

Current Perspectives in Post-stroke Cognitive Impairment

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Abstract

Post-stroke cognitive impairment (PSCI) is a particularly serious consequence of cerebral ischaemia and often inhibits or retards patient rehabilitation. Current treatments do not improve long-term outcomes for a significant proportion of patients and remain a substantially unmet medical need. Initiatives to address the challenge of post-stroke rehabilitation have included therapies that modify multiple pathogenetic mechanisms and provide protection to neural networks and facilitate their regeneration. Promising biological agents have been tested, but few have so far yielded clinically conclusive evidence further emphasising the shortage of therapies available to treat this disease. The multimolecular agent Actovegin[®] has been shown to stimulate capillary flow and neurometabolism after stroke and to provide promising results in the treatment of mixed dementia. Clinical trials are now in progress to fully evaluate this pleiotropic neurometabolic therapy.

Keywords

Post-stroke cognitive impairment, blood–brain barrier, neurovascular unit, diagnostic variability, lack of consensus, emerging treatment

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This article summarises the content of a symposium that took place during the 21st World Congress of Neurology in Vienna, Austria. It aims to describe the vascular and cellular processes that are involved in the maintenance of the blood–brain barrier (BBB), the cells involved in the neurovascular unit (NVU) and its dysfunction in stroke resulting in post-stroke cognitive impairment (PSCI) for many patients. There is substantial variability in reported rates of PSCI and this is largely a result of differing assessment methods used to assess the condition and inconsistent treatments and times to treatment initiation in different territories. The lack of agreed guidelines and of consensus among healthcare professionals also contributes to variable levels of diagnosis and treatment outcomes in PSCI. This article will additionally consider these critical matters and discuss the development of a new treatment approach for PSCI that has shown potential and is being evaluated in clinical trials.

The Role of the Blood–Brain Barrier and the Neurovascular Unit in Cerebral Ischaemia

An important concept in the development of stroke and consequent cognitive impairment is the fact that the brain has no reserve of energy or oxygen. It must therefore be constantly perfused through the normal blood supply to supply these factors and to remove metabolic products, particularly carbon dioxide. Any interruption in this continuous process is liable to have a serious effect on the brain region in which it occurs.¹ The BBB comprises a diverse set of cellular components some of which participate in the NVU. The interaction between these cells is important

in the pathophysiology of PSCI and other neurological diseases (see *Figure 1*).^{2–4}

The tissues of the central nervous system (CNS) make high metabolic demands of the vascular system and the microcirculation of the brain must be responsive to changing requirements.^{5,6} The NVU is central to this process and maintains a ‘metabolic coupling’ between brain activity and blood flow. In neurological disease or injury there is a danger of exposure to metabolic products that are toxic to brain tissue and may cause neuronal damage.^{4,7} ATP-sensitive potassium channels play a major role in sensing metabolic requirements and provide protection of brain tissues against these effects of neurological disease or injury.⁸ Some functional magnetic resonance imaging (fMRI) studies have suggested that following stroke there is an uncoupling between metabolic requirements, especially for oxygen and vascular supply and this can worsen outcomes.⁹

Within the NVU, astrocytes provide trophic support to neurons and maintain synaptic functions and dynamic signalling. The end-feet structures of astrocytes have a close contact with cerebral endothelial cells and provide a physical link to the microvasculature. Astrocytes are therefore uniquely positioned to exercise control over local changes in cerebral blood flow as well as regulating tight junction integrity.^{1,10,11} Pericytes are important in regulating blood flow by contracting or relaxing in response to vasoactive stimuli from surrounding cells.^{12,13}

Microglial cells are cerebral monocytes with a stellate morphology and release a range of pro- and anti-inflammatory mediators but their role in the NVU is as yet, unclear.^{14–16} In response to changes in neuronal activity, perivascular-released neurotransmitters and other mediators can activate receptors on both smooth muscle cells and astrocytes to alter the tone of brain microvessels.¹⁷

Cellular communication within the NVU involves various signalling pathways of neurovascular coupling and interactions among astrocyte, vascular smooth muscle, neuronal and endothelial compartments. These processes comprise numerous factors including cytochrome P450 epoxygenase metabolites, signalling initiated by metabotropic glutamate receptor (mGluR) activation, potassium signalling, 20-hydroxyeicosatetraenoic acid (20-HETE acid) signalling, adenosine signalling, carbon monoxide signalling and calcium (Ca²⁺) efflux. In addition, the regulation of blood flow by astrocytes may involve both vasodilating and vasoconstricting components.¹⁸

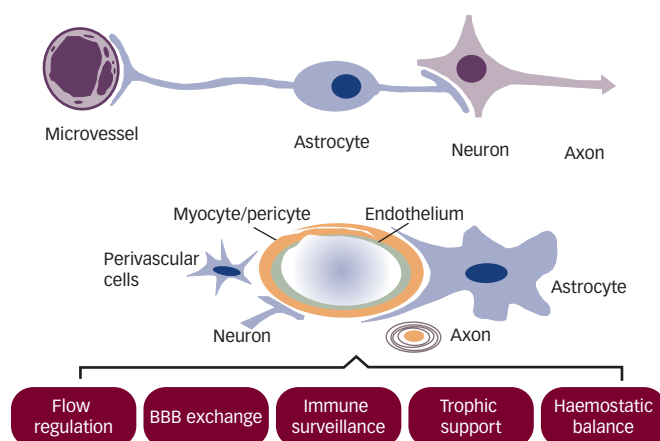
Several neurotransmitters are important in vascular coupling in the NVU. Glutamate is the main excitatory neurotransmitter in the brain and may trigger responses via indirect signalling.¹⁹ The release of glutamate during neuronal activation may act on astrocytic mGluR receptors to increase Ca²⁺ in astrocytes and elicit a vasodilatory effect.²⁰ Nitric oxide is released from activated neurons following N-methyl-D-aspartate (NMDA) receptor activation²¹ and is one of the major vasoactive substances whose role is of prime importance in maintaining endothelial homeostasis. Calcium waves are another form of neurotransmitters and are a type of non-electrical impulse in which increased blood flow results in greater intracellular Ca²⁺ concentrations in astrocytes and the signal is propagated by release of Ca²⁺ to surrounding cells or by extracellular ATP signalling.²²

Several CNS conditions have overlapping pathogenic processes and molecular mechanisms associated with the NVU. For example, vascular dementia (VAD), Alzheimer's disease (AD) and traumatic brain injury have common pathways, including excitotoxicity factors (glutamate, calpain and CDK-5), neuroinflammation (interleukin [IL]-1, IL-6, tumour necrosis factor-alpha [TNF- α]), oxidative stress (reactive oxygen species), apoptosis (TNF- α , glycogen synthase kinase-3 [GSK-3b]), proteinopathies (β -amyloid) and neurotrophic alterations (brain-derived neurotrophic factor [BDNF], insulin-like growth factor type 1 [IGF-I], vascular endothelial growth factor [VEGF]).¹¹ These processes and secreted factors lead to neurovascular damage and degeneration. In AD, these effects arise from vascular risk factors, elevated cholesterol and ageing on the NVU leading to vascular fibrosis, β -amyloid accumulation, synaptic loss and, ultimately, to progressive cognitive impairment.²³

Future therapeutic strategies in the detection and treatment of PSCI are likely to include the use of biomarkers of NVU integrity.²³ An example is asymmetric dimethylarginine (ADMA), a marker of endothelial dysfunction and a newly recognised independent risk factor for adverse cerebrovascular events in small vessel disease. A recent study reported significantly increased plasma levels of ADMA in 16 patients with cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy compared with controls ($p < 0.05$).²⁴

The BBB, therefore, is a critical interface in sustaining the brain's need for constant perfusion and consists of a dynamic and functional NVUs that are formed from astrocytes, microglia, capillary endothelium, neurons, pericytes and extracellular matrix all acting in a coordinated

Figure 1: The Neurovascular Unit Involving Complex Interplay between Neurons, Astrocytes and Microvessels



BBB = blood–brain barrier.

Source: Adapted, with permission, from del Zoppo 2010.²

manner. Astrocytes, as well as other cellular components of the NVU, appear to play a crucial role in monitoring changes in synaptic activity and signalling between microvascular units. In CNS disease, however, the ordered structure of the NVU breaks down resulting in breaches in the BBB leading to neuronal damage and cognitive impairment.

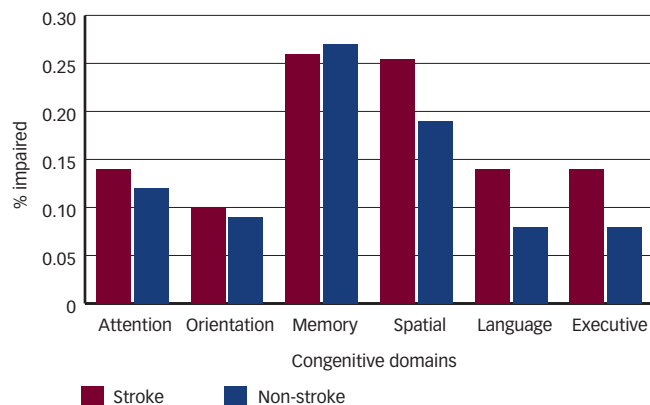
Post-stroke Cognitive Impairment Critical Concerns

Dementia and cerebrovascular diseases (CVD) account for a substantial proportion of the global burden of disability.²⁵ In terms of prevalence, PSCI is a subset of the VADs and represents a major part of this burden. The estimated total annual cost of dementia, including PSCI, was estimated to be €105 billion in Europe in 2010.²⁶ There are, however, substantial discrepancies of reported incidence and prevalence of post-stroke dementia between hospital- and population-based cohorts of first-ever stroke.²⁷ Initiatives to improve diagnosis and management of PSCI are therefore of great importance but these are complicated by some critical factors, particularly variability in the definition of the condition and a general lack of consensus and comparability between studies and evaluation tools.

PSCI can be identified in patients using two diagnostic criteria: the presence of a cognitive disorder (i.e. dementia or vascular cognitive impairment [VCI]) and a history of clinical stroke or vascular disease by neuroimaging.²⁸ There is a close relationship between stroke and dementia and prevalence data show that one patient in 10 already has dementia when stroke occurs, one in 10 will develop dementia after a first-ever stroke and one in three will develop dementia following a stroke recurrence.²⁹ Factors most strongly associated with pre-stroke dementia include a family history of dementia, media temporal lobe atrophy, leukoaraiosis and previous stroke. Factors most strongly associated with post-stroke dementia include dysphasia, incontinence, early seizure and previous strokes.²⁷

A notable survey of population-attributable prevalence fractions (PAPF) that included 15,020 participants aged 65 years in low- and middle-income countries, ranked stroke second after dementia as contributing to disability.²⁵ A more recent, large study conducted in the US evaluated the long-term rate of change in memory functioning before and after

Figure 2: Impairment of Cognitive Domains in Patients Following Mild Stroke Compared with Stroke-free Controls



Source: Srikanth et al. 2003.³³

stroke onset in 1,574 participants.³⁰ The findings demonstrated that although stroke onset induced large memory decrements, differences in memory were apparent years before the occurrence of stroke. A population-based study conducted over 24 years in France found that among 3,201 patients with first-ever stroke, 20.4 % had post-stroke dementia.³¹ An increasing prevalence of post-stroke dementia was associated with age, vascular risk factors, hemiplegia and pre-stroke use of antiplatelet agents. These studies show that cognitive impairment is common following stroke and constitutes a substantial world health burden that is likely to increase with ageing populations and emphasise the critical need for effective treatments.

In addition, disease categories of VAD, mild cognitive impairment (MCI), mixed-dementia and prodromal-state of AD are not sufficiently defined or accepted by neurologists. These shortcomings were identified in a review of barriers for patients with dementia in Europe which concluded that multidisciplinary approaches are needed to improve diagnosis and treatments for all patients with cognitive complaints.³² The authors recommended that these approaches should include dementia training for all healthcare professionals, regular updates of treatment guidelines and greater public awareness to destigmatise dementia.

The variability of post-stroke cognition assessment methods is highlighted by the finding that in patients with MCI (without dementia) 3 months after a stroke varies from 17–66 % depending on the criteria used for testing.³³ In addition, the degree of impairment varies with different cognitive domains (see *Figure 2*). To limit the variability in assessment, training is necessary to standardise scoring and to select the most best-performing test instruments. This was emphasised in a comparison of cognitive tests conducted in Canada on 110 patients after a stroke and 45 age-matched controls with stroke risk factors. The results showed that the Montreal Cognitive Assessment (MoCA) battery of tests was more sensitive in detecting disease than the Mini-Mental State Examination (MMSE).³⁴ In addition, the Trail Making Test A and B and the Digit-Span Forward and Backward Test can be rapidly completed and are helpful in diagnosing and monitoring cognitive decline.³⁵

Following the onset of a stroke there is a delay before cognitive impairment becomes apparent. The dynamic properties and molecular development of this process are not well understood and this creates difficulties for

practitioners regarding diagnosis and treatment. The patient-related risk factors that increase the prevalence of dementia after stroke include personal factors such as increasing age, CNS diseases (e.g. pre-stroke cognitive decline without dementia), cardiovascular disease (e.g. atrial fibrillation), other factors (e.g. diabetes) and stroke-related factors (e.g. severity, location and dementia due to vascular lesions).²⁹ It is significant that the rate of dementia is at least twice as high after recurrent stroke²⁷ and it is therefore essential that vascular risk biomarkers such as inflammatory markers are developed to predict the risk of a recurrence.²⁶

The future management of PSCI will require, first, a better understanding of cognitive impairment following stroke and, second, the development of reliable pre-stroke biomarkers. If VCI is to be treated effectively to halt any progression to dementia, therapies to selectively target major pathological processes will be required. Multiple pathways should be targeted to improve neurometabolism and neurorecovery in PSCI.

Current and Future Developments in the Treatment of Post-stroke Cognitive Impairment

The growing health, social and economic burden of PSCI is driving the demand for clinical studies that evaluate the benefits and risks of pharmacological and nonpharmacological therapies. Prevention and treatment of PSCI are, in fact, one of the critical priorities for clinical care and research. Better understanding of the risk factors and estimation of the risk scores for post-stroke dementia are important for selection of patients for preventive clinical trials (on neuroprotective agents, cognitive rehabilitation and other strategies).

Important avenues in VAD treatment are: symptomatic improvement of the core symptoms (cognition, function and behaviour), slowing of progression and treatment of neuropsychiatric symptoms. Controlled clinical trials with donepezil and galantamine demonstrated improvement in cognition, behaviour and activities of daily living; however, a number of adverse events were observed. Trials using memantine showed that it was well tolerated, improved function and reduced care dependency in treated patients compared with placebo. Evidence-based assessment of the efficacy and safety of the number of interventions including cerebrolysin, antidepressants and hyperbaric oxygen therapy have been recently published.^{36–46}

No drug treatment to date, however, has shown convincing clinical evidence of restoring cognitive function or preventing further decline after stroke. There is also uncertainty regarding patient characteristics that might predict response to treatment.

A number of important clinical trials in post-stroke dementia and treatments are ongoing (www.ClinicalTrials.gov) or have recently been completed. The Tel-Aviv Brain Acute Stroke Cohort (TABASCO) trial, with up to 10 years' follow-up after stroke, is focused on the association between predefined demographic, psychological, inflammatory, biochemical, neuroimaging and genetic markers, measured during the acute phase. It is also monitoring long-term outcome including subsequent cognitive deterioration, vascular events (such as recurrent strokes), falls, affective changes, functional everyday difficulties and mortality.⁴⁷

The DEterminants of DEMentia After Stroke (DEDEMAs) trial is a 5-year observational study in Germany, recruiting 600 patients with acute stroke but without prior dementia. Sophisticated neuroimaging will be utilised in patients developing cognitive impairment (with or without dementia) and in a subgroup of matched individuals without cognitive

decline. This trial will focus on interactions between vascular and neurodegenerative mechanisms. Another trial (SMARTease) will use a 16-week telerehabilitation cognitive strategy, during which a trained rehabilitation coach speaks to post-stroke patients regarding their condition by telephone twice weekly.

Motivation and lifestyle intervention are being evaluated in several trials. The Austrian Polyintervention Study to Prevent Cognitive Decline After Ischemic Stroke (ASPIS) is a multicentre, randomised, observer-blind, parallel group clinical trial to evaluate multiple lifestyle interventions following stroke. It will provide essential data about the feasibility and efficacy of lifestyle intervention after stroke in order to develop a new approach to prevent cognitive decline in patients with mild ischaemic stroke.⁴⁸ In addition, a number of trials are focused on pharmacological treatments. One such trial, for example, is evaluating the efficacy of gliatiline on post-stroke patients with VCI.

Aspirin has been used in the treatment of stroke for many years and there is a large body of evidence to support this.^{49–51} However, there is little evidence suggesting that non-steroidal anti-inflammatory drugs (NSAIDs) are effective in preventing cognitive decline following stroke. Indeed, most studies indicate little difference between NSAIDs or other treatments or placebo in terms of cognitive impairment.^{52–54}

Neurometabolic agents are potential therapies for PSCI. Actovegin[®], for example, contains more than 200 different small molecules, such as oligopeptides, oligosaccharides, eicosanoids and other compounds. It is protein free, its constituent molecules are all less than 5,000 Da and it is derived using a sophisticated calf blood ultrafiltration technology. Actovegin increases aerobic oxidation and has emerged as a promising treatment for VCI based on findings from cellular studies, animal models and some clinical experience within mixed and VAD.⁵⁵ This treatment has been successfully used to treat stroke, traumatic brain injury and diabetic neuropathy.⁵⁶ Experience in VCI, however, is much more limited. In early clinical trials in the frequency of adverse events and discontinuation due safety concerns with Actovegin has been low and often comparable with placebo.⁵⁷

The Efficacy and Safety of Actovegin in Post-stroke Cognitive Impairment (PSCI) (ARTEMIDA) is in progress. This is a phase III, randomised, placebo-controlled trial in which patients commence 6 months of treatment within 7 days of a stroke followed by 6 months of follow-up.⁵⁷ The endpoints

are Alzheimer's Disease Assessment Scale change at 6 months and disease-modifying effects (difference between slopes). The recruitment is completed to this study and the results are expected in 2015. This study is pivotal: the findings are awaited with interest and will establish whether Actovegin is a valid approach for the clinical management of PSCI. The dosage of Actovegin in this trial was driven by levels used in other indications but since the effects are apparently dose dependent, dose-ranging clinical trials are needed to establish optimum treatment regimens in PSCI.

The use of a complex mixture to treat PSCI is an intriguing change of approach to treatment. To develop effective drug treatments for this disease, either a single compound with more than one mode of action or a combination or mixture of therapies with different modes of actions are required, these would target multiple mechanisms of ischaemia and may thus achieve greater efficacy than single-action entities.

Conclusions

The processes involved in neurodegenerative and ischaemic disease have common multifactorial molecular mechanisms related to the NVU. A better understanding of the cellular and molecular processes involved in NVU dysfunction may lead to improved treatments for PSCI and other neurological disease. Future therapeutic strategies may include the use of biomarkers of NVU integrity to assess the extent of neurological damage and may be used as prognostic indicators and guide treatment. The functions of the NVU are complex and effective neuroprotective and neuroregenerative treatments for PSCI need to influence multiple different pathophysiological mechanisms in order to limit neuronal damage and aid recovery.

There is a need to better understand the molecular mechanisms contributing to neuronal damage in VCI and develop better means of assessing it. Pre-stroke epigenetic, imaging and laboratory markers are needed to better determine the risk of cognitive impairment. Interventions with multifactorial effects are needed to improve prognosis of patients with cognitive complaints following stroke.

Among developing treatments for PSCI, evidence from preclinical studies has shown that Actovegin, a multimolecular product manufactured using a calf blood ultrafiltration technology, is a promising neurometabolic therapeutic option. The ongoing phase III clinical trial will determine its efficacy in treatment of PSCI. ■

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