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Review

The 20-Year Voyage Aboard the Journal of Alzheimer's Disease: Docking at 'Type 3 Diabetes', Environmental/Exposure Factors, Pathogenic Mechanisms, and Potential Treatments

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Abstract. The *Journal of Alzheimer's Disease* (JAD), founded in 1998, played a pivotal role in broadening the field of research on Alzheimer's disease (AD) by publishing a diverse range of clinical, pathological, molecular, biochemical, epidemiological, experimental, and review articles from its birth. This article recounts my own journey as an author who contributed articles to JAD over the 20 years of the journal's existence. In retrospect, it seems remarkable that a considerable body of work that originated from our group marks a trail that began with studies of vascular, stress, and mitochondrial factors in AD pathogenesis, exploded into the concept of 'Type 3 Diabetes', and continued with the characterization of how environmental, exposure, and lifestyle factors promote neurodegeneration and which therapeutic strategies could reverse the neurodegeneration cascade.

Keywords: Ceramides, dementia, diabetes, insulin resistance, neuroinflammation, nitrosamines, obesity, streptozotocin, Type 3 diabetes, vascular steatohepatitis

HINDSIGHT-20/20

In 1998, the birth of the *Journal of Alzheimer's Disease* (JAD) as a hub for publishing reports based on new concepts that did not necessarily fall in line with tightly controlled mainstream theories felt tantamount to granting 1st amendment rights to biomedical scientists studying neurodegeneration. JAD was founded before open-access journals entered the stage, and at a time when it was difficult to publish data supporting alternative pathogenic mechanisms of Alzheimer's disease (AD), i.e., concepts that were unrelated to either the amyloid or tau hypothesis. Without publications, there can be no funding. Without funding, research cannot be pursued and participation in the peer-review process of funding is virtually impossible. Thus, the peer-reviewed free spirit publication concept linked to JAD from its inception was critical for broadening research and publicizing a range of viable concepts on the pathogenesis and potential diagnostics and treatments of AD. Sadly, the virtually closed shop strategy of the then standard print journals, set the field behind and

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restricted the conceptual breadth of young scientists interested in studying AD. The dominant hypothesis then and now is that AD is caused by the aging brain's propensity to abnormally accumulate and aggregate hyperphosphorylated tau (pTau) and amyloid-β (Aβ) peptides. The logical extension of this concept is to conclude that if the brain could be rid of those menacing molecules, AD would be cured. However, the outcomes of clinical trials indicate otherwise. Despite non-trivial flaws, the emergence of open-access scientific journals provided an additional boost to the diversification of AD research. Nonetheless, credit for leadership in this domain should be given to JAD. JAD took time to gain traction, in part due to the lack of indexing in PubMed, but also the perception that JAD was not on par with the more established journals. A great deal of credit for the eventual success of JAD should be attributed to George Perry, Mark Smith, and the associate editors. By encouraging submission of conceptually diverse manuscripts on AD research, they expanded the content of JAD and succeeded in generating 12 regular monthly issues per year. Giving the cover a make-over also helped with JAD's re-branding. Over the years, JAD's table of contents section repeatedly showed balance and commitment to publishing both human and experimental model data that covered various aspects of neurodegeneration.

VASCULOPATHY, OXIDATIVE STRESS, AND MITOCHONDRIAL DYSFUNCTION IN AD

One of our earliest publications in JAD showed that cerebrovascular lesions ranging from small infarcts to leukoaraiosis were responsible for pushing subclinical AD pathology to clinically manifested dementia with features that were indistinguishable from *bone fide* AD [1]. Although that work was not well accepted when presented at a national meeting, it was nonetheless awarded the first Alzheimer Award, an honor bestowed annually by editorial board members for the best publication in JAD. Today, the concept that cerebrovascular disease contributes to AD has gained considerable traction. Perhaps its best validation stems from the recent decline in AD rates, which has been attributed to effective curbing of cardiovascular risk factors [2].

Although human studies, including postmortem, can be enlightening, experiments are always needed to demonstrate proof of principle and unravel disease mechanisms. To mechanistically extend the concepts embodied in our 1998 human study, we conducted experiments to examine contributions of factors related to ischemic injury, including hypoxia, oxidative stress, free radical injury, and impaired mitochondrial function, which could mediate or accelerate molecular pathological changes associated with AD neuropathology [3–5]. Certainly our group was not alone in this quest, as demonstrated by concurrent JAD publications from other investigators examining the roles of oxidative injury and mitochondrial dysfunction as pathogenic factors in AD [6–13]. Despite encouraging data, the story was obviously incomplete because so many people experience significant hypoxic or ischemic insults to the brain, yet very few ever develop AD. What else is needed? Neuronal metabolic and molecular abnormalities produced by short-term *in vitro* exposures often are reversible. What factors and cellular responses render neuronal injury following hypoxic-ischemic insults irreversible and headed down the path of AD-type neurodegeneration?

Since AD-specific biomarkers are few in number, researchers mainly rank severity of AD based on brain and cerebrospinal fluid (CSF) levels of Aβ and pTau. However, the continued use of these indices as diagnostic gold standards reinforces the misconception that the principal pathogenic factors in AD are almost exclusively linked to aberrant cellular processing and accumulation of Aβ and pTau, and side-steps the complexity of other factors. Perhaps one of the best illustrations of why we must expand our thinking beyond these two favorite molecules was provided by one of our case reports published in JAD [14]. In brief, a patient diagnosed with amyotrophic lateral sclerosis was demonstrated to be cognitively intact throughout her clinical course, based on formal neuropsychological testing; the last evaluation was performed within 1 month of death. Postmortem examination of her brain revealed extensive and diffuse Aβ accumulations in senile plaques, blood vessels, and cells in all cortical and medial temporal regions [14], without accompanying pTau structural lesions or neuronal inclusions. Although the case was highly unusual, it provided sufficient evidence that abnormalities other than Aβ accumulations were likely critical mediators of AD pathogenesis.

EMERGENCE OF THE TYPE 3 DIABETES CONCEPT

By far, the biggest impact JAD had in relation to own research was the publication of a 6-manuscript

series in 2005 and 2006, including: 1) a review article on the expression and function of insulin and insulin-like growth factor (IGF) signaling networks in the brain [15]; 2) the first primary research article demonstrating brain insulin resistance and insulin deficiency in AD [16]; 3) a follow-up report showing AD Braak-stage dependent declines in insulin and IGF signaling molecule expression and function in the brain [17]; 4) characterization of AD Braak stage-associated increases in brain oxidative stress and mitochondrial dysfunction, paralleling declines in insulin/IGF signaling network functions [5]; 5) neuropathological and molecular characterization of the intracerebral streptozotocin (i.c. STZ) model and its relevance to sporadic forms of human AD [18]; and 6) the demonstration that AD-type neurobehavioral deficits and neuropathology in the i.c. STZ model could be prevented by treatment with peroxisome proliferator-activated receptor (PPAR) agonist-insulin sensitizer drugs [19]. That body of work drew worldwide media attention—both positive and negative, but also helped bring attention to JAD, which in those days, was still not regarded as mainstream. Even during press interviews, I received memorable cutting remarks by reporters who doubted the story, but nonetheless felt it should be aired. One can only imagine the vitriolic reviewers' comments received along with rejection notes from several major journals before we decided to submit this work for publication in JAD.

The review article was especially important because it provided documentation that the major distributions of insulin and IGF signaling networks were localized in brain regions that are characteristically targeted in AD and discussed potential adverse consequences of impaired insulin signaling in the brain [15]. The initial companion research article provided the first description of impaired insulin and IGF signaling in brains with advanced AD [16]. Although that manuscript was published in 2005, the research was conducted over the previous 3.5 years when molecular techniques were still quite labor intensive and many critical reagents were not commercially available. The study demonstrated significant AD-associated abnormalities in the expression of insulin and IGF receptors and ligands, together with impaired ligand-receptor binding in the brain. The surprising concept that emerged was that the main abnormalities in the brain overlapped with core abnormalities in both Type 1 and Type 2 diabetes mellitus, prompting us to coin the term 'Type 3 Diabetes' to better conceptualize the underlying nature of AD [16].

Even before the initial manuscript had been completed, we initiated a follow-up study to examine when and how impairments in brain insulin and IGF signaling emerged with respect to AD progression, i.e., severity (Braak stage) [17]. That study demonstrated progressive declines in brain expression of insulin and IGF-1 ligands (growth factors) and receptors, ligand interactions with receptors, and downstream signaling through insulin receptor substrate (IRS) and phosphoinositol-3-kinase (PI3K)-Akt, together with increased activation of glycogen synthase kinase-3β (GSK-3β) with AD progression. These findings suggested that Type 3 diabetes begins early in the course of AD and progresses with increasing severity of neurodegeneration. Since insulin regulates glucose metabolism in the brain, AD Braak-stage dependent declines in insulin signaling through metabolic pathways (PI3K-Akt) corresponds with the progressive reductions in brain glucose utilization detected by PET imaging [20, 21].

Further studies linked AD-associated impairments in insulin and IGF signaling to progressive increases in oxidative and nitrosative stress and reductions in mitochondrial function in the brain [5]. Since insulin and IGF signaling through PI3K-Akt pathways support energy metabolism, ATP production, cellular homeostasis, neuronal and glial survival, neuronal plasticity, cholinergic function, myelin maintenance, and neuronal cytoskeletal function, we suggested the unifying and parsimonious hypothesis that molecular and biochemical abnormalities associated with impairments in insulin and IGF signaling via declines in trophic factor availability and receptor responsiveness, could account for virtually all major neuropathologies in AD. It was not until 2012 that the human postmortem studies were repeated by independent investigators who confirmed significant impairments in insulin signaling through IRS and PI3K-Akt in AD brains [22, 23].

INSULIN SENSITIZERS AS THERAPEUTIC MEASURES FOR AD

The human studies on Type 3 diabetes were actually inspired by the serendipitous observation that rats treated with intracerebral streptozotocin (i.c. STZ) developed cognitive impairment with AD-type pathology [18]. Although the i.c. STZ model had been described earlier and shown to be associated with metabolic dysfunction in the brain [24–27], the AD-type neuropathological lesions, including Aβ

deposits had not been described previously. The i.c. STZ experimental model was generated in conjunction with other projects concerning the role of brain insulin signaling in relation to cognitive and motor functions [28–31]. The hypothesis tested was whether chemical- or toxin-induced brain insulin resistance would cause cognitive impairment. Although the neurobehavioral effects of i.c. STZ expected, the histopathological findings were. Publishing the i.c. STZ experimental data in JAD [18], shortly after the human studies [16, 17], was extremely valuable for demonstrating continuity of scientific thought and connecting human pathology with proof-of-concept experiments.

The toxic effects of STZ that cause Type 1 diabetes mellitus are mediated in part by killing insulin producing cells in the pancreas [32]. However, at lower doses, STZ causes insulin resistance and other pathologies of Type 2 diabetes [33]. In the i.c. STZ model, impairments in spatial learning and memory were associated with loss of neurons, neuroinflammation, increased oxidative stress, and accumulations of phospho-tau and Aβ in cortical-limbic structures that characteristically undergo neurodegeneration in AD [34]. Molecular and biochemical studies demonstrated that i.c. STZ-induced neurocognitive deficits and neuropathological abnormalities were associated with significantly reduced expression of mRNA transcripts encoding insulin, IGF-1, and IGF-2 polypeptides, insulin and IGF receptors, and insulin receptor substrate (IRS) proteins [18], reduced binding to insulin and IGF receptors [18], and decreased levels of immunoreactivity to the insulin and IGF-1 receptors, IRS protein, Akt, p70S6K, mTor, tyrosine phosphorylated insulin and IGF receptors, and phosphorylated GSK-3β in the brain [34]. These findings suggest that i.c. STZ kills insulin and IGF-1 receptor expressing cells that utilize IRS to transmit signaling downstream through Akt metabolic pathways. The loss of insulin producing cells is characteristic of Type 1 diabetes, whereas impaired receptor expression and binding mark states of insulin resistance, as occurs in Type 2 diabetes. To convey the concept that the molecular and biochemical neuropathologies of human AD and experimental i.c. STZ are linked to both insulin deficiency (due to loss of neurons and insulin gene expression) and insulin resistance (decreased receptor expression and receptor binding) and thus share features of Type 1 and Type 2 diabetes, we coined the term 'Type 3 diabetes'. Concomitant loss of IGF-1, IGF-2, IGF-1 receptor, and IGF-2 receptor expressing cells and reduced IGF-1/IGF-2 receptor binding could be explained by STZ-mediated killing of cells that co-express insulin and IGF-1 or IGF-2 or their receptors [15]. Of further note is that in AD and the i.c. STZ model of sporadic AD, insulin/IGF deficiency and resistance mediated neurodegeneration is associated with inflammation, oxidative, and endoplasmic reticulum stress, microvascular disease, and metabolic dysfunction, all of which occur in diabetes mellitus.

The sixth article in the 2005-2006 Type 3 diabetes manuscript series was pivotal for demonstrating that cognitive impairment and neurodegeneration could be ameliorated by early treatment of the i.c. STZ model of sporadic AD with PPAR agonists [19]. The most effective PPAR agonists had specificity for the delta receptor subtype followed by PPAR gamma, corresponding with their relative levels of expression in the brain [5, 35–37]. PPAR agonists are insulin sensitizers that have anti-oxidant/anti-inflammatory properties [38] and have been used to treat Type 2 diabetes mellitus and other insulin resistance diseases [38]. More recently, our group extended those efforts by demonstrating that a novel, orally administered hybrid PPAR-delta/gamma agonist (T3D-959) was effective in remediating deficits spatial learning and memory and motor function, and prevented neurodegeneration in the i.c. STZ model [36, 37]. Mechanistically, T3D-959 was shown to enhance insulin and IGF-1 signaling through PI3K-Akt pathways, reduce inflammatory markers in the brain [34], and reverse white matter myelin lipid abnormalities associated with neurodegeneration [39]. T3D-959 is currently being evaluated in Phase IIb clinical trials. By publishing the Type 3 diabetes series in JAD, the full arc of this early research on the roles of brain insulin deficiency and insulin resistance as mediators of AD-type neurodegeneration, from direct observations in human brains to experimental testing of the underlying hypothesis, and finally implementation of therapeutic interventions in preclinical models was associated with a single journal. Perhaps one of the most rewarding follow-up trends was the sharp increase the number of research articles related to brain insulin resistance and metabolic derangements that were subsequently published in JAD.

LINKS BETWEEN AD AND NITROSAMINES/ENVIRONMENTAL EXPOSURES

The brain pathology in the i.c. STZ model drove the next question about how such a limited exposure

to a single agent could cause disease that shares many features in common with sporadic AD, and whether humans were somehow exposed to STZ-related toxins that increased the rates of sporadic AD over time. The realization that the chemical structure of STZ corresponds to a nitrosamine, yet again shifted the laboratory's focus to assess the potential role of other nitrosamines in the pathogenesis of AD. Acknowledging the public health importance yet controversial nature of the concept that we might be poisoning ourselves caused us to intentionally target JAD for our publications in this field.

The nitrosamine-related studies were initiated by conducting an epidemiological analysis to correlate age-stratified, time-dependent shifts in AD, diabetes mellitus, and other disease prevalence rates with population exposures to processed and preserved foods that contain nitrosamines or nitrates and nitrites which can be converted to nitrosamines with heating and digestion [40]. Data extracted from U.S. statistical databases showed that from 1980 to 2006, death rates from AD, Parkinson's disease, and diabetes mellitus increased across all age-groups among people 50 years and older, and that those trends paralleled the increases in nitrosamine exposures [40]. Importantly, the results did not support the hypothesis that increasing rates of AD were consequences of increased longevity since the proportions of diseased individuals increased over time within each age group, i.e., 51–60, 61–70, 71–80, and 81–90. Furthermore, the relatively rapid time-dependent increases in AD, Parkinson's disease, and diabetes mortality rates were more consistent with exposure, i.e., environmental, lifestyle, or dietary than genetic effects [40]. In a subsequent study, Parkinson's disease dementia and dementia with Lewy body disease were demonstrated to have brain impairments in insulin, IGF-1, IGF-2, and neurotrophin signaling, which experimentally were produced by *in vitro* exposure to manganese [41].

Since epidemiologic studies show associations rather than causality, proof of concept experiments were needed. Experiments were designed to demonstrate neurodegenerative and neurotoxic effects of low, sub-mutagenic exposures to nitrosamines, rather than high doses which were already known to be carcinogenic and therefore not relevant to the over-arching question. Besides STZ, the adverse effects of N-nitrosodiethylamine (NDEA), which is widely present in processed/preserved foods, tobacco-specific nitrosamine ketone (NNK), which is present in tobacco, and more recently, arecoline hydrobromide (AH), which is present in Areca nut (Betel quid), have been studied in relation to neurodegeneration with brain insulin/IGF resistance and deficiency, oxidative stress, and inflammation. NDEA treatment of cultured neurons caused AD-type molecular and biochemical abnormalities, including oxidative injury, DNA damage, Aβ and pTau accumulations, mitochondrial dysfunction, and impaired signaling through insulin and IGF pathways [42]. Parallel *in vivo* studies demonstrated that low-dose NDEA caused diabetes, steatohepatitis with liver insulin resistance, i.e., non-alcoholic fatty liver disease, and neurodegeneration with brain insulin resistance and AD-type molecular and biochemical abnormalities [43]. The long-term adverse effects of NDEA occurred after both intracerebral or intraperitoneal exposures. The latter finding was of particular interest because it provided fresh hints about potential environmental causes of sporadic AD. At the same time, the results suggested that AD and other insulin resistance diseases could be prevented via lifestyle modifications. Due to press releases by JAD and considerable interest from the news media, the public was informed about avoidable harmful exposures. Since publication of those articles, the list of supermarket foods labeled as nitrate/nitrite-free has grown.

ROLES OF OBESITY, TYPE 2 DIABETES, AND PERIPHERAL INSULIN RESISTANCE IN AD: TOXIC LIPIDS AND THE LIVER-BRAIN AXIS

Within two years of publishing the initial papers on Type 3 diabetes, new data emerged linking obesity and type 2 diabetes to cognitive decline and dementia [44–48]. Although obesity had already been linked to insulin resistance diseases, it was not known whether the brain was just another organ rendered insulin resistant by the same processes that cause peripheral insulin resistance diseases, or if brain involvement was consequential to peripheral insulin resistance. On the surface, the association between obesity and cognitive impairment seemed to contradict the Type 3 diabetes hypothesis. Therefore, it was imperative to reproduce the responses in experimental models.

The approach was to evaluate the integrity of brain insulin and IGF signaling networks in mouse [49, 50] and rat [51, 52] models of obesity produced by chronic high fat diet feeding. The high fat diet fed mice and rats developed visceral obesity with Type 2 diabetes and steatohepatitis. However,

brain insulin resistance and neurodegeneration were detected only after significant steatohepatitis had developed, suggesting a link between fatty liver disease and neurodegeneration. Review of the liver pathology in the i.p. administered NDEA experiments revealed a similar relationship between the emergence of steatohepatitis and neurodegeneration. The NDEA experiments were extended by evaluating the independent and interactive effects of chronic high fat diet feeding and low-dose i.p. NDEA exposures in Long Evans rats. Those investigations demonstrated that while high fat diet feeding and i.p. NDEA each caused deficits in spatial learning and memory, brain insulin resistance, and neurodegeneration, dual exposures produced greater severities of fatty liver disease, brain insulin resistance, cognitive impairment, and neurodegeneration [51, 52].

The mechanism conceptualized to explain how visceral obesity and fatty liver disease might negatively impact the brain was that dysregulated lipid metabolism causes toxic lipids to accumulate in visceral adipose tissue and liver. With cellular injury and death due to endoplasmic reticulum and oxidative stress, toxic lipids are released into the circulation, and due to their lipid soluble properties, they can cross the blood-brain barrier and cause neurotoxic injury, inflammation, insulin resistance, and neurodegeneration [53]. Ceramides were postulated to be the offending sub-class of lipids [54] because the toxic effects of ceramides include inhibition of insulin signaling through PI3K-Akt pathways and activation of cellular stress mechanisms [53–62].

To address the hypothesis that toxic lipids generated in states of hepatic insulin resistance with dysregulated energy metabolism are mediators of brain insulin resistance and neurodegeneration, we measured liver and serum ceramide levels in mice and rats that were chronically fed with high fat diets, and in rats treated by i.p. injection of NDEA. Those studies detected significantly increased ceramide levels in sera, livers, and brains in conjunction with steatohepatitis and brain insulin resistance with neurodegeneration [50, 54]. Furthermore, *in vitro* exposures to synthetic ceramides caused molecular and biochemical abnormalities similar to NDEA-mediated *in vivo* pathology, and i.p. injected fluorescent ceramides crossed the blood brain barrier and were detected in brain [54, 62].

Altogether, the chronic high fat diet feeding and nitrosamine exposure experiments support human data relating obesity and Type 2 diabetes to cognitive impairment and brain insulin resistance with neurodegeneration. However, compared with the effects of intracerebral delivery of STZ or other nitrosamines, the neuropathological and neurodegenerative responses to visceral obesity, diabetes, and steatohepatitis were modest to moderate. Moreover, most individuals diagnosed with AD do not have clinically manifested peripheral insulin resistance. Therefore, it is probable that brain insulin resistance-mediated neurodegeneration can occur via two mechanisms: 1) direct injury with predominant involvement of the brain as occurs in most cases of AD; or 2) indirect injury mediated by systemic insulin resistance diseases associated with metabolic derangements leading to toxic lipid (ceramide) release from injured cells, into the blood stream and across the blood-brain barrier [53].

SMOKING IN THE PATHOGENESIS OF NEURODEGENERATION—JUST ANOTHER NITROSAMINE EXPOSURE

Chronic cigarette smoking has been linked to increased rates of cognitive impairment [63–65] and structural abnormalities in the brain including alterations in cerebral white matter volume [65–67], and atrophy of gray matter structures in the temporal and parietal lobes [65, 67, 68] as demonstrated with various neuroimaging methods [67, 69–77]. In addition, meta-analysis revealed significant correlations between smoking and atrophy of gray matter in the anterior cingulate, prefrontal cortex, and cerebellum [78]. Epidemiological studies have provided supportive data in showing higher rates of cigarette smoking in people with AD than normal aging [76, 79–85].

The above clinical and epidemiological data, together with laboratory generated evidence that nitrosamine exposures contribute to the pathogenesis of AD and other neurodegenerative diseases that are linked to impaired insulin and IGF signaling caused us to examine the potential roles of tobacco smoke [86–88] and the tobacco-specific nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), as mediators of neurodegeneration. Studies involving NNK stemmed from the realization that the toxic effects of tobacco consumption (smoking, chewing, sniffing) were mediated by tobacco-specific nitrosamines [89–92]. Smoking and NNK exposures produced similar types of neurodegeneration, impairments in insulin and IGF signaling, increases in oxidative and nitrosative stress, alterations in cerebral white matter myelin

lipid composition with reductions in sulfatides and certain phospholipids, and increases in ceramide content [86–88].

ENVIRONMENTAL AND LIFESTYLE TOXIN EXPOSURES IN AD PATHOGENESIS: MORE WORK IN NEEDED

Our research has demonstrated that low-dose, chronic exposures to various types of nitrosamines disrupt brain and systemic insulin signaling responses, promote oxidative injury, cellular stress, and inflammation, but they differ with respect to their dominant pathogenic effects. STZ mainly disrupts insulin signaling and causes neuroinflammation. NNK is a strong promoter of oxidative injury and inhibits signaling through metabolic pathways. NDEA has mixed adverse effects on insulin/IGF-1 signaling, cellular stress and radical injury. These observations set the stage for identifying other environmental and lifestyle exposures that produce similar adverse effects in the brain. For example, in a recent collaborative review article, evidence was presented that high environmental exposures to particulate matter 2.5 (PM2.5) in heavily polluted air increase risk for obesity, insulin resistance, AD-associated cognitive impairment, and dyslipidemic states in children, especially girls carrying the apolipoprotein E $\varepsilon 4$ allele [93]. The importance of that work was that it established a novel means of inter-relating genes $\times$ environment $\times$ gender in the path toward AD.

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The over-arching theme of the considerable body of data published by our group in JAD from 1998 to 2017 has been to identify major factors contributing to the pathogenesis of AD-associated structural (neuroanatomical), molecular, and biochemical pathologies, and then strive to uncover their mechanisms and treatments. The aggregate findings suggest that relevant exposure factors produce similar patterns of multimodal chronic, progressive injury leading to AD-type neurodegeneration because they converge mechanistically by disrupting insulin and IGF networks, including their cross-talk with Notch and Wnt pathways. These conclusions also imply that the principal culprits in AD and probably other forms of neurodegeneration, are controllable or preventable. In retrospect, it seems that without the open spirit of JAD, this conceptual trajectory of our research might not have come to fruition.

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