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Theoretical Article

A model of lipid dysregulation and altered nutrient status in Alzheimer's disease

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Abstract

Introduction: Dysregulated lipid metabolism and nutrient status are thought to play a role in the pathophysiology of Alzheimer's disease (AD). However, the precise involvement is not well understood, and it remains unclear exactly how such dysregulated lipid metabolism and altered nutrient status, especially changes in phosphatidylcholine, B12, and folate, are connected to the hallmark pathology in AD (i.e., amyloidogenesis).

Methods: We have postulated that genetic susceptibility (i.e., APOE ε4/ε4) to environmental exposure to emissions of nitrous oxide (N_2O) could underlie the onset of AD and its early neuropsychiatric correlates

Results and Discussion: The current theoretical editorial describes, using clinical, preclinical, and in vitro evidences, how this model contributes not only to amyloidogenesis but also other nonopioid effects, specifically altered lipid metabolism, depletion of vitamin B12, and disruption of the folate-mediated one carbon metabolic pathway.

Keywords: Alzheimer's disease; Phospholipids; Dynorphin; Nitrous oxide; Vitamin B12; Folate; Choline

Alzheimer's disease (AD) is a progressive neurodegenerative condition that comprises the most common cause of dementia [1]. In developed economies, AD is a leading cause of mortality and, while most of the risk is commonly attributed to genetics, the role of environmental factors is increasingly being suspected to play an interactive role in modulating this genetic susceptibility [2]. The disease is characterized clinically by memory loss and other cognitive functioning decline. The disease's etiopathology is attributed to the accumulation of amyloid plaques between nerve cells (neurons) in the brain and insoluble twisted fibers known as neurofibrillary tangles (consisting of aggregates of hyperphosphorylated tau protein) found inside the brain's cells [3]. These manifestations are thought to contribute to the degradation of neurons over time and the onset of disease symptoms.

Dysregulated lipid metabolism and altered nutrient status are thought to play a role in the pathophysiology of AD. The recent meta-analysis from De Wilde et al. [4] showed that patients with AD have lower CSF/brain availability of docosahexaenoic acid, choline, vitamin B12, folate, vitamin C, and vitamin E. However, the precise involvement of these metabolic alterations is not well understood. It remains unclear exactly how such dysregulated lipid/nutrient metabolism is connected to the hallmark pathology in AD. This theoretical editorial provides a parsimonious explanation, suggesting that individual exposure to a novel environmental factor may contribute to the hallmark neurobiology of AD but also non–AD-related effects, including altered lipodome and nutrient status.

1. Environmental nitrous oxide (N_2O) exposure and AD pathology

We have postulated that genetic susceptibility to environmental exposure to emissions of nitrous oxide (N_2O) could

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underlie the onset of dementia and its early neuropsychiatric correlates, such as attention-deficit hyperactivity disorder (ADHD) [5–7]. N_2O is an air pollutant that is derived from soil management practices in agriculture as well as from mobile and stationary combustion sources. Although N_2O has also been and continues to be used widely as an analgesic during labor, dentistry, and other medical procedures for over a century, the human health effects from chronic exposure do exist and include an increased risk of headache, dizziness, tachycardia, oxidative damage/stress, vitamin B12 deficiency among operating room personnel chronically exposed to N_2O [8–10], as well as increased long-term risk of myocardial infarction among a noncardiac surgery population [11].

Recent case reports have also provided anecdotal evidence associating chronic N_2O use with subacute combined degeneration and limb weakness [12], myeloneuropathy [13], pernicious anemia [14], hematologic changes and risk of thrombosis [15,16], myocardial infarction [17], pneumomediastinum [18], vitamin B12 deficiency with lower motor neuronal degeneration [19,20], and stroke [21], and many conditions that are considered significant risk factors for AD onset, including headache [22], anemia [23], gait imbalance/ataxia [24], thrombosis [25], stroke [26], and myocardial infarction [27]. Moreover, clinical evidence suggests that trace N_2O exposure induces impairments in the Digit Span Test [28], a test that has predictive power in identifying cognitive decline in participants with mild cognitive impairment (MCI)—a condition often prodromal to AD [29].

Molecularly, N_2O, especially at lower doses, induces endogenous release of dynorphin (DYN) and activation of its cognate kappa opioid receptor (KOR) [30]. The release of DYN opioid peptides and KOR activation putatively regulate acute elevations in N_2O-induced mesolimbic dopamine release [31]. Although, maturational decline in KOR constitutive activity occurs in rats [32], which could differentially affect KORs ligand efficacy and impart consequential age-related effects. Age-dependent decline in KOR activity or its desensitization likely explain the N_2O-induced, DYN-mediated activation of the nonopioid targets responsible for amyloidogenesis, including modulation of glutamate receptors [33] and caspase activation. Consistently, significantly elevated DYN levels have been shown in AD brain [34]. These age-dependent mechanisms of toxicity are discussed next and form the basis of the hypothetical argument that chronic exposure to trace environmental N_2O induces AD.

At high concentrations and exposure times for 4 or 72 hours, DYN-induced striatal neurotoxicity in mouse brain involved activation of α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA)/kainate receptors with concomitant concentration-dependent increases in cytochrome C and caspase-3 activity [35]. Kolaj et al. [36] demonstrated that, at much lower concentrations (1 μM), DYN induced an initial (10 minutes) depressant effect (KOR-dependent) and late potentiating effect (KOR-independent) on the transient component of AMPA-induced currents, suggesting that KOR desensitization (or maturational decline) permits DYN nonopioid toxicity via ionotropic glutamate receptor activation. In this regard, we have proposed a novel pathway, consistent with the *in vitro* evidence of N_2O-induced caspase activation [37] and α 7 nicotinic acetylcholine receptor (α7) inhibition [38], through which reduced KOR constitutive activity and greater responsivity to endogenous ligand due to aging yields excess brain DYN from N_2O that facilitates amyloidogenesis (i.e., trace environmental N_2O-induced DYN release → AMPA receptor late potentiation and caspase activation → α7 nicotinic acetylcholine receptor inhibition → nitric oxide synthase uncoupling → oxidative stress/amyloidogenesis) [See a general schematic shown Fig. 1]. This model suggests that targeting proteins involved in amyloid synthesis, as has been historical practice in preclinical AD research, is a late-stage focus and therefore, a limited biological intervention in AD therapy. We suggest that consideration ought to be given to novel AD therapeutics that are designed to target not late pathological manifestations of the hypothesized disease process (i.e., amyloid synthesis) but rather early apoptotic events thought to be triggered by environmental N_2O-induced caspase activation via endogenous DYN release. We next highlight one novel AD therapeutic that has caught our interest insofar as the drug could halt the proposed neurodegenerative cascade induced from environmental N_2O.

Wang et al. [39,40] published data on the effectiveness using a intracerebroventricular Aβ42 infusion mouse model, a triple-transgenic (3xTg) mouse model of AD, as well as postmortem AD brain tissue of a novel therapeutic candidate, PTI-125, in the reversal of hallmark AD pathology including reduced tau hyperphosphorylation, aggregated Aβ42 deposition, neurofibrillary tangles, and neuroinflammation. The novel mechanism of PTI-125 is thought to involve the differential binding affinity to altered filamin A (FLNA), a 280-kD actin-binding protein, and restoration of the protein to its native conformation. This action averts the altered FLNA associations with α7-nicotinic acetylcholine receptor and toll-like receptor 4 that foster amyloid-β1-42–induced tau phosphorylation and neuroinflammation, presumably through impaired α7-induced calcium permeability and uncoupled nitric oxide synthesis. Critically, the authors demonstrate that these effects of PTI-125 on FLNA effectuate a virtually nondiseased state. The studies conducted so far implicate altered FLNA as an integral protein constituent mediating pathological AD signaling.

In vitro screening shows that filamin is a substrate of caspase-3 [41], as etoposide-induced caspase-3 activation cleaved filamin from 280 kDa to 170, 150, and 120 kDa major N-terminal and 135, 120, and 110 kDa major C-terminal fragments. Consistently, the procleavage effects of caspase-3 on filamin were inhibited by a cell permeable inhibitor of caspase-3–like protease [41]. FLNA silencing in human tumoral cells significantly reduced caspase-3/7 activation

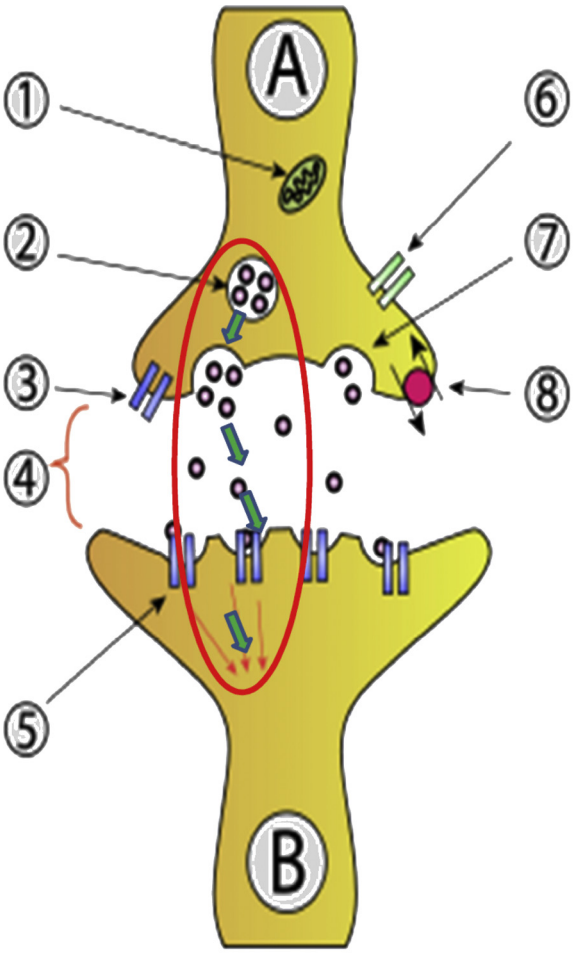

Fig. 1. Within mesolimbic neurons [A, B], trace nitrous oxide (N_2O) stimulates the release of opioid peptides, including dynorphin (DYN) A (1-17), contained within synaptic vesicles (2) and ultimately released into the synaptic membrane (4) via vesicular fusion (7). These peptides act on cognate opioid receptors such as the kappa opioid receptor (KOR) (6). Owing to aging, KOR constitutive expression declines, leaving the receptor more sensitive to chronic ligand-induced stimulation (i.e., downregulation). This receptor modulation permits DYN-induced activation of several nonopioid targets (indicated by multiple red arrows), including activation of α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA)/kainate receptors (5), triggering an apoptotic pathway that involves cytochrome c release from mitochondrion (1), caspase-3 activation, and restricted calcium influx via inhibition of the α7 receptor (8), as well as leakage from phospholipid vesicles contained within the neuronal membrane in an attempt to restore free choline (See text). These AD-related effects are hypothesized to co-occur with the well-documented effects of N_2O on cobalamin and folate metabolism through the inactivation of the methionine synthase enzyme.

[42]. Activated caspase-3 immunoreactivity was elevated in AD brain, and this activity appeared to co-occur with neurofibrillary tangles and plaque formation [43]. Therefore, altered FLNA processing and conformation may be concomitantly related to N_2O-induced caspase-3 activation in AD. We believe this paradigm of neurodegeneration accompanies other nonopioid effects, including altered lipid metabolism and dysregulated nutrient status, mediated, as well, by trace environmental N_2O exposure.

2. Altered lipodome

Clinically relevant concentrations of N_2O (30 minute exposure) increased phospholipid methylation in rat synaptosomes, which are isolated synaptic terminals from a neuron and are often used to study synaptic transmission [44]. Phospholipid methylation is a reaction in which phosphatidylethanolamine is converted to phosphatidylcholine (PtdCho) by PE-methyltransferase via three sequential methylations by S-adenosyl methionine [45]. Increased phospholipid methylation from N_2O mirrors PC synthesis induced from catecholamine stimulation, especially dopamine [46], which occurs with acute N_2O exposure [31]. These data augment other findings from infrared spectroscopy demonstrating sites of N_2O-lipid interaction, especially in an aqueous solution of PC vesicles [47], as well as N_2O-induced reduction in the phase transition in smectic mesophase of dipalmitoyl PtdCho by 0.58° C/atm [48]. These effects are consistent with the elemental thermodynamic description of anesthetics, including N_2O, as freezing point depressants.

However, under conditions of prolonged exposure to N_2O, both S-adenosyl methionine levels and vitamin B12 are reduced [10,49], theoretically compromising endogenous synthesis of PtdCho by methylation [50]. Moreover, brain dopamine levels, especially in the mesolimbic pathway, are dramatically reduced under subchronic, trace N_2O exposure [51], indicative of activation of the KOR/DYN system. Alford et al. [52] clarified DYN interactions with phospholipid membrane, demonstrating that dynorphin A (1-17) induces leakage from phosphatidylserine and PtdCho vesicles. Fagone and Jackowski reviewed the cytidine diphosphocholine pathway of PtdCho biosynthesis and concluded that "serum PtdCho or lysoPtdCho provide substantial amounts of phospholipid for cells and can provide the choline in serum-based cell culture models to buffer against depletion of free choline" [53], a phenomenon that occurs in N_2O-exposed subjects [54]. Indeed, the argument of "autocannibalism" of choline-containing membrane phospholipids in AD as a means of free choline restoration has been put forward previously [55], albeit without the critical link to environmental N_2O as the precipitating factor of choline dysregulation via endogenous DYN release [56]. In some cases, this "autocannibalism" may rescue choline status during AD progression [55], although the meta-analytic evidence from De Wilde et al. [4] suggests such compensatory mechanisms may still be insufficient in most AD cases.

3. Dysregulated nutrient status

In addition to modulation of apoptotic pathways, a review of the case literature indicates that N_2O is associated with depletion of vitamin B12 and disruption of the folate-mediated one carbon metabolic pathway [20]. In this pathway (Fig. 2), a carbon unit from serine or glycine is

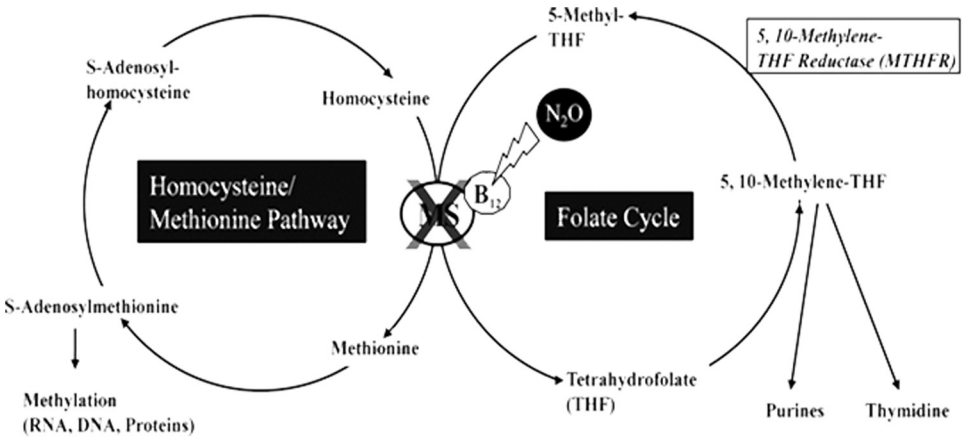

Fig. 2. A schematic showing N_2O-induced inactivation of methionine synthase in the folate-mediated one carbon metabolic pathway. (Figure from [57])

transported to tetrahydrofolate (THF), which yields methylene-THF, a key endogenous one-carbon donor for the synthesis of thymidine, which is incorporated into DNA. Methylene-THF can also be reduced to 5-methyl-THF by methylenetetrahydrofolate reductase (MTHFR gene) which can be used to methylate homocysteine to form methionine. The latter reaction, along with simultaneous conversion of 5-methyl-THF to THF, is catalyzed by a B12-containing methionine synthase. The N_2O-induced inactivation of methionine synthase putatively disrupts maternal and embryonic folate metabolism in rats, with a significant reduction in nonmethylated folate in embryonic tissues [58]. Plasma folate increases have been recorded in rats and humans during N_2O exposure, but this is followed by a fall in folate levels, presumably due to excretion or normal host catabolism [59], which can be prevented by dietary and/or supplemented forms of folate. Elderly subjects with reduced levels of both vitamins have doubled AD risk [60], indicating that consideration of exposures capable of modulating both of these biochemical parameters is warranted in AD research.

To further investigate these possible links, we used the GAAIN Interrogator tool to understand whether vitamin B12 deficiency, a deleterious toxicity from N_2O, is more common in patients with AD versus normal cognitive controls [61]. The three cohorts that we extracted from the National Alzheimer's Coordinating Center (described previously [62]), are based on diagnosis and include MCI, AD, and normal cognitive functioning. Because our preliminary analyses thus far have indicated a relationship between anthropogenic farm nitrogen (greatest source of environmental N_2O) and age-adjusted AD mortality, and N_2O is clinically implicated in B12 deficiency, we expected to replicate previous findings that B12 deficiency increases AD risk [60].

The odds ratios presented in Fig. 3 show increased odds of B12 deficiency among subjects in the AD cohort (cases) in the National Alzheimer's Coordinating Center data set, compared with normal cognitive functioning and MCI cohorts (controls). This finding confirms previous research of a link between low B12 and dementia risk. However, linear regression analysis using clinically diagnosed patients

Variables	Analysis	Controls	Cases	Odds Ratios	P Value
Age	B12DEF - MCI vs AD	avg = 73.64	avg = 75.38	1.02 (1.01 to 1.02)	P<0.001
	B12DEF - NL vs AD	avg = 71.26	avg = 75.38	1.04 (1.04 to 1.04)	P<0.001
B12DEF	B12DEF - MCI vs AD	avg = 0.07	avg = 0.08	1.12 (1.02 to 1.24)	0.02
	B12DEF - NL vs AD	avg = 0.05	avg = 0.08	1.30 (1.19 to 1.42)	P<0.001
Subjects:	B12DEF - MCI vs AD	n = 7,312	n = 9,400		
	B12DEF - NL vs AD	n = 13,305	n = 9,400		

Fig. 3. The logit model results (GAAIN output screenshot) show greater odds of B12 deficiency among subjects diagnosed with AD compared with those subjects diagnosed with mild cognitive impairment (MCI) or normal cognitive subjects (NL).

with AD (N = 19) from the Layton Aging & Alzheimer's Disease Center does not support a link between increasing plasma B12 and scores on the Mini-Mental State Examination, suggesting that B12 is not correlated with the level of cognitive impairment in subjects with AD. The small sample size limits any conclusion that can be drawn. Although, an evidence-based analysis suggests that vitamin B12 treatment does not significantly improve cognitive function in patients with dementia regardless of B12 status [63]. Cumulatively, these GAAIN data show that the odds of B12 deficiency are significantly higher in AD, although the extent to which such deficiency contributes to the cognitive decline in this disease is not clear and may be incidental.

4. Considerations for future research

We earlier proposed that individual genetic susceptibility (APOE ε4/ε4) to environmental drivers of N_2O emissions may be associated with age-adjusted AD mortality, and this link is consistent with the nutritional and lipodome phenotypes that ostensibly manifest in AD. We have repeatedly recommended that efforts be undertaken to begin monitoring environmental emissions of N_2O as a risk exposure in the development of dementias and co-occurring changes in lipid metabolism and blood nutrient status, specifically vitamin B12 and folate.

Although we are aware of a great deal of research endeavoring to understand the role of environmental N_2O as a greenhouse gas pollutant in global climate change, virtually no effort has been made to quantify human exposure, even though preclinical study reveals significant neurochemical changes occur from trace long-term N_2O exposure. Such data are needed to further investigate our proposed hypothesis and could better clarify the inconclusive epidemiological literature on AD risk and air pollution [64]. Given the lack of exposure assessments currently available and preliminary evidence from the E.P.A. of "considerable" street-level N_2O emissions in Ohio [65], our current efforts seek to follow-up on the recommendations of other researchers by undertaking an appropriate program of individual-level N_2O monitoring using state-of-the-art, high-resolution infrared laser technologies [66].

One suggestion we have is to conduct a longitudinal investigation (1 year) using these monitors at an individual (adult) level and associating seasonal N_2O emission exposures with psychometric assessment of ADHD symptoms. Our previous work has focused specifically on ADHD [5–7]—a neurodevelopmental disorder often diagnosed in childhood that is also characterized by altered lipodome, changes in B12 [67,68], as well as tau accumulation [69]. Our main hypothesis to be tested is supported with recent evidence linking ADHD with both agricultural and combustion sources [70]. Then, these individuals could be followed up for several decades to test the second hypothesis that higher level of N_2O exposures earlier in life increases AD risk in later life. Such data could clarify the question about whether these two conditions do, in fact, represent a possible continuum of brain degeneration over the lifespan [71], perhaps due to chronic exposure to environmental N_2O. Related to this line of inquiry, we recommend that further study specifically focus on the presence of the aforementioned AD changes in early neuropsychiatric correlates of AD. Moreover, long-term prospective studies should also attempt to follow-up operating room personnel to observe whether an increased AD incidence occurs in such populations, in addition to the increased risks of headache, dizziness, tachycardia, oxidative damage/stress, and vitamin B12 deficiency that have already been documented from chronic exposure to trace anesthetic gases, such as N_2O.

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RESEARCH IN CONTEXT

1. Systematic review: The current editorial discusses findings from a recent meta-analysis conducted by De Wilde et al. [4] showing altered nutrient status in Alzheimer's disease (AD).
2. Interpretation: Findings from the meta-analysis are integrated into an etiopathological framework suggesting that the age-dependent, non-opioid toxicity induced by chronic exposure to trace emissions of nitrous oxide (N_2O) facilitates amyloidogenesis.
3. Future directions: Future work should entail a comprehensive environmental monitoring program of N_2O emissions as well as prospective cohort studies assessing AD risk among operating room personnel chronically exposed to trace anesthetic gases, specifically N_2O.

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