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Featured Article

Alzheimer's disease in humans and other animals—A consequence of postreproductive life span and longevity rather than aging

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Abstract Two diseases of the modern world—Alzheimer's and diabetes mellitus—are linked by epidemiology, genetics, and molecular pathogenesis. They may also be linked by the remarkable observation that insulin signaling sets the limits on longevity. In worms, flies, and mice, disrupting insulin signaling increases life span leading some to speculate that caloric restriction might extend life span in man. It is our contention that man is already a long-lived organism, specifically with a remarkably high postfertility life span, and that it is the reason that results in the high prevalence of Alzheimer's and diabetes. We review evidence for this hypothesis that carries specific predictions including that other animals with exceptionally long postreproductive life span will have increased risk of both diabetes and Alzheimer's disease and present novel evidence that Dolphin, like man, an animal with exceptional longevity, might be one of the very few natural models of Alzheimer's disease.

Keywords: Longevity; Insulin signaling; Alzheimer's pathology; Animal models; Tau; Amyloid; GSK-3

1. Diabetes mellitus and Alzheimer's disease

As populations all over the world age, enormous challenges are posed by chronic disorders such as Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM). AD in particular is a devastating condition. With a long prodromal period of perhaps 10 to 20 years followed by another decade of clinical symptoms, AD and related dementia conditions are becoming a priority for many governments, not least as it is estimated that 1% of global gross domestic product is spent on dementia care (http://www.alz.co.uk/research/files/WorldAlzheimerReport2010.pdf). As well as growing older, the populations of the developed economies are also growing obese and sedentary. Although this is most marked in the developed nations, it is truly an international trend, and as children in particular show dramatic increases in body mass index, this is a deeply concerning indicator of health problems to come. These health problems are significant as obesity increases risk of cancers, cardiovascular disease, and metabolic syndromes including T2DM.

These two health challenges—an aging population at risk of neurodegenerative disease such as AD and an increasingly obese population at risk of metabolic conditions such as T2DM—may seem unconnected and unfortunate consequences of modern civilization. It could be suggested that improved health care and sanitation leading to older populations, combined with seemingly unlimited access to highly processed and calorific foods and an increasingly sedentary lifestyle, suggests entirely independent and environmental, or more specifically social and historical, causes of the

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twin challenges of AD and T2DM. It is our contention however that this construct is only partially explanatory and that there is a molecular link between longevity and both AD and T2DM that suggests a relationship whereby both arise not as an unfortunate consequence of growing older in the modern world but are intrinsic to it. In other words that AD and T2DM are conditions not of *aging* as they are usually considered, but of *longevity*. It is not so much how long an organism lives for that governs whether the organism is vulnerable in particular to AD, but the molecular mechanisms that underlie this period; a period that is highly characteristic for any given species. Moreover, that this longevity-associated disease risk explains why AD and T2DM are disorders principally of man. Here we propose a hypothesis that AD and T2DM are the price we pay for the molecular underpinning that allows us to be *almost uniquely* long-lived animals.

AD is a form of dementia characterized by two main pathological lesions, the amyloid plaque and the neurofibrillary tangle (NFT). Although it remains contentious whether these lesions are themselves causative of the neuronal loss that results in functional deficits or whether they are simply indicative of an underlying process, the evidence from molecular genetics and experimental neuroscience is compelling that the amyloid cascade is at the heart of the pathology of AD [1]. This cascade involves first the generation of β amyloid (Aβ) from the amyloid precursor protein (APP) and subsequently the aggregation of highly phosphorylated tau protein. Other processes including neuroinflammation clearly play a role, perhaps to exacerbate the amyloid cascade, perhaps triggered by the cascade, or perhaps independently. In addition to genetic causes of familial early-onset AD and genetic influences on late-onset AD, a considerable effort has been expended on searching for environmental influences on AD. Despite this, relatively few have been identified and arguably, other than age itself only two—head injury and obesity/diabetes—have been unambiguously replicated [2,3]. The evidence that diabetes and obesity increase the risk of dementia has been consistently reported from many epidemiological studies, themselves the subject of multiple systematic reviews [3–8]. The mechanism underlying this risk might be at multiple levels, the most parsimonious of which might be that metabolic complications increase vascular damage to the brain and this either exacerbates AD pathology or is an additive or independent insult [3]. However, insulin resistance predicts the development of cerebral amyloid pathology as measured by positron emission tomography imaging [9] and considerable evidence from cell and animal models suggests that a *failure of insulin signaling* directly contributes to AD pathological processes, including the formation of tau pathology as we discuss in the following sections.

2. Insulin actions: role of glycogen synthase kinase-3

For a failure of insulin signaling to effect the risk of AD directly rather than through a mediating factor such as vascular damage, then insulin resistance in the periphery should be reflected in insulin resistance in the brain. Considerable evidence suggests that this is in fact the case [10–12]. For example, in midlife, peripheral insulin resistance is associated with central glucose metabolic abnormality as well as with poorer cognitive performance [13,14] and predicts amyloid deposition [9]. In turn, there is evidence that central insulin signaling failure or abnormality can induce peripheral insulin resistance. In mice, ablation of insulin receptors (IRs) either from the whole brain (neuronal-specific IR knockout) or specifically from hypothalamus or midbrain dopamine neurons induces hyperphagia, body weight gain, and peripheral insulin resistance [15–17]. Also, brain-specific genetic inactivation of the insulin receptor substrate 2 (IRS2), that is essential for insulin signaling, results in obesity and diabetic phenotypes [18].

These data demonstrate a critical link between the CNS and the periphery, and importantly, both mice lacking the neuronal IR and those with IRS2 deleted are characterized by elevated tau phosphorylation and cognitive alterations, both are characteristics of AD [19,20]. Moreover, animal models of aspects of AD pathology show dysregulated metabolism [21] providing further experimental evidence for an intertwining of the molecular mechanisms of metabolic function and insulin signaling with AD. This link, and the increased risk of dementia in people with diabetes, suggests that there may be therapeutic opportunities for AD in enhancing insulin signaling, or tackling insulin resistance. Real-world data studies suggest that the commonly used therapy for T2DM, pioglitazone a PPARγ agonist that enhances insulin signaling, reduces the incidence of AD [22], and intranasal insulin beneficially alters APP processing and reduces cognitive impairment in early AD [23–25]. Large-scale trials of both intranasal insulin and pioglitazone are now underway. Although the outcomes of these trials are some years away, it is clear that systemic insulin signaling disruption increases the risk of AD and might do so through shared molecular mechanisms and not simply through end-organ damage as a consequence of vascular or other T2DM-induced pathology.

One such molecular mechanism that might plausibly underlie this link between insulin signaling in the brain and AD processes is mediated by glycogen synthase kinase-3 (GSK-3), initially discovered through its ability to phosphorylate glycogen synthase [26]. Given its critical role in insulin signaling, it is not surprising that GSK-3 has been implicated in the pathogenesis of obesity and insulin resistance [27,28], but it has also been shown to have a fundamental role in the pathogenesis of AD [29,30]. Tau is a physiological substrate of GSK-3, and transgenic mice with increased GSK-3 activity have neurodegeneration phenotypes including tau hyperphosphorylation and cognitive impairments [31]. Even before neurodegeneration sets in, GSK-3 overactivity suppresses long-term potentiation [32], while inhibition of GSK-3 is required following long-term potentiation to block long-term depression [33] suggesting that the normal