Possibilities for the prevention and treatment of cognitive impairment and dementia

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Summary The human brain has a remarkable capacity for plasticity, but does it have the capacity for repair and/or regeneration? On the basis of controversial new evidence we speculate that the answer may be 'yes', and suggest that clinicians should therefore approach cognitive impairment and dementia with a new, cautious optimism.

Declaration of interest None.

NEURAL PLASTICITY, ANGIOGENESIS AND NEUROGENESIS

It is widely accepted that physical activity, learning and social factors exert alterations in gene expression, giving rise to changes in patterns of neural connectivity and functionality throughout life (Kandel, 1998). These changes are achieved through mechanisms of neural plasticity, synaptogenesis, angiogenesis and possibly neurogenesis. The evidence for neurogenesis in the adult human brain, however, is controversial (Bhardwaj *et al*, 2006). A number of studies have demonstrated neurogenesis in the healthy adult human brain, in the hippocampus (Eriksson *et al*, 1998; Draganski *et al*, 2004) and in the olfactory bulb (Bedard & Parent, 2004). Studies have also demonstrated neurogenesis in the hippocampus of patients with Alzheimer's disease (Jin *et al*, 2003), in the subependymal layer adjacent to the ventricles in patients with Huntington's disease and Alzheimer's disease (Curtis *et al*, 2003), and around areas of cerebral cortical infarction in younger adults with stroke (Jin *et al*, 2006).

Neural plasticity, synaptogenesis and neurogenesis require parallel angiogenesis. New vessels develop in response to tissue demands, mediated principally by vascular endothelial growth factor, which responds to local factors such as inflammation, blood pressure, oxygen saturation, lipid levels, insulin levels and tissue perfusion (Fam *et al*, 2003). Many vascular risk factors may therefore modify and promote these processes of neural plasticity, synaptogenesis, angiogenesis and neurogenesis.

CARDIOVASCULAR AND CEREBROVASCULAR DISEASE AND COGNITIVE IMPAIRMENT

The respective associations between cardiovascular disease, cerebrovascular disease and cognitive impairment are well known. The risk factors for cardiovascular disease – hypertension, diabetes, obesity, smoking, low levels of high-density lipoprotein (HDL), high levels of low-density lipoprotein (LDL), high concentrations of fibrinogen and of homocysteine, and alcohol misuse – are also risk factors for cerebrovascular disease. Additional risk factors for cerebrovascular disease include cardiac arrhythmia, carotid atheroma, hypotension, transient ischaemic attacks, coronary artery bypass grafts, angioplasty, ischaemic heart disease and metabolic syndrome. These can all then be considered to be risk factors for cognitive impairment and most of the dementias (for review, see O'Brien *et al*, 2003).

MECHANISMS OF NEUROVASCULAR DAMAGE AND REPAIR IN THE BRAIN

Vascular risk factors lead directly or indirectly to oxidative stress and a cascade of inflammatory events that result in vascular damage in the brain, compromising neural activity and hence causing cognitive impairment (Yaffe *et al*, 2005). Oxidative stress may occur peripherally in response to obesity, smoking, alcohol, inactivity, atherosclerosis, hyperlipidaemia and psychosocial stress, and centrally in response to hypertension, diabetes, hyperhomocysteinaemia, hypoperfusion, protein aggregation in Alzheimer's disease and ischaemia (McEwen, 2002). Oxidative stress then leads to inflammation, and this in turn results in a loss of endothelial wall integrity, further compromising perfusion and leading to increased surrounding cell damage and loss. It would therefore seem reasonable to speculate that repair of cell damage in the brain caused by oxidative stress, inflammation and vascular damage can be expected if the conditions promoting the latter events are treated or prevented, and the potential for angiogenesis, neural plasticity, synaptogenesis and neurogenesis is maximised.

POSSIBILITIES FOR TREATMENT AND PREVENTION

Exercise has been shown through observational studies to be associated with enhanced reaction time and a variety of cognitive executive control processes, retrospectively, cross-sectionally, prospectively and by meta-analysis; and observational studies suggest the cognitive benefits of exercise are achievable in young and old individuals with and without pre-existing cognitive impairment (Larson *et al*, 2006).

Similarly, structured formal learning has been implicated as a way of enhancing targeted cognitive abilities in a sustained manner, including verbal episodic memory, reasoning and speed of information processing (Ball *et al*, 2002). Additionally, complex environments that stimulate problem-based learning promote structural and functional neuronal changes, and older people may respond by recruiting neural circuitry in a fashion that is different from younger individuals (Grady *et al*, 2003).

Social engagement is associated with positive effects on cognition in humans, and similar positive effects have been observed in relation to supportive psychotherapy and problem-solving therapy, social relations and social support, social ties and marital status, and living arrangements and social network indices (Helmer *et al*, 1999; Alexopoulos *et al*, 2003). The biological mechanism is proposed to be neural plasticity (the cognitive reserve hypothesis), neurogenesis and vasculogenesis (the vascular hypothesis) and cortisol regulation (the stress hypothesis) (Fratiglioni *et al*, 2004).

Dietary regulation and supplementation could also be reasonably expected to play a part in providing the chemical substrates necessary to improve neurovascular

function. Increased HDL and decreased LDL concentrations and marine omega-3 polyunsaturated fatty acid consumption are associated with better cardiovascular and cognitive function (Kalmijn *et al*, 2004). Reduced energy intake with nutritional maintenance may suppress oxidative stress, stabilise calcium homoeostasis, induce neurotrophic factors and may reduce the β-amyloid deposition associated with Alzheimer's disease (Patel *et al*, 2005). There is also speculation that intake of antioxidant compounds in red wine, dark chocolate, curcumin, some fruits, grains and vegetables, vitamin E and vitamin C may improve neurovascular function (Engelhart *et al*, 2002).

Medical interventions including cessation of smoking, treatment of depression, control of hypertension, folic acid plus vitamin B_{12} supplementation sufficient to reduce raised homocysteine levels and melatonin may provide reduction of risk for cardiovascular, cerebrovascular and depressive illness (Hickie *et al*, 2005). Although the limited benefits of cholinesterase inhibitors and *N*-methyl-D-aspartate receptor antagonists in dementia are generally acknowledged (Götz *et al*, 2006), there is ongoing controversy with regards to the role of other pharmacological agents such as non-steroidal anti-inflammatory drugs, statins and hormone replacement therapy (Rosenberg, 2005).

CONCLUSION

Recent advances in the neurosciences suggest that young, old and impaired human brains may be able to respond to the demands of activity, experience and environmental factors by creating new functional synapses, neurons and networks through the intimately related processes of angiogenesis, neural plasticity, synaptogenesis and neurogenesis. These advances are particularly exciting in relation to the convergence of evidence regarding the contribution of vascular risk factors, genes, diet, physical activity, cognitive activity, psychological functioning and social functioning to the aetiology of acquired cognitive impairment and dementia. Taken together, these findings open the door to an array of possible new directions in the treatment and prevention of cognitive impairment and dementia through interventions that promote mental health, lifelong education, functional intimate relationships and social engagement, and that target healthy eating, dietary supplementation, exercise and effective cardiovascular treatment (when needed). In our opinion, where the prior paradigm of dementia as an inevitably progressive neurodegenerative disease was often a cause for clinical pessimism and inaction, there is now an emerging evidence base for a more optimistic, proactive approach to cognitive impairment and dementia.

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