Does the Clinical Benefit of Ketamine Treatment Offer Any Clues to Autism Spectrum Disorder Etiology?

To the Editor: Wink et al[1] reported the first case study demonstrating clinical improvement in mood and eye fixation scores from intranasal ketamine treatment in a "complicated" subject with autism spectrum disorder (ASD). Arnold et al[2] recently highlighted perioperative differences among patients with or without ASD, finding that the most salient difference was the use of premedication types. ASD patients were 3 times more likely to use nonstandard premedicants (eg, intramuscular ketamine) versus standard medications (eg, midazolam). These studies suggest that ketamine, regardless of its delivery, may exert positive benefit in stressed ASD subjects, although the mechanism underlying this pharmacologic benefit is less clear, particularly given the oculomotor impairment often observed after ketamine administration, including gaze-evoked nystagmus.[3–5]

Consistent with other epidemiologic studies[6] suggesting an association between air pollution and ASD, I have previously proposed that early gestational exposure to the environmental air pollutant nitrous oxide (N_2O) may be the underlying etiology of ASD and similar neurodevelopmental conditions.[7] Others have noted that the μ-receptor agonist sufentanil relieved impairments in human lung function attributable to exposure to ozone, suggesting opioidergic activity may modulate the physiological response to similar air pollution exposures.[8]

Ketamine is similar to N_2O in terms of its physiological targets, including acting as both a κ-opioid receptor (KOR) full agonist and an *N*-methyl-D-aspartate (NMDA) receptor antagonist.[9] NMDA receptor antagonism has been shown to mitigate physical opiate dependence[10]; however, a psychological desire to seek the drug may persist given the drug's targeting of KORs,[11] confirming the involvement of multiple neurochemical substrates in the effects of N_2O exposure. KORs may be particularly relevant in ASD given that the receptor functionality remains intact in the μ-receptor knockout mice,[12] a genotype that displays autistic-like social deficits.[13]

Interestingly, Richardson and Shelton[14] were unable to demonstrate N_2O-like stimulus effects from midazolam administration, further supporting the hypothesis that nonstandard medications, like ketamine, may be preferentially used during stressful experiences in ASD populations due to their outstanding N_2O mimicry and satiation of an amplified dynorphin/KOR system developed in utero. Additional research is needed to understand which physiological mechanisms may be able to explain the increased use of nonstandard premedications, like ketamine, in ASD populations, as found by Wink et al[1] and Arnold et al.[2]

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