Leptin: The Missing Link in Alzheimer Disease?

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In Western societies, life expectancy is increasing steadily. As a consequence, more individuals are suffering from age-related disorders such as Alzheimer disease (AD).² The prevalence of AD is predicted to rise rapidly in the coming decades, which is likely to pose a huge burden on healthcare services in the future. Although significant advances have been made in this field in recent years, our understanding of the principle cellular changes that occur in the initial stages of this disease and the means to identify these changes clinically are limited. Thus key research priorities are to determine the key cellular events that underlie the development and pathogenesis of AD and identify possible biomarkers associated with the early stages of AD. Studies in these areas are of paramount importance, as they are likely to aid in the detection of the early brain changes in AD and could potentially lead to the development of novel therapies to treat this debilitating neurodegenerative disorder.

Combinations of factors, such as lifestyle, genetic, and vascular influences, are known to modify the risk of developing AD. Several lines of evidence also support a link between midlife obesity and an increased risk of AD, but the mechanisms responsible for this association are not entirely clear. Recent studies have identified the endocrine hormone leptin as a possible factor linking obesity and AD. Leptin plays a pivotal role in the regulation of food intake and body weight via its actions on specific nuclei within the hypothalamus. In addition, leptin receptors are expressed in many extrahypothalamic brain regions, and numerous studies indicate that leptin is a pleiotropic hormone with diverse actions reported throughout the central nervous system (CNS). In particular, limbic structures such as the hippocampus display high levels of leptin receptor expression, and several studies have identified a role for leptin in regulating cognitive processes in this brain region. Specifically, leptin has been shown to markedly influence the cellular events underlying hippocampal-dependent learning and memory (1). Indeed, activation of leptin receptors enhances N-methyl-D-aspartic acid (NMDA) receptor function and facilitates the induction of hippocampal long-term potentiation (LTP) (1). In addition, leptin promotes rapid alterations in hippocampal dendritic morphology and the density of hippocampal synapses, which are likely to contribute to leptin-driven changes in excitatory synaptic strength (2). Studies performed in obese leptin-insensitive rodents (db/db mice; Zucker fa/fa rats) have detected deficits in hippocampal synaptic plasticity and in spatial memory tasks performed in the Morris water maze (3). More recent studies also provide support for a link between impaired and/or altered leptin function and the development of AD. Indeed, circulating concentrations of leptin are reported to be significantly lower than normal in individuals with AD and are markedly attenuated in murine models of AD. Furthermore, application of leptin improves memory processing in AD models. In neuronal cell lines, leptin has been shown to act in concert with insulin to attenuate the phosphorylation of τ, a protein that is a key component of neurofibrillary tangles, a pathological hallmark of AD. It is not yet known, however, if the circulating levels of leptin in healthy individuals show any correlation with the risk of developing AD later in life.

In a new prospective study by Lieb et al. (4), the plasma concentrations of leptin were evaluated in 785 individuals from the original Framingham study cohort (5), to determine if the baseline plasma concentrations of leptin relate to the incidence of AD. None of the 785 individuals had dementia at the start of the study. All were assessed periodically for impairments in cognitive function and dementia using standard neuropsychological and neurological tests. Moreover, a subset of 198 individuals underwent volumetric brain MRI to evaluate 2 recognized markers of early AD pathology, the temporal horn volume (THV), which is an inverse measure of hippocampal volume, and the total cerebral brain volume (TCBV). The main findings of this prospective study are that higher baseline plasma concentrations of leptin correlated with a significantly lower risk of dementia and AD. Indeed, individuals

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Nonstandard abbreviations: AD, Alzheimer disease; CNS, central nervous system; NMDA, N-methyl-D-aspartic acid; LTP, long-term potentiation; THV, temporal horn volume; TCBV, total cerebral brain volume; TNF, tumor necrosis factor; ApoE, apolipoprotein E; APP, amyloid precursor protein.
Thus another possibility is that leptin protects neurons against β-amyloid–induced toxicity. In support of this, leptin reduces toxic β-amyloid levels in vitro and increases apolipoprotein E (ApoE)-dependent uptake of β-amyloid into cells. Leptin may also influence the amount of β-amyloid in cells by directly altering β-amyloid processing. Indeed, the activity of β-secretase, a protease that cleaves amyloid precursor protein (APP), is reduced by the hormone leptin.

In accordance with previous studies, Lieb et al. (4) found that plasma leptin was significantly higher in women compared with men. It is well known that differences exist in the susceptibility of men and women to develop certain age-related neurodegenerative diseases. However, the incidence of AD is significantly higher in the female population (approximately 68%). Thus it needs to be addressed why the incidence of AD is not significantly lower in the female population given the higher leptin concentrations in females. This disparity between the sexes suggests that distinct risk factors and/or combinations of risk factors contribute to development of AD in males vs females. Further studies are required to determine what, if any, sex-specific factors play a role in contributing to the increased incidence of AD in females.

In conclusion, the study of Lieb et al. (4) provides good, prospective evidence for an association between the circulating concentrations of leptin and the incidence of AD, such that a lower incidence of AD is linked with higher leptin in nonobese individuals. Although further research is required to address the precise cellular mechanisms underlying the reduced incidence of AD when leptin concentrations are high, it is possible that leptin may be a good indicator of susceptibility to AD in the elderly population.

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