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CRITICAL REVIEW

Obesity and Alzheimer's Disease

A BRIDGE BETWEEN TWO WORLDS

ABSTRACT

Obesity and Alzheimer's disease (AD) are two chronic illnesses with far reaching effects. Although both diseases are manifested in physiologically different ways, they share many molecular similarities and affect millions of individuals. Three mechanistic links for these two diseases include: brain derived neurotrophic factor (BDNF), insulin, and chronic inflammation. BDNF has long been associated with neuronal growth and synaptic plasticity but has also been linked to hunger control. Studies independently investigating obesity and AD have shown down-regulation of BDNF in both pathologies. While insulin functions as a critical regulator of blood glucose, insulin resistance and feedback inhibition of insulin production have both been described in the initiation and maintenance of obesity and AD. Lastly, chronic inflammation may lead to and result from AD and obesity. For example, brain inflammation in AD may lead to neurodegeneration, while obesity may also place the body in a state of chronic inflammation. This review seeks to elucidate and bridge the gap between obesity and AD, thus identifying new therapeutic targets common to both diseases.

INTRODUCTION

In 1997 the World Health Organization stated that "...obesity should now be regarded as one of the greatest neglected public health problems of our time..." In fact, the onset of a 'globesity epidemic' was predicted, with more than 1 billion adults being overweight and at least 300 million of these being clinically obese (defined by a body mass index greater than 30).¹

The negative impact of obesity on cognitive function is attributable to vascular defects, impaired insulin metabolism and signalling, or a defect in glucose transport mechanisms in the brain. Interestingly, recent studies in humans have also detected impaired insulin signalling in the brain of patients afflicted by Alzheimer's disease (AD).² AD is the most common form of dementia affecting 5-10 percent of North Americans over the age of 65.³ Recent studies have noted the marked increase of AD susceptibility with older age, diabetes, and obesity.⁴⁻⁶

This review seeks to elucidate the relationship between the two seemingly different pathologies, discuss possible treatments, and promote further research in this field. Both intercellular and intracellular mechanisms of disease onset and progression will be examined for both AD and obesity, but particular emphasis will be placed on the pathophysiological similarities between the two diseases.

BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF)

BDNF, a member of the neurotrophin family, plays a key role in enhancing survival, differentiation and growth of certain neural populations.⁷ It is particularly important for synaptic plasticity and long-term potentiation, which underlie learning and memory.^{8,9} In the cerebral cortex and hippocampus, regions of the brain important for memory and cognitive function, a high level of BDNF expression functions to promote neuronal survival and growth.¹⁰⁻¹²

Notably, BDNF mRNA and protein expression are dramatically reduced in patients afflicted with AD.^{10,13,14}

BDNF is also an important mediator of energy balance, and its loss has been implicated in obesity. Acting downstream to the melanocortin-4 receptor, BDNF expressed in the hypothalamus is able to suppress hunger.¹⁵ Chronic injections of BDNF into rat ventricles have resulted in suppressed hunger and a decrease in body weight.¹⁶

Conversely, studies on food deprivation have shown decreased levels of BDNF in the dorsal vagal complex of the brainstem.¹⁷ In addition, this region has already been shown to possess the highest density of melanocortin-4 receptors. However, BDNF expression in response to food deprivation has yet to be demonstrated in other parts of the brain.^{18,19} Kernie et al. conducted *in vivo* studies on heterozygous BDNF knockout mice and observed phenotypes consistent with obesity.²⁰ For example, transgenic BDNF heterozygous mutant mice showed increased weight (4-fold increase in lipid to water percentage and adipose cell hypertrophy) compared to wild types.²⁰ Supportive data has been described with an obese phenotype in postnatal mice containing a BDNF gene deletion.^{21,22} Moreover, human disorders that have been associated with defects at the BDNF gene locus are also characterized with elevated levels of adiposity.²⁰

IN 1997 THE WORLD HEALTH ORGANIZATION STATED THAT

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BDNF signaling may serve as a potential link between AD and obesity. Further research should investigate the effects of BDNF on the adipocytes and neural cells of AD and obese patients to establish a clear link.²³

INSULIN

Insulin, a peptide hormone synthesized by the pancreas, is responsible for various roles such as fat metabolism and control of gene expression in cells. Generally, many obese individuals become resistant to the effects of insulin on glucose uptake, metabolism, or storage.²⁴ With regards to AD, insulin functions as a key molecule in the phosphoinositide-kinase (PI3-K) pathway – a pathway heavily implicated in neurodegeneration and the aging process, as well as diabetes and obesity.²⁵

BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) SIGNALING MAY SERVE AS A POTENTIAL LINK BETWEEN AD AND OBESITY. FURTHER RESEARCH SHOULD INVESTIGATE THE EFFECTS OF BDNF ON THE ADIPOCYTES AND NEURAL CELLS OF AD AND OBESE PATIENTS TO ESTABLISH A CLEAR LINK.²³

Several studies have implicated insulin deficiency and insulin resistance with the clinically-defining histological findings of AD.²⁶ In particular, protein fragments termed amyloid-beta ($A\beta$) are thought to be one of the key hallmarks of AD. $A\beta$ is cleaved from the amyloid precursor protein (APP).²⁵ Pathology occurs when $A\beta_{42}$ (the 42- amino acid length product) aggregates to form cytotoxic soluble oligomers and extracellular senile plaques.²⁷⁻³⁰

The resulting $A\beta$ aggregation is thought to be one of the initiating triggers for the characteristic cognitive decline observed in AD.^{31,32}

$A\beta$ also plays an important role in modulating the PI3-K/Akt/mTOR signalling pathway, which is involved in both obesity and AD.

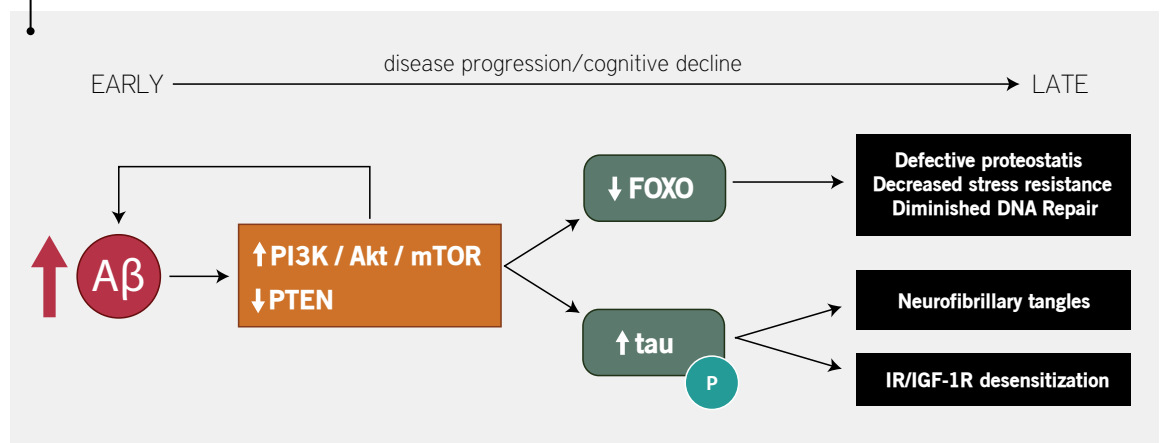
Increased production of $A\beta$ overactivates the PI3-K pathway by competitively binding to insulin receptors (IR), inducing IR internalization.^{33,34} This effect of IR internalization is further compounded by $A\beta$ -induced activation of the Jun N-terminal Kinase (JNK) pathway.²⁵ Activation of this pathway thereby leads to decreased levels of insulin,^{35,36} as JNK is involved in a feedback inhibition loop of insulin production.^{25,37} Consequently, the complex signaling network established by insulin may promote obesity and AD through a number of mechanisms.

INFLAMMATION

Recent research initiatives have explored the link between obesity and high sugar/fat diets with immune cells functioning as the key mediators of this link. Obesity is regarded by some as an inflammatory disease due to the secretion of high concentrations of inflammatory regulators.^{38,39} Research efforts are in progress to develop drugs to block specific inflammatory proteins in order to prevent and possibly treat obesity, which is the precursor to several cardiovascular and cognitive degenerative diseases.³⁹

Insulin plays an important role in memory and brain function, and individuals who suffer from insulin resistance may be at risk for AD. Obesity may also be a consequence of elevated insulin levels as a compensatory mechanism to insulin resistance, as seen in many diabetic patients. The association of age-related obesity with increased inflammation in blood vessels as a result of insulin signaling has been further described in disrupting the blood-brain barrier in the elderly population. The resulting neuroinflammation and oxidative stress as observed in the mouse hippocampus may be

FIGURE 1: A schematic diagram outlining the mechanisms by which sustained activation of the PI3-K/Akt/mTOR pathway due to amyloid-beta ($A\beta$) leads to decreased Forkhead box-O class transcription factors (FOXO), increased phosphorylation of protein tau – leading to neurofibrillary tangles (NFTs), as well as insulin receptor (IR)/insulin growth factor (IGF) receptor desensitization.¹⁹



one mechanism for the phenotypic cognitive decline seen in aged obese animals.^{40, 41}

FUTURE INQUIRY

In modern Western society, sedentary lifestyles and the access to caloric-rich foods are becoming increasingly prevalent. These two factors have led to an obesity epidemic and possibly an increased vulnerability to neurodegenerative diseases such as AD. However, recent studies have identified exercise, an antioxidant diet, and intermittent energy restrictions to not only combat obesity but reverse dementia through the up-regulation of BDNF and IGF-1.⁴²⁻⁴⁴ In adolescent studies, cognitive functions were significantly better in those who played sports and kept active lifestyles than those who did not.⁴⁵ Thus, maintaining an active lifestyle with a low-calorie, antioxidant-rich diet is one approach to combat the negative effects of obesity and AD.

Although the previously mentioned therapy is accessible and practical, it is by no means a silver bullet that can cure obesity or AD. Both pathologies are a result of highly complex mechanisms of which researchers have only skimmed the surface. Manipulations at very specific sites have yielded both negative and positive results; thus researchers must first elucidate the mechanisms behind each signalling

network. This review skims the surface of a highly complex relationship between obesity and AD with hopes that it may inspire individuals to delve further into this field.

CONCLUSION

Obesity has transformed from being simply a state of disruption in metabolism into a global epidemic that is affecting over one-seventh of the world's population. In addition to contributing to cardiovascular disease, obesity negatively impacts the brain. AD is a neurodegenerative disease resulting from a multitude of different pathogenic mechanisms, including decreased neurotrophic support, energy metabolism, oxidative stress, and inflammation. Obesity and AD surprisingly share numerous similarities in terms of both intercellular and intracellular communication. Researchers have already identified several factors that connect obesity and AD, such as the down-regulation of BDNF in both insulin resistance and chronic inflammation. The PI3K/Akt/mTOR pathway downstream of both BDNF and insulin receptors provides an additional point of convergence. Great progress has been made to elucidate the mechanisms behind these common factors, promising future treatments and preventative therapies. By integrating the seemingly unrelated fields of immunometabolism and neuroscience, a viable solution may be attainable. ■

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EDITED BY ARLINDA DENG

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