

Hormones in Relation to CSF Biomarkers and Cognition in Mild Cognitive Impairment

Background

Dementia, defined as pathological decline of cognitive function, imposes an increasing burden to individuals and health care, with 24 million cases worldwide in 2005 and an redoubling every 20 years to 42 million expected cases in 2020 (Ferri, Prince et al. 2005). The condition of mild cognitive impairment (MCI) describes individuals at greater risk for developing dementia. Individuals with MCI show cognitive decline greater than expected for 'normal' ageing, but preserved activities of daily life and lack of fulfillment of the criteria for manifest dementia (Petersen, Smith et al. 1999; Winblad, Palmer et al. 2004). MCI is often considered a transitional state between 'normal' aging and dementia, and is reflected by intermediate levels of cerebrospinal fluid (CSF) biomarkers for Alzheimer's disease (AD), such as A β 42, total tau and phosphor-tau (Hansson, Zetterberg et al. 2006; Herukka, Helisalmi et al. 2007; Zetterberg, Pedersen et al. 2007; Brys, Pirraglia et al. 2009). Reported conversion rates of MCI to dementia are approximately 50% (Mitchell and Shiri-Feshki 2009). Since MCI criteria do not specify any given etiology of the cognitive impairment, it is heterogenous and the course is variable. It is a major area of interest within the field of MCI research to identify factors that contribute to cognitive deterioration.

Hormones may be risk as well as resilience factors in normal and pathological ageing. Growing evidence links alterations of endocrine axes to cognitive impairment and dementia. While age related decline of hormone levels of the somatotropic, -gonadotropic and -thyrotropic axes, paralleled by deterioration of cognitive function are normal (Sherwin 1994; Rollero, Murialdo et al. 1998; Aleman, Verhaar et al. 1999; Volpato, Guralnik et al. 2002; Muller, Aleman et al. 2005), reduced hormone levels are a common observation among cases with dementia compared to healthy age matched controls.

Hormones may be involved in dementia etiology via four mechanisms. First, dysregulation of a variety of hormones are associated with a variety of physical conditions known to be risk factors for dementia, such as cardiovascular disease, metabolic syndrome (Rosmond, Wallerius et al. 2003; Walsh, Bremner et al. 2005) and depression (Duval, Mokrani et al. 2006). Second, adequate levels of growth-hormones, sex steroids and thyroid hormones are crucial for neurogenesis, neural metabolism, plasticity and maintenance of neuron function as well as neuroprotection against a variety of insults. Third, hormones may be directly involved in the neuropathology of Alzheimer's diseases (AD). Growth hormones, sex steroid hormones and thyroid hormones have been shown to modulate Amyloid Precursor Protein (APP) processing, aggregation of A β in plaques and A β clearance (Latasa, Belandia et al. 1998; Li, Shen et al. 2000; Carro, Trejo et al. 2002; Morinaga, Hirohata et al. 2007); as well as AD typical hyper-phosphorylation of tau protein (Hong and Lee 1997; Papasozomenos 1997; Alvarez-de-la-Rosa, Silva et al. 2005). Finally, hormones such as cortisol are involved in the generation of reactive oxygen species and excitotoxicity, which under compromising conditions such as A β toxicity and ischemic insults may accelerate neurodegeneration (Reagan and McEwen 1997). Also, hormones of the HPA suppress the somatotropic (Beauloye, Ketelslegers et al. 1999), gonadotropic (Gore, Attardi et al. 2006), and thyrotropic axes (Helmreich, Parfitt et al. 2005), leading to a misbalance of counter-effective hormones to cortisol (Smith, Betancourt et al. 2005).

Little research has focused on the role of hormones relating to cognitive impairment in MCI. In the existing literature on hormones in MCI and dementia, crude staging and screening instruments have been utilized to measure cognitive function. This thesis is comprised of two aims. First, cognitive function, measured using a comprehensive neuropsychological test battery, is evaluated cross-sectionally in MCI cases and controls and related to endocrine axes. Second, in the same sample, the relationship of hormones to CSF-biomarkers is evaluated. Hormones in these analyses include: cortisol, IGF-1, sex steroid hormones and thyroid hormones. CSF markers include: total tau, phospho-tau181 and A β 42 levels.

Methods

Fasting serum samples from MCI cases, diagnosed according to criteria suggested by Winblad et al (Winblad, Palmer et al. 2004), and healthy control subjects will be assayed for total testosterone, oestradiol, IGF-1 and SHGB and non-fasting serum samples for measurement of TSH, total T4, free T4 and total T3. HPA function will be assessed by sampling saliva cortisol five times during the course of two consecutive days, before and after a dexamethasone load, for cortisol awakening response, midday and evening levels. CSF samples will be collected by lumbar puncture and assayed for total tau, phospho-tau181 and A β 42 levels. Cognitive function will be examined utilizing a comprehensive neuropsychological test battery comprising tests comprising tests of speed and attention, learning and episodic memory, language, visuospatial and executive functions. The analyses will examine cortisol, IGF-1, sex steroid hormones and thyroid hormones i) in MCI subjects compared to healthy controls, ii) the relationship of cortisol to other hormones, and iii) in relationship to cognitive function and CSF-biomarkers.

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