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Editorial

Neuroplasticity: The Critical Issue for Alzheimer's Disease and Links to Obesity and Depression

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STATEMENT OF THE QUESTION: IS AD RELATED TO OBESITY AND DEPRESSION THROUGH INFLAMMATION OR NEUROPLASTICITY?

In their paper, Ly et al. link obesity, Alzheimer's disease (AD), and depression, with the consideration that there are neuroinflammatory mechanisms linking these conditions, and, accordingly, there should be anti-inflammatory approaches for managing and preventing all three conditions. The primary question addressed in the discussion here is whether the bases of the established linkages between AD and obesity and depression are related to neuroinflammation, as suggested by Ly et al. paper, or whether AD is an attack on neuroplasticity, which also interacts with adiposity and depression.

WHAT IS THE PATHOPHYSIOLOGICAL MECHANISM THAT LEADS TO AD?

Ly et al. present strong empirical supporting evidence that neuroinflammation links AD, depression, and obesity. However, these three common conditions have numerous metabolic pathways associated with them, so it is not immediately clear that the links are causally related to neuroinflammation or that this perspective may have significant potential therapeutic value. There is no question that inflammatory mechanisms are active in AD.[1] However, the cause(s) of AD and the reason for neuroinflammatory action are more difficult to resolve. An important issue is to understand the underlying pathophysiological mechanisms, particularly the neuroplasticity at the root of Alzheimer's disease, to pursue interventions that might be beneficial.

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THE COGNITIVE AND ANATOMIC PATHOLOGY OF ALZHEIMER'S CASE

First, it is necessary to understand the mechanisms in the brain which are attacked by AD. Alois Alzheimer,[2] describing his patient, a 51-year-old woman, stated that after the first symptom of suspiciousness, the patient developed "...a rapidly increasing memory impairment," with many specific stigmata, including the suspiciousness, indicating memory dysfunction. On clinical evaluation, "Her ability to encode information is most severely disturbed. If one shows her objects, she usually names them correctly. Immediately thereafter, however, she has forgotten everything." Examining the patient's brain at autopsy, "reveals a consistently atrophic brain without macroscopic foci." Alzheimer provides an elegant description of the development of the neurofibrillary changes, later determined to be composed of paired-helical filaments of hyper-phosphorylated microtubule-associated protein-tau (TAU), and other protein deposits, particularly in the upper layers of the cerebral cortex, that turned out to be beta-amyloid (A-beta) in the senile plaques. He also notes that the glia had formed abundant fibers, and many glial cells show large fatty sacs.

THE INADEQUACY OF THE CHOLINERGIC HYPOTHESIS OF AD

It was the association of AD with memory dysfunction,[3] the loss of the acetylcholine-producing enzyme choline-acetyl-transferase (ChAT), and the known association of acetylcholine with memory that led to the first double-blind study of an acetyl-cholinesterase (AChE) inhibitor (physostigmine) to treat AD.[4,5] However, this therapy has only been shown to have modest symptomatic benefits and no substantial long-term disease-modifying effect.[6] Therefore, based on the failure of AChE inhibiting drugs to stop or reverse the course of Alzheimer's pathology, a better understanding of AD pathophysiology was needed.

NEUROPLASTICITY AS THE VULNERABLE SYSTEM ATTACKED BY THE AD PATHOPHYSIOLOGICAL PROCESS

Since the functional system most clearly attacked in AD is memory, and the physiological mechanism subserving memory is neuroplasticity, AD might be most completely understood as an attack on neuroplastic mechanisms in the brain.[7–9] With approximately 100 billion neurons in the human brain, each with an average of 10,000 synapses, a total of a quadrillion synapses, which have an average half-life of 100-days,[10] then the average number of old synapses destroyed and new synapses made is close to 5 trillion per day. Note that the turnover rate of synapses is much higher in the hippocampus, where synapses can persist for over 8 hours or be lost in less than 2 hours.[11] The daily creation and removal of synapses is the substrate of the constantly adapting memory of the human brain, and this turnover of such a large numbers of synapses must require substantial support. The disproportionate metabolic demands of the brain presumably serve this natural neuroplasticity process of synaptic turnover, but, likely, there is also utilization of glial cells to remove the synapses marked for removal, intrinsically an inflammatory mechanism. But, with AD there is a tilt towards destroying more synapses than making new ones. Further, it is the natural response of the glial cells, presumably as Alzheimer described, forming such a large excess of A-beta production that the glial cells cannot manage its removal, leading to abundant intracellular fibers and fatty sacs as well as deposits in cerebral blood vessels. Accordingly, the inflammatory mechanisms associated with AD are more likely a response to the pathological process than a cause.

Regarding AD pathology, since 1966 there is progressively greater recognition that the earliest and most important changes associated with AD are in the brainstem, including the norepinephrine neurons of the locus coeruleus, the serotonin neurons of the dorsal raphe, and the cholinergic neurons of the nucleus basalis of Meynert.[5,12–21] In the progression of AD, these neurotransmitters are affected in the brainstem in a specific order, first norepinephrine, then serotonin, then acetylcholine.[15] These brainstem neurotransmitters are centrally involved in neuroplasticity with each playing a unique role in neuroplasticity, information encoding, and memory.

The critical role for these brainstem neurotransmitters, norepinephrine, serotonin, and acetylcholine, in AD, is that they are specific stimulators of the amyloid-protein precursor (APP) alpha-secretase cleavage enzyme (APP-AS). When this enzyme acts on APP, the beta-amyloid component of APP is cut near its

middle, irreversibly disabling its capability of forming A-beta, and APP or the components formed by the APP-AS cleavage of the APP act with neurexins to form a new synapse.[22] Alternatively, when the APP-AS is not activated, the default protein is the APP beta-secretase (APP-BS), which leads to the cleavage of one of its products by the APP gamma-secretase (APP-GS) and the formation of A-beta, which is toxic to synaptic membranes and destroys them for removal, as well as producing an APP intracellular domain (AICD), which may be responsible for the phosphorylation of TAU and the retraction of the synaptic machinery. This dichotomy is presumably the fundamental factor underlying normal neuroplasticity and memory. Thus, the cortical changes in the cerebrum of AD, including the pathological stigmata and loss of other neuronal mechanisms, are likely a direct result of the loss of the brainstem input.[23,24]

THE ROLE OF THE BRAINSTEM IN ENERGY MANAGEMENT AND DEPRESSION AND OBESITY

The brainstem is central to energy management and manages most of the systems of the body and brain.[25] The norepinephrine and serotonin neurons of the brainstem have been linked to depression, and the predominant antidepressant medications work on these neurotransmitter systems. Obesity is directly related to the body's energy management system, which is basically the brainstem, and the traditional pharmacologic agents for weight loss have been amphetamines, stimulating catecholamine pathways, including norepinephrine, which project from the brainstem, and antidepressant serotonin reuptake inhibitors are associated with weight loss. Hence, AD, depression, and obesity are all related to brainstem mechanisms, particularly those involved in neuroplasticity.

RELATIONSHIPS BETWEEN AD AND DEPRESSION

Depression has a complex relationship to AD, and these two conditions are linked in several possible ways. As noted in the Ly et al. article, early-life and mid-life depression are associated with an increased risk of developing AD later in life. Norepinephrine neurons in the locus coeruleus and serotonin neurons in the dorsal raphe are affected early in AD. Accordingly, the underlying AD pathophysiological mechanism affecting these neurotransmitters could be contributing to depression earlier in life. Alternatively, the decreased brain stimulation and involvement in activities associated with depression could predispose to AD. Similarly, later-life depression may be related to the further deterioration of these brainstem nuclei. The link between these neurotransmitters and both AD and depression could be related to a complex interaction with other brain regions and memory-related processes, or a separate relationship related to brainstem energy management systems. Also, the loss of memory associated with AD, which may itself be most closely related to the loss of these two neurotransmitter systems may be a stressful disability leading through other psychological mechanisms to depression. And memory loss and confusion themselves could instigate chronic depression.

A relevant question brought up in the Ly et al. article is the involvement of glycogen-synthase-kinase-3-beta (GSK3b), which is associated with inflammation.[26] GSK3b is a promoter of the phosphorylation of TAU. And lithium, an effective treatment of bipolar disorder (which includes depressive and manic cycles), inhibits GSK3b, potentially decreasing TAU phosphorylation and thus, the formation of neurofibrillary threads and tangles, which appear to cause loss of neuronal arbors in dendrites and axons.[27] By decreasing TAU phosphorylation, lithium may stabilize the neuroplastic activity of widely-projecting NE, 5HT neurons, explaining its role in reducing mood swings. And several studies have suggested that lithium may delay AD[28–30] through such a mechanism, related to neuroplasticity.

THE RELATIONSHIPS BETWEEN AD AND OBESITY

The relationship between obesity and AD and depression is also complex, and as noted in their paper, obesity, and depression are epidemiologically related. However, age makes a difference, with only midlife obesity related to AD, and patients with AD tend to have an immediate premorbid history of weight loss. However, obesity is a major risk for

arteriosclerotic vascular disease and also puts strain on the whole body, which must provide blood flow, energy, and waste removal from adipose tissue, decreasing the overall capacity to provide adequate sustenance for the brain. And obesity is substantially related to hypertension and diabetes, both of which are related to arteriosclerosis. Thus, obesity is more likely related to cerebral anoxia and stroke, major causes of memory impairment and dementia, than AD. With reference to racial and ethnic disparities, there are cultural and dietary issues that also predispose to arteriosclerotic disease, which would be most associated with cerebrovascular disease, not particularly AD. Alternatively, as patients with AD develop dementia, they tend to move more (including pacing) and eat less, contributing to weight loss, as well as impaired sleep. And such activities are related to the brainstem energy management systems. Another consideration is that increased movements could be related to frontal lobe dysfunction and disinhibition, which are major features of other types of dementia, not AD, though beta-amyloid deposition occurs early in the frontal lobe, but is not clearly related to the development of dementia. Thus, it could be that early AD pathological changes in the brainstem or other areas of the brain could predispose to obesity, while later changes cause loss of weight.

The weight loss that occurs early in AD may also have implications for understanding AD pathology. AD is associated with a loss of sense of smell, which can also decrease the appeal of food, even for individual food preferences. The sense of smell develops due to n-methyl-d-aspartate (NMDA) receptor learning mechanisms, which likely evolved in the olfactory system. The olfactory bulb is the embryological and evolutionary origin of the cerebral cortex,[31] which during evolution came under the control of brainstem projections to the cerebrum. A lack of neuroplasticity in the brain can be associated with less reward-related learning and a loss of motivation for eating, and hence weight loss. And in addition to the loss of attraction to food, as AD dementia progresses and there is impairment of activities of daily living (ADL), difficulties with preparing food develop and can contribute to weight loss. Late in dementia difficulty with self-feeding becomes a problem for weight maintenance.

Ly et al. discuss obesity and inflammation. Certainly, there can be relationships between these two phenomena, particularly when the body is significantly beyond its energy management capacity and ability to perfuse tissue. And dietary habits which lead to obesity may be counter to diets which have been shown to reduce Alzheimer's risk.[32] Such diets may improve energy efficiency, though such food selections may be similar to "anti-inflammatory diets". And exercise, which can reduce obesity, has also been among the possible prevention approaches which have been most related to the reduction of AD risk.[32,33] These factors suggest there is not necessarily a link between obesity through inflammation to AD.

Tied into the obesity and AD relationship are the roles of insulin and leptin. Leptin is primarily produced in fat cells. Patients with mild cognitive impairment and AD have reduced levels of leptin.[34–36] Patients with AD are known to have lower concentrations of leptin as compared with amyloid-negative participants.[35,36] This low level might just be an indicator of the weight loss in early AD discussed by Ly et al. and indicate dysfunctional appetite signaling pathways involving the hypothalamus and central feeding drive. However, leptin has been related to neuroplasticity in the brain, and its reduction may thus increase the risk of AD.[37] Another consideration related to the Ly et al. premise is that excess leptin production in obese individuals in middle age could lead to leptin resistance, predisposing to AD, and leptin is also an inhibitor of GSK-3b,[37] providing yet another potential locus of interaction. Similarly, there is a relationship between the insulin and beta-amyloid-degrading metallopeptidase neprilysin and insulin-resistance and the removal of beta-amyloid, as discussed in Ly et al.'s article So, both of these proteins may be involved in the relationship between obesity and AD, but the causal components of the relationships need further study, potentially related to fundamental neural processes rather than inflammation.

IS AD RELATED TO INFLAMMATION?

Regarding inflammation, one of the strong supports for a relationship of inflammation to AD is the epidemiological data suggesting that NSAIDs reduce the risk of AD. However, only certain NSAIDs might be useful for reducing AD risk. The real factor associated NSAID protection from AD may be the

modulation of gamma-secretase,[38] reducing the production of the more toxic beta-amyloid molecules and tempering the usual destruction of synapses as the synaptolytic and synaptogenic balance is tilted towards excess synapse destruction,[23,24,39] not an anti-inflammatory mechanism.

There is an important issue concerning the relationship between the brain functions and control of inflammation. The brainstem, including norepinephrine, has an important role in activating and controlling inflammation. The Ly et al. article discusses many of the central issues regarding these interactions. Still, there are the questions of exactly what each component of the neural-inflammation axis is contributing to these common conditions, whether the conditions themselves are activating inflammation, or are there interactions between them. More research in this area central to Medicine is needed.

AD CAUSATION AND GENETICS

The most critical causal issue in AD is genetic, particularly apolipoprotein-E (APOE) genotype.[40–42] The evolutionary relationship of APOE to AD remains unclear,[43] but APOE does relate to neural stress.[44] A likely causative scenario involves the process of turning over 5 trillion synapses per day, which requires moving a tremendous amount of membrane lipids, particularly cholesterol, from degenerating synapses to new synapses. Inefficient APOE chaperoning of cholesterol will harm the most active and tenuous neuroplastic machinery, which may be an important evolutionary factor in preventing dementia in elderly humans.[41] The most vulnerable axonal arbors are those of the norepinephrine and serotonin neurons with their extremely diffuse axonal projections, which have had to tremendously expand with the evolutionary enlargement of the cerebral cortex and survive the increased human longevity.

CONCLUSION ABOUT THE AD RELATIONSHIPS TO DEPRESSION AND OBESITY

As clearly described by Ly et al., there are numerous relationships between AD and both depression and obesity. The conclusion from the discussion here is that inflammation is not necessarily the mediator of these relationships as there are several other interactions involved. Further, understanding the centrality of neuroplasticity in AD provides a clear understanding of the pathophysiology of AD and opens for consideration numerous pathways which could be targeted to stop or reverse AD. Also, with an understanding of AD pathophysiology, research on causal mechanisms, preventive interventions, and treatments can advance.[45]

POTENTIALLY MODIFIABLE STEPS FOR AD PREVENTION AND TREATMENT

In the discussion of the relationships between obesity, AD, depression, and inflammation, Ly et al. touch on extremely important topics to be considered for AD and dementia prevention. Outlined here are ten specific directions for research and further study, including numerous approaches that have already shown some promise:

1) Weight control in early and midlife may be a fundamental focus for AD and dementia prevention. There is a clear relationship between weight and hypertension, which can lead to cerebrovascular disease, dementia, and stroke (the third leading cause of death in the US). So, attention to weight and blood pressure is an important part of maintaining health that can reduce the risk of dementia. Further, excess weight has been related to an increased risk of type-2 diabetes (diabetes is the eighth leading cause of death in the US). And diabetes is also related to cerebrovascular disease, clearly related to dementia, but unclear about direct relation to AD risk.
2) Physical exercise has become the factor most associated with AD risk reduction, but exercise can also prevent depression, help maintain healthy body weight, and prevent type-2 diabetes.
3) Diet has been specifically related to lowering AD risk (Mediterranean diet, MIND diet, and other healthy diets) and can also decrease the risk of obesity.
4) Statins, which control hyperlipidemia and thus may help control obesity, have been shown epidemiologically to decrease AD.[46] The failure of

statins to stop the progression of AD may be related to its use too late in the illness, and it may be that the benefit is preventing substantial arteriosclerosis and other types of dementia.[47] Note that a reduction of hyperlipidemia with statins (HMG-CoA reductase inhibitors) may reduce proinflammatory mediators and increase microglial activation.[48] However, the evidence is mixed as to whether statins and related treatments may improve cognitive function in AD.[49,50] It is possible that statin use may be more effective in reducing AD pathology at an earlier stage, not necessarily related to inflammation, rather than after irreversible cognitive changes have occurred.

5) Leptin deficiency is related to AD, though the causal relationship is unclear. A recombinant form of leptin is approved for treating lipodystrophy and has potential therapeutic action for AD.[51]
6) Insulin has also been shown to have indirect relationships to AD. The insulin-degrading enzyme, neprilysin, also degrades amyloid. Brain insulin resistance is an early feature of AD and develops before the onset of AD symptoms. Insulin has an important role in the regulation of energy metabolism and neuronal vitality in neurons and acts as a growth factor in the brain. Insulin signaling mechanisms in the brain is essential for the formation of synapses and neuroplasticity, and thus must play an important role in cognitive functions that could be related to a beneficial treatment.[52] Also, insulin signaling mediated by the GSK-3 pathway is involved in neurogenesis and synaptic plasticity as noted above. Disruption of this pathway in insulin resistance has been associated with impaired stress adaptation and aberrant reward circuitry, both drivers of depressive-like behaviors.[26] While treatment with insulin may not be beneficial for AD, drugs such as metformin, which control diabetes, may be useful for preventing AD,[53] especially if they can be shown to slow or stop AD pathology and can be used early enough in the course of the disease.
7) The traditional antidepressant medications, serotonin and/or norepinephrine reuptake inhibitors, have not shown evidence of benefit for preventing AD. The failure of such trials may be related to studying AD too late in the course of the disease and with inadequate assessment tools.[39,45,54,55] However, other treatments which affect these neurotransmitters could be beneficial,[21] such as the effect of formoterol on central noradrenergic mechanisms.[56]
8) Good sleep may also help to prevent AD. Trazodone, an anti-depressant that works on both norepinephrine and serotonin, has been shown to delay AD, and this inexpensive drug is widely used to increase deep sleep. Further, the deep-sleep epoch could be the time period in which beta-amyloid, which has built up during the day is removed from the brain under normal circumstances.[24] And poor sleep can also lead to the weight loss observed in elderly AD patients. Melatonin, a substance produced by the pineal gland to promote sleep, can be taken as an over-the-counter supplement to improve sleep, though a specific reduction of AD risk with melatonin is not established. Further, other agents which can reduce cortical pyramidal neuron excitability, such as magnesium or anticonvulsant medications, could also have a benefit to reduce Abeta toxicity.[57] Also, a dual orexin receptor antagonist, suvorexant, has been shown to have potential for reducing TAU phosphorylation and A-beta deposition, potentially through a similar effect on sleep.[58]
9) Lithium, as noted above, has been used for mood stabilization in bipolar disorder. Lithium can be beneficial for behavioral problems in AD patients if the dose is kept adequately low (personal observation). Further, there have been suggestions that lithium treatment may reduce the risk of AD, possibly through its inhibition of GSK3b, as discussed above. And there may be other approaches to modulating TAU phosphorylation, such as methylene-blue.[59]
10) Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown epidemiologically to reduce AD risk substantially. Large-scale epidemiological studies and meta-analyses have previously indicated that general NSAID use, not specific to any individual agent, is associated with a decreased risk of Alzheimer's disease.[60,61] However, specific trials in AD patients have not shown a slowing of progression. A critical

question is whether only those NSAIDs which modify the APP gamma-secretase (APP-GS) are the ones beneficial for helping to prevent AD.[38]

This list is modified from a similar list created in 2002 for the July Newsletter of the Long Island Alzheimer's Foundation at the request of the founder, who was discovered to have an APOE-e4/4 genotype (being informed on a nationally broadcasted TV show). There are many additional suggestions unrelated to the current discussion that could be added, including regular health visits, such as the Medicare Annual Wellness Visit[45] and monitoring levels of vitamin of D and B12, as well as important minerals, and keeping those levels in the upper midrange of normal.

FAILURE OF THERAPIES THAT REMOVE BETA-AMYLOID TO STOP OR REVERSE AD PATHOLOGY

Therapies that remove A-beta deposits from the brain have been left out of this discussion because A-beta deposits themselves are not related to dementia, extensive focus on their removal has shown unclear benefit and no reversal of dementia or prevention of progression, and the discussion here has been therapies which can prevent AD progression.

DIRECTIONS FOR FUTURE RESEARCH ON AD TREATMENT AND PREVENTION

At this time, the major focus of attention on AD has turned to early recognition and prevention. In any case, understanding pathophysiological mechanisms is important. And if some treatments can help obesity, depression, and AD, then efforts should be made to establish the mechanisms and develop beneficial approaches to prevention and treatment. This discussion has emphasized the Neuroplasticity Hypothesis of Alzheimer's disease,[7,8,23,24] and the broad potential that this hypothesis has for explaining the pathophysiology of AD and leading research to successful prevention and treatment of AD. The potential role of inflammation in causation or treatment of AD remains, but the approach suggested by Ly et al. does not appear to provide the explanatory capability or promise of successful treatments that the neuroplasticity perspective offers. However, clinical trials are needed which are efficient and show strong effect sizes, which can be implemented with attention to genetics and better recruitment and testing strategies[39,45,54,55] to prevent and treat AD.

AUTHOR CONTRIBUTION

J. Wesson Ashford is the sole contributor to this article.

DATA STATEMENT

The data has not been previously presented orally or by poster at scientific meetings.

DISCLOSURES

J. Wesson Ashford does not have any conflicts to declare.

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