Immunology of delirium: new opportunities for treatment and research

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EPIDEMIOLOGY AND OUTCOME

Delirium is a common clinical syndrome. It is the clinical manifestation of disruption of the neuroendocrine homoeostasis. It presents in a wide variety of physical conditions and is associated with a poor prognosis. Prospective studies on elderly hospitalised medical patients demonstrate outcomes of increased mortality, increased length of hospital stay and increased likelihood of institutionalisation, with a significant minority having residual cognitive impairment (O'Keefe & Lavan, 1997). No studies have examined the interface between the neuroendocrine and immune systems in delirium.

NEUROENDOCRINE/ IMMUNE MEDIATION

Cytokines are released from brain cells in response to brain insult. They aid the immune response but also can contribute to neuronal death (Tarowski *et al*, 1995). Raised levels of cytokines occur in common causes of delirium such as infection. Their infusion promotes delirium in 30–50% of patients receiving the cytokine interleukin-2 as treatment for cancer (Rosenberg *et al*, 1989). Insulin-like growth factor I (IGF-I) and somatostatin are peptides that have important neurotrophic properties. In particular, somatostatin inhibits the release of cytokines (ten Bokum *et al*, 2000).

In 1999 Venters *et al* demonstrated that the cytokine tumour necrosis factor alpha (TNF-α) exerted its cytotoxicity by inhibiting IGF-I activity. Loddick & Rothwell (1999) subsequently drew on this work in explaining some associated findings concerning the role of cytokines in neurodegeneration. Both TNF-α and interleukin-1 (IL-1) clearly enhance experimental neurodegeneration, yet even at high doses they fail to cause cell death in the healthy brain. These findings imply that these agents are not inherently neurotoxic but influence survival by inhibiting the protective effect of an endogenous growth factor that is produced in the injured brain. Tumour necrosis factor alpha, IL-1 and other pro-inflammatory cytokines are produced in the central nervous system (CNS) in response to systemic insults such as infection or inflammation and act as mediators of an array of host defence responses, including fever, appetite suppression and neuroendocrine changes. Even though cytokine production does not lead to overt neurodegeneration, there is evidence that systemic infections worsen clinical neurological conditions such as stroke and multiple sclerosis. Consequently, in otherwise healthy brains cytokine production may have no deleterious effect, but when neuronal damage is present they may enhance neurodegenerative processes.

The neurotrophic properties of IGF-I are wide ranging. Animal studies demonstrate that it regulates stem cell differentiation into neurons (Brooker *et al*, 2000) and induces neurogenesis of the hippocampus (Aberg *et al*, 2000). Further studies support the neuroprotective role of these peptides (De Marinis *et al*, 1999) in finding a reversible increase in IGF-I, mirrored by changes in somatostatin in post-head-injury comatose patients. The release of both hormones is closely linked to feedback mechanisms within the growth-hormone-releasing hormone/somatostatin–growth hormone–IGF-I axis.

There is evidence that both somatostatin and IGF-I may have a role in the pathogenesis of Alzheimer's disease. Both cerebrospinal fluid levels and brain somatostatin are reduced in Alzheimer's disease and other dementias (Leake & Ferrier, 1993). There is also a selective reduction of somatostatin receptor type 2 (SSRT-2) in the frontal cortex and hippocampus of patients with Alzheimer's disease (Krantic *et al*, 1992). Hong & Lee (1997) have demonstrated that IGF-I reduces τ-phosphorylation and has been shown to protect and even to rescue neurons from β-amyloid peptides (Dore *et al*, 1997). The inhibitory effects of IGF-I on cell death (anti-apoptotic effects) are compromised by presenilin-1 mutations (Tanii *et al*, 2000), processes that have been implicated in the aetiology of Alzheimer's disease. Also, significant reductions in serum IGF-I have been found in some familial Alzheimer's disease yet normal levels are found in the carriers who do not develop this condition (Mustafa *et al*, 1999).

IMPLICATIONS AND RESEARCH OPPORTUNITIES

Somatostatin and IGF-I would appear to be important peptides in relation to cognitive function. Infusion of a somatostatin analogue has been found to improve memory in patients with Alzheimer's disease (Craft *et al*, 1999) and IGF-I administration attenuates the cognitive deficit in brain-injured rats (Saatman *et al*, 1997). Reversible somatostatin reduction has been found in delirious patients with no overt CNS disease, suggesting a temporary and reversible involvement of somatostatinergic neurons during and immediately after delirium (Kaponen *et al*, 1994). The relationship between delirium, exercise and these neurotrophic agents presents some intriguing associations. Exercise is known to increase plasma IGF-I and growth hormone levels. Carro *et al* (2000) examined these issues further in rats, demonstrating that physical activity increased IGF-I uptake by the brain. A large clinical study subsequently demonstrated a potentially protective role of exercise in the management of delirium in medically ill in-patients (Inouye, 2000), implicating a neuroprotective role of IGF-I.

This is a rapidly developing field. We have attempted to draw together some of the evidence concerning the relationship between cytokines, the neuroprotective roles of IGF-I and somatostatin, cognitive function, Alzheimer's disease and delirium. Elevated levels of IGF-I and somatostatin may represent a general neuroprotective response to brain injury. If this is the case, then they have a potential role in the treatment or prevention of delirium (Saatman *et al*, 1997; Craft *et al*, 1999). They may have a role also in the treatment of related conditions such as Alzheimer's disease (Dore *et al*, 1997), stroke disease (Gluckman

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et al, 1998) and head injury (Hatton *et al*, 1997).

DECLARATION OF INTEREST

None.

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