The current high life expectancy is overshadowed by neurodegenerative illnesses that lead to dementia and dependence. Alzheimer’s disease (AD) is the most common of these conditions, and is considered to be a proteinopathy, with amyloid-β42 as a key factor, leading via a cascade of events to neurodegeneration. Major factors involved are oxidative stress, perturbed Ca homeostasis and impaired energy metabolism. Protection against oxidative stress by micronutrients (including secondary bioactive substances) has been shown in transgenic Alzheimer model systems to delay AD. Epidemiological evidence is less conclusive, but the vast majority of the evidence supports a protective effect on cognitive functions in old age and AD. Thus, a diet rich in fruits and vegetables but also containing meat and fish is the most suitable to provide adequate micronutrients. The strong link between cardiovascular risk and AD may be explained by common pathogenetic mechanisms mediated, for example, by homocysteine and thus dependant on B-vitamins (folate and vitamins B12 and B6). However, micronutrients may also be harmful. The high affinity of amyloid for metals (Fe, Al and Zn) favours the generation of reactive oxygen species and triggers an inflammatory response. Micronutrients in a balanced diet have a long-lasting, albeit low, protective impact on brain aging, hence prevention should be life long.

Alzheimer’s disease: Oxidative stress: Cognitive function

Dementia, and thus its major cause Alzheimer’s disease (AD), has become one of the major health challenges of the 21st century in industrialized societies. Prevalence studies (Jorm & Jolley, 1998) and incidence studies (The Canadian Study of Health and Aging Working Group, 2000) consistently show a single exponential increase with age, which is consistent with involvement of a large number of complex genetic and environmental interactions. Among these factors, nutrition, intimately linked to aging, plays an important role. However, despite the strong age-related link, AD is not an inevitable consequence of a long life. The incidence levels at age 90 years and in centenarians indicate that many individuals in this age-group are barely affected by AD (Ritchie & Lovestone, 2002). The present review explores the extent to which micronutrients may influence the onset of AD and related dementias either by preventing or delaying the disease or by fuelling the pathology.

The clinical diagnosis of AD is characterized by a progressive deterioration of memory, as well as other cognitive functions, and impairment of affective and emotional control, resulting in disability in daily living and loss of autonomy. Neuropathology remains the diagnostic gold standard, characterized by deposits of amyloid-β (abeta; a fragment of the large amyloid precursor protein (APP)) in plaques and in vessel walls and aggregated tau-proteins in tangles, reactive microgliosis and astrocytosis, leading to neuronal death with subsequent atrophy of the brain and enlargement of the ventricles. One of the first events is the loss of synapses, leading to neuronal dysfunction (Lovestone & McLoughlin, 2002). The elucidation of the mechanism leading to the hallmarks of AD, i.e. the loss of synapses, the formation of amyloid plaques and fibrillary tangles, should yield valuable hypotheses on how nutrients, lifestyle factors or drugs might modify this otherwise largely intrinsic process linked to aging.

The pathological cascade is apparently triggered in susceptible individuals many years before clinical symptoms emerge. Thus, environmental factors and nutrients may play an important role early in the life cycle (Fig. 1). The late onset of the disease further indicates that genetic controls diminish with advancing age and the impact of external factors becomes more prominent. However, the similar prevalence and incidence over a wide range of

Abbreviations: abeta, amyloid-β; AD, Alzheimer’s disease; APP, amyloid precursor protein.

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dietary habits and social settings in different societies, at least in the industrialized world, suggests that diet and nutritional habits may only have a small effect on the manifestation of the disease. Furthermore, the epidemiology of AD supports the notion that the response of the aging brain to accumulating stress of endogenous origin, such as free radicals generated during mitochondrial energy production (Turner & Schapira, 2001; Aliev et al. 2002) and by exogenous factors, is non-specific. Thus, the question arises as to how micronutrients affect these processes. Micronutrients are essential for growth and function, and their metabolic effects were elucidated during the last century by investigating deficiency states. In this context deficiency of I, leading to goitre and cretinism, and also deficiencies of some vitamins were found to affect brain function. Subsequently, the regulatory agencies set the recommended dietary intake at a level sufficient to prevent signs and symptoms related to deficiency. There is evidence that higher intakes of certain micronutrients may be beneficial in reducing the risk of AD (Bates et al. 2002).

**Oxidative stress and antioxidants in Alzheimer's disease**

Oxidative stress is thought to be an early event in AD, and also to be increased by the disease process in a vicious circle. As a consequence, antioxidant defence should retard or even prevent the development of the disease. Brain metabolism requires a high and constant energy supply by mitochondria, leading to a constant load of free radical formation (Aliev et al. 2002; Engelhart et al. 2002b; Cutler et al. 2004), which suggests that a high antioxidant intake as nutrients in food and beverages might be protective (Joseph et al. 1996).

However, several mechanisms seem to interact. Thus, insulin seems to improve the energy supply to the brain and enhance brain function. However, high glucose levels and hyperinsulinaemia indicate insulin resistance and the formation of advanced glycation end products that by itself contributes to radical formation, with detrimental consequences to nerve cells and blood vessels (White, 2003). On the other hand, the defence mechanism may be directly related to nutrients, or the nutrients may exert their influence indirectly. For example, there is an increased risk of AD in the presence of vascular risk factors, leading to hypoxia, oxidative stress and neuronal damage (Hofman et al. 1997; Seshadri et al. 2002). Another example is folic acid, vitamin B_{12} and vitamin B_{6}, which affect homocysteine metabolism and indirectly influence oxidative stress, but also protect DNA against reactive oxygen species and radiation damage by methylation (Fenech, 2001). It has been observed (Fusek, 2001) that parenteral substitution of low vitamin B_{12} levels (<180 pmol/l) is associated with a markedly better cognitive performance in AD-patients after 1 year, but only if the substitution occurs within 24 months after the onset of the first symptoms.

Epidemiological evidence suggests that a high intake of antioxidants in food correlates with a lower incidence of cognitive decline (Gray et al. 2003). For antioxidants nutrients, particularly vitamins C and E but also carotenoids such as lycopene, epidemiological studies (Haller et al. 1996; La Rue et al. 1997; Masaki et al. 2000) have shown correlations between intakes, plasma levels and cognitive function. On the other hand, the findings of intervention studies of the effect of antioxidants in patients with AD (Rutten et al. 2002; Gilgun-Sherki et al. 2003) have been mostly disappointing. One explanation may be that the effect of altering one antioxidant has no substantial impact on the cellular redox system, or that the intervention is too late to be of clinical significance.

Plasma antioxidant levels have been shown to predict memory performance over a 20-year period in the
Basel Study (Perrig et al. 1997; Fig. 2) and also in the unrelated cross-sectional SENECA study (Haller et al. 1996), in which higher plasma levels were found to be associated with better memory performance. However, epidemiological surveys have provided a mixed picture. In the Rotterdam Study (Engelhart et al. 2002b) lower risk of AD was found to be associated with high intakes of vitamin E and C, and also β-carotene and flavonoids in smokers, in a 6-year follow-up, while vitamins E and C in the diet or as supplements were found to have no effect on cognition in the Washington Heights-Inwood Columbia Aging Project 4-year follow-up (Luchsinger et al. 2002). On the other hand, the intakes of vitamin C and E supplements have been reported to be associated with lower incidence of AD (4-3 years follow-up; Morris et al. 1998). However, the provision of supplements remains controversial. It has been observed that vitamin E appears to be protective when derived from the diet but not when provided as a supplement, and then only in apolipoprotein E-negative subjects (Morris et al. 2002). However, in the Honolulu Asia Aging Study it was found that vitamin E and C supplements appear to protect against vascular dementia and improve cognitive function in later life (Masaki et al. 2000), although midlife dietary intake of antioxidants has no apparent effect on dementia in later life (Laurin et al. 2002). In the Nurses’ Health Study vitamin E supplements but not vitamin C supplements were found to be related to modest cognitive benefits in older women (Grodstein et al. 2003), while in the Cache County Study vitamin E and C supplements in combination were reported to reduce the prevalence and incidence of AD (Zandi et al. 2004).

A widely published but controversial study relating to the mechanism of action of extremely high doses of vitamin E (2000 mg/d) in patients with AD suggests that such levels can lead to a delay in institutionalization (Sano et al. 1997). The French Paquid Study has demonstrated that high flavonoid intake is associated with a reduction in risk of dementia to a relative risk of 0.49 (Commenges et al. 2000), and in the SENECA Study (Haller et al. 1996) cross-sectional analysis (Table 1) has shown a consistent and significant, albeit weak, correlation between memory performance and plasma concentrations of carotenoids, folate ($P<0.05$) and α-tocopherol ($P<0.05$).

An important point remains that although higher vitamin C intake predicts better memory function, factors such as education are far more important than differences in micronutrient intakes (Perrig et al. 1997; Fig. 2). The epidemiological findings to some extent contradict the vast amount of experimental work in cell culture, and in transgenic models of AD in which bioactive antioxidant compounds show a profound effect on markers of AD and behaviour. Thus, numerous phenolic substances have been shown to be protective (Joseph et al. 1998a,b, 2005), probably by affecting Ca homeostasis in neuronal cells (Joseph et al. 2004).

### Metals, oxidative stress and Alzheimer’s disease

#### Copper and zinc

Of particular interest is the role of metals. The interaction between Fe, Cu and Zn, and also Al and other metals (e.g. Hg, As etc.), and amyloid and the amyloid-β (abeta) fragment of the APP molecule is complex and may depend on cholesterol metabolism (House et al. 2004; Fisher & Naughton, 2005; Maynard et al. 2005; Valko et al. 2005). APP has Cu-binding sites and experimental findings (Maynard et al. 2005) indicate that a high Cu content stabilizes APP. The function of APP is still largely unknown, but one of the possible functions might be the regulation of metal homeostasis (Fisher & Naughton, 2005). Low Cu levels actually increase amyloid and abeta concentrations and high Cu levels stabilize APP. Increasing brain Cu availability decreases levels of abeta and amyloid plaque formation. Lowering Cu concentrations leads to a down-regulation of the transcription of APP (Maynard et al. 2005).

APP is catabolized either by α-secretase and subsequently by γ-secretase leading to non-toxic fragments or, if...
internalized in the endoplasmic reticulum and Golgi apparatus, by β-secretase and γ-secretase. The resulting abeta fragment is a key pathogenic intermediate in AD (Lovesstone & McLoughlin, 2002; Selkoe & Schenk, 2002). Hence, APP is a large membrane-bound Cu-binding protein that is essential in maintaining synaptic function. Both APP and abeta oxidize cholesterol, requiring Cu. Oxysterols inhibit α-secretase but not β-secretase, thus accelerating abeta production. Furthermore, oxysterols have a 200-fold higher affinity to abeta than to APP. Thus, at a given point Cu may become a powerful enhancer of reactive oxygen species formation and the APP stabilizing effect will be lost (Nelson & Alkon, 2005).

A fascinating hypothesis emerges from experiments with transgenic animals in which a diet deficient in n-3 fatty acids perinatally up regulates Zn transport proteins in the brain that remain up regulated into adulthood, leading to a Zn overload in the brain and displacement of Cu from APP binding sites, thus favouring abeta formation (Jayasooryiya et al. 2005).

Iron, aluminium, selenium and mercury
Fe and Al co-localize with abeta plaques (Exley, 2005). High cholesterol levels are thought to be a risk factor for AD (Engelhart et al. 2002a), but as a single factor they are probably of minor importance (Hofman et al. 1997); however, together with a high Fe load the risk is markedly elevated. The National Health and Nutrition Examination Survey I 18-year follow-up (n > 6500) has found that the risk ratio for developing AD is 3.19 (95% CI 1.31, 7.75) when both transferrin saturation and cholesterol are above the 75th percentile (Mainous et al. 2005).

Levels of advanced glycation end products and lipid peroxidation products in the brain, cerebrospinal fluid and plasma of patients with AD are potentiated by Al and Fe (House et al. 2004).

Al affects neuronal structures (synapses etc.; Jing et al. 2004), and chronic exposure to Al in drinking water increases inflammatory variables selectively in the brain (Campbell et al. 2004), while presenilin 2 production (aberrant splicing isoform, a diagnostic feature of sporadic AD) induced by hypoxia is accelerated by chronic Al exposure (Matsuzaki et al. 2004).

Despite the importance of Se as an antioxidant and key trace element for antioxidant enzymes there is little information relating to Se and AD (Cornett et al. 1998; Meseguer et al. 1999; Tabet et al. 2001; Chen & Berry, 2003). Of interest is the interaction between Se and Hg. Uptake of Hg into cells may be effected by the same transport mechanisms as Se uptake (Bridges & Zalups, 2005). Thus, in theory low Se levels in food may expose cells to higher Hg loads. The formation of a Hg–Se complex seems to be protective, as is suggested by findings in marine animals (Endo et al. 2002) and in cell cultures (Frisk et al. 2003). A relationship between Hg exposure (e.g. by dental fillings) and AD (Fung et al. 1997) has not (Fung et al. 1997) been established, even though a correlation has been shown between Hg concentration and Fe (Barany et al. 2005) and dental fillings (Fung et al. 1997; Barany et al. 2003).

Conclusions
The uniform single exponential increase with age of dementia and AD, with comparable rates in many socioculturally-different societies, indicate that endogenous genetic–metabolic factors are prominent. Nevertheless, micronutrients may affect the rate of disease via protection against reactive oxygen species, directly as antioxidants or indirectly by stabilizing sensitive structures or improving metabolism. The effect of pro-oxidant nutrients, on the other hand, may catalyse the development of disease by interaction with proteins and lipids involved in the pathophysiology of AD and other neurodegenerative disorders. Based on these premises the impact of micronutrients is most effective if present over a long period during the lifetime, while interventions later in the disease process are of minor effectiveness (Launer & Kalmijn, 1998; Tabet et al. 2001). Of potentially far-reaching consequences is the concept that nutritional conditions in early life may programme metabolic functions, leading over time to an increasing imbalance and thus favouring the emergence of diseases states. A macronutrient and micronutrient intake that has preventive effects against CVD is most likely also to be effective against neurodegenerative disorders.

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