are etiological factors in the development of depressive symptoms [95, 126, 135]. The most consistent finding has been the association of elevated cytokines IL-6 and IL-8 with depressive symptoms [126, 129].

Successful antidepressant treatment may reduce the level of proinflammatory markers by improving brain perfusion and by restoring the endothelial function [118, 129, 136, 137]. This, Etanercept, a soluble tumor necrosis factor-α receptor, and Celecoxib, a cyclooxygenase-2 inhibitor, and Infliximab, reduced depressive symptoms in patients with inflammatory diseases [123, 138–141].

### Aging, neuroinflammation and small vessel disease

In older individuals, inflammatory mechanisms have been linked to the pathogenesis of dementia and recent evidence suggests that systemic and local neuroinflammation significantly contributes to cSVD-vascular dementia. For example, the adhesion molecules are increased in serum of patients who have white matter lesions [152, 153]. Since chronic inflammation plays an important role in hypertension, a relationship between inflammatory processes and cSVD may also be assumed [154]. One hypothesis is that these microvascular changes result in a state of chronic hypoperfusion leading gradually to oligodendrocyte death and degeneration of myelinated fibers. This may not only cause progressive white matter damage on a macroscopic scale, but also foster inflammatory processes chronically. Further, increased low-grade inflammation amplifies the risk of stroke [20] (Figure 1). However, the available data are still controversial. Thus, in a cross-sectional study investigating the possible link between biomarkers of systemic inflammation and functional status in older patients with late onset Alzheimer’s disease and elderly patients with vascular dementia, it was found that IL-6 plasma levels negatively correlated with vascular dementia [2–4, 155–157].

### Conclusions

Although neuropathological conditions differ in the etiology of the inflammatory response, cellular and molecular mechanisms of neuroinflammation are probably similar in aging, hypertension, depression and cognitive impairment. Moreover, a number of common risk factors such as obesity, hypertension, diabetes and atherosclerosis are increasingly understood to act as “silent contributors” to neuroinflammation and can underlie the development of disorders such as cerebral small vessel disease and subsequent dementia. On the other hand, acute neuroinflammation such as in response to traumatic or cerebral ischemia aggravates the acute damage and can lead to a number of pathological such as depression, post-stroke dementia and potentially neurodegeneration. All of those sequelae impair recovery and most of them provide the ground for further cerebrovascular events, and a vicious cycle develops. Therefore, understanding the mechanisms associated with vascular dementia, stroke and related complications is of paramount importance in improving current preventive and therapeutic interventions. Likewise, understanding of molecular factors and pathways associated with neuroinflammation will eventually enable the discovery and implementation of new diagnostic and therapeutic strategies indicated in a wide range of neurological conditions.
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Figure 1 – The vicious cycle underlying cerebrovascular events and their consequences. Cellular and molecular mechanisms of neuroinflammation are probably similar in aging, hypertension, depression and cognitive impairment. Moreover, a number of common risk factors such as obesity, hypertension, diabetes and atherosclerosis are increasingly understood to act as “silent contributors” to neuroinflammation and can underlie the development of disorders such as cerebral small vessel disease (cSVD) and subsequent dementia. Acute neuroinflammation aggravates the damage after traumatic or stroke and can lead to a number of pathological such as depression, post-stroke dementia and potentially neurodegeneration. TBI: Traumatic brain injury.

Conflict of interests
The authors declare that they have no conflict of interests.

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