Tau Protein Levels in ADHD

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To the Editor,

Alzheimer's disease (AD) is a progressive neurodegenerative condition that comprises the most common cause of dementia. In developed economies, AD is a leading cause of mortality and, while a majority 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. 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. These manifestations are thought to contribute to the degradation of neurons over time and the onset of disease symptoms. Emerging epidemiological and cohort studies have begun to illuminate early neuropsychiatric correlates of dementia risk, including attention-deficit hyperactivity disorder (ADHD).

Cetin and Simsek [1] evaluated serum levels of neurodegenerative molecules, including α -synuclein and tau, in children with ADHD compared to controls. Using ELISA, the authors showed that serum tau protein levels were elevated in ADHD, although α -synuclein levels were not statistically significantly different between the two groups [1]. Prior epidemiological work linked dementia pathology with antecedent ADHD, a common neuropsychiatric disorder that is characterized predominantly by

cognitive impairments in sustained attention and behavioral dysregulation, including hyperactivity and impulsivity [2]. These studies provide both population-based and case-control evidence linking ADHD and dementia risk. To further elucidate this apparent neurobiological connection, we integrate into the discussion an environmental factor that has previously been implicated in ADHD etiopathology. Increasing environmental exposure to anthropogenic nitrogen (as the greatest source of, and therefore the best proxy for, unmeasured emissions of the agricultural and combustion air pollutant, nitrous oxide, N_2O) has been linked to healthcare utilization for severe ADHD pathology [2]. A review highlighted several pathophysiological mechanisms by which trace environmental exposure to the agricultural and combustion pollutant, N_2O , may increase risk for ADHD, including action upon glutamatergic (N-methyl-D-aspartate receptor antagonism), opioidergic (kappa family opioids), cholinergic systems ($\alpha 7nAChR$), and mesolimbic dopaminergic stimulation [2]. Clinical reports link trace N_2O exposure with impairments in working memory and attention-related processing. Pre-clinical studies in mice reveal deficits in striatal dopaminergic transmission, a key pharmacological target in ADHD psychostimulant therapy, from sub-chronic exposure to trace levels of N_2O [2]. Moreover, chronic psychostimulant exposure at pharmacologically relevant levels in rats alters brain apoptosis signaling pathways, including modulation of caspase-3 activation (a cysteine-aspartate protease that acts upon specific substrates for proteolysis), implicating caspase 3 overactivation in ADHD etiopathology [3].

Population-based studies indicate that repeated general anesthesia exposures may induce neurotoxic mechanisms and thereby elevate dementia, including AD and Lewy body dementia (LBD) risk [2]. Molecular evidence shows

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significant increases in caspase-3 activation from treatment with a combination of 70% nitrous oxide (N₂O) and 1% isoflurane for 6 h induced caspase-3 activation. Interestingly, N₂O alone also markedly increases caspase-3 activation in H4 naïve cells stably-transfected to express full-length amyloid precursor protein (APP), but there was no evidence of apoptosis and increased A β levels [4]. Though, APP over-expression in SH-SY5Y and primary cultured neurons leads to increased protein and mRNA levels of α 7 nicotinic acetylcholine receptors (α 7nAChR), a pentameric ligand-gated ion channel present in the central nervous system and also a part of the non-neuronal cholinergic system (i.e., immune cells) [5]. As low-dose N₂O exposure has been shown to reversibly inhibit ACh-induced currents of recombinant human α 7nAChR [6], the effect of N₂O on caspase-3 activation without evidence of apoptosis or A β deposition in H4-APP cells suggests that APP overexpression-induced α 7 modulation may compensate for N₂O-mediated α 7nAChR inhibition, consistent with clinical reports of enhanced α 7 in AD brain [2]. In other words, N₂O induces caspase-3 activation, which is associated with impaired α 7nAChR signaling along with amyloid- β 1-42-induced tau phosphorylation and neuroinflammation. In this sense, impaired α 7nAChR action is the requisite link between N₂O-induced caspase-3 activation and potential amyloidogenesis and tau accumulation [7]. Therefore, in vitro AD models (i.e., APP overexpression) wherein α 7nAChR is upregulated or otherwise modulated would reveal null findings on N₂O-induced amyloidogenesis and tau accumulation. This is a critical methodological point to address since activated caspase-3 immunoreactivity is elevated in AD brain and co-occurs with neurofibrillary tangles and plaque formation.

Since population-based [2] and molecular studies [4] have now linked N₂O exposures to risk of dementia pathobiology, we propose that trace environmental N₂O exposure mediates the link between antecedent ADHD and later dementia risk. The neurobiological basis for the link, specifically concerning tauopathy, relies upon in vitro evidence of N₂O-induced caspase 3-mediated α 7nAChR dysregulation in both neuronal and non-neuronal cell populations. But, this mechanism may be unique to AD since other dementia subtypes do not show alterations in α 7nAChR [2]. Preclinical studies demonstrate altered catecholaminergic neurotransmission (i.e., dopamine) in brain stem from trace subchronic and intermittent N₂O exposure at 50 ppm (i.e., lowest exposure dose), with 2-week exposure significantly increasing brain stem dopamine and no difference in DA at 13-week exposures. Given the putative role of DA neuron physiology in synucleinopathies, the N₂O-induced biphasic changes in brain DA could reveal endogenous compensatory mechanisms to moderate initial dopaminergic stimulation. Activation of

opioidergic systems in mid-brain, specifically the kappa opioid receptors (KOR) which are primarily found in the CNS and are stimulated during N₂O exposure, reduces DA release in cultured rat neurons [8]. Though, synucleinopathies, including Parkinson's disease, show very low KOR mRNA levels [9]. This evidence suggests that endogenous compensatory mechanisms to modulate chronic N₂O-dopaminergic stimulation are flagging in synucleinopathies, perhaps due to innate disease processes, polymorphic variation in the gene that encodes KOR (*OPRK1*), or maturational changes in KOR physiology [10]. The lack of any difference found by Cetin and Simsek [1] in serum α -synuclein between ADHD children and controls is inconsistent with cohort studies demonstrating an increased risk of antecedent ADHD with a LBD diagnosis. Perhaps contrary to tau accumulation in ADHD, this suggests that endogenous mechanisms inducing synucleinopathies (i.e., KOR) are likely age-dependent and are, most critically, localized to neurochemical dysregulation in brain, thereby lessening the utility of peripheral biomarkers as an early diagnostic indicator of neurodegenerative processes.

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Compliance with Ethical Standards

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The author declares no conflict of interest.

References

1. Cetin I, Simsek S. A preliminary study on investigation of serum α -synuclein and tau protein levels in children with attention deficit hyperactivity disorder. *Indian J Clin Biochem.* 2017;32(3):285–91. <https://doi.org/10.1007/s12291-016-0602-9>.
2. Fluegge K, Fluegge K. Antecedent ADHD, dementia, and metabolic dysregulation: a U.S. based cohort analysis. *Neurochem Int.* 2018;112:255–8. <https://doi.org/10.1016/j.neuint.2017.08.005>.
3. Réus GZ, Scaini G, Jeremias GC, Furlanetto CB, Morais MO, Mello-Santos LM, et al. Brain apoptosis signaling pathways are regulated by methylphenidate treatment in young and adult rats. *Brain Res.* 2014;1583:269–76. <https://doi.org/10.1016/j.brainres.2014.08.010>.
4. Zhen Y, Dong Y, Wu X, Xu Z, Lu Y, Zhang Y, et al. Nitrous oxide plus isoflurane induces apoptosis and increases β -amyloid protein levels. *Anesthesiology.* 2009;111(4):741–52. <https://doi.org/10.1097/ALN.0b013e3181b27fd4>.
5. An Y, Qi XL, Pei JJ, Tang Z, Xiao Y, Guan ZZ. Amyloid precursor protein gene mutated at Swedish 670/671 sites in vitro induces changed expression of nicotinic acetylcholine receptors and neurotoxicity. *Neurochem Int.* 2010;57(6):647–54. <https://doi.org/10.1016/j.neuint.2010.08.001>.

6. Suzuki T, Ueta K, Sugimoto M, Uchida I, Mashimo T. Nitrous oxide and xenon inhibit the human (alpha 7)5 nicotinic acetylcholine receptor expressed in *Xenopus* oocyte. *Anesth Analg*. 2003;96(2):443–8.
7. Yu W, Mechawar N, Krantic S, Quirion R. $\alpha 7$ Nicotinic receptor activation reduces β -amyloid-induced apoptosis by inhibiting caspase-independent death through phosphatidylinositol 3-kinase signaling. *J Neurochem*. 2011;119(4):848–58. <https://doi.org/10.1111/j.1471-4159.2011.07466.x>.
8. Ronken E, Van Muiswinkel FL, Mulder AH, Schoffelemeier AN. Opioid receptor-mediated inhibition of evoked catecholamine release from cultured neurons of rat ventral mesencephalon and locus coeruleus. *Eur J Pharmacol*. 1993;230(3):349–55.
9. Yamada M, Groshan K, Phung CT, Yamada M, Hisamitsu T, Richelson E. The expression of mRNA for a kappa opioid receptor in the substantia nigra of Parkinson's disease brain. *Brain Res Mol Brain Res*. 1997;44(1):12–20.
10. Sirohi S, Walker BM. Maturational alterations in constitutive activity of medial prefrontal cortex kappa-opioid receptors in Wistar rats. *J Neurochem*. 2015;135(4):659–65. <https://doi.org/10.1111/jnc.13279>.