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FOCUS PAPER

NMDA Glutamate Receptor Antagonism and the Heritable Risk for Alcoholism: New Insights from a Study of Nitrous Oxide

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There is an urgent need for biomarkers of neuroadaptations to alcohol exposure and the risk for heavy drinking. In this issue, Walsh et al. (2016) present a provocative new finding: social drinkers (average consumption of approximately 21 drinks/wk) with a family history of alcohol dependence compared with drinkers without this family history show a shift in the reward valence of the response to nitrous oxide, whereby it is more stimulating (rewarding) and less sedating. What could this mean and why would understanding its significance help to deepen our understanding of the neurobiology of the risk for heavy drinking?

The current findings may provide additional insight into the role of N-methyl-D-aspartate glutamate receptors (NMDA-R) in alcohol dependence and the risk for heavy drinking (for review, see Krystal et al., 2003b; Trudell et al., 2014). NMDA-Rs are tetramers typically comprised of 2 GluN1 subunits and 2 GluN2 (2A-2D) subunits. The NMDA-R tetramer forms a channel permeable to cations, particularly calcium. Under resting conditions, the channel is typically blocked by magnesium ions. But, in a context where the coagonists (glycine, D-serine, D-alanine) are bound to the receptor and when the membrane is depolarized, perhaps by stimulation of neighboring AMPA-Rs, the magnesium block falls away and the binding of glutamate molecules to the NMDA-R complex opens the channel, producing excitation. There are many types of NMDA-R antagonists; some drugs compete with glutamate or the coagonists for binding (competitive antagonists and other drugs [uncompetitive antagonists: phencyclidine, ketamine, memantine]) bind to the open channels and prevent cation entry. A third class of substances, including ethanol and nitrous oxide, are allosteric modulators of NMDA-R activity. Ethanol appears to inhibit NMDA-Rs via binding to a pocket in the transmembrane domain of the GluN1, thereby reducing NMDA-R function. Nitrous oxide inhibits NMDA-Rs by binding to a site distinct from that of ethanol and other inhaled anesthetics (Ogata et al., 2006).

The Walsh et al. finding could be interpreted as suggesting that there is a type of cross-tolerance between biological factors associated with a family history of alcoholism and the effects of nitrous oxide. This observation would be consistent with other data suggesting that individuals with a family history of alcoholism are less sensitive to the intoxicating effects of NMDA-R antagonists including alcohol (Ramchandani et al., 1999) and ketamine (Petrakis et al., 2004; Yoon et al., 2016). Low alcohol response is a predictor of subsequent alcohol use disorders (Schuckit, 1994). As alcohol tolerance is associated with upregulation of NMDA-R function, the reduced familial sensitivity to alcohol, ketamine, and nitrous oxide may also reflect upregulation of NMDA-R function. This upregulation in NMDA-R function might increase the risk for heavy drinking by decreasing unpleasant effects of ethanol and reducing cues that normally serve to help people regulate their drinking (Krystal et al., 2003a). The latter part of this hypothesis is consistent with evidence that individuals tolerant to ethanol have difficulty accurately estimating their blood alcohol level, even when trained to do so (Lipscomb and Nathan, 1980).

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The reported increase in the ratio of stimulant to sedative effects in individuals with a family history of alcoholism reported in the Walsh et al. study replicates a finding previously reported for ketamine (Yoon et al., 2016). This may reflect enhancement of euphoric effects of ethanol attributable to its actions at NMDA-Rs. Before concluding that this is the case, one needs to make sure that this increase in euphoric effects is not simply a reflection of the reduction in dysphoria, i.e., that these two processes are statistically independent. Nonetheless, there appears to be evidence that NMDA-R antagonists (ketamine, phencyclidine, ethanol) may produce rewarding effects via both dopamine-dependent (Kegeles et al., 1999; Urban et al., 2010) and dopamine-independent (Carlezon and Wise, 1996; Krystal et al., 1999) mechanisms. Thus, it is possible that adaptations in other systems (cholinergic, GABAergic, etc.) might play a role in the enhanced euphoria associated with nitrous oxide administration in the study by Walsh et al.

The current study is particularly important, because clinical research rarely has access to the most selective agents to probe human biology. Ketamine, for example, binds to a number of sites in the brain besides NMDA-Rs (Hustveit et al., 1995). The observation that nitrous oxide, another NMDA-R antagonist, replicates differences in drug sensitivity in individuals differing by their family history of alcoholism found with ketamine helps to make a stronger case that these differences are mediated by their common action, i.e., NMDA-R antagonism. Consistent with this view, there is growing evidence that nitrous oxide shows efficacy for conditions where ketamine also shows efficacy, including neuropathic pain (Ben Boujema et al., 2015) and depression (Nagele et al., 2015).

Evidence of upregulation of NMDA-R function may have important implications for understanding the biology of alcoholism risk. NMDA-Rs are critical for reward-related neuroplasticity, and enhancement of this process may contribute to the hijacking of reward mechanisms during repeated exposures to ethanol. In addition, NMDA-R antagonists might play a role in the prevention of alcohol use disorders, as there is initial evidence that the NMDA-R antagonist memantine may normalize striatal reward signaling (G. Pearlson, unpublished observation) and reduce alcohol craving (Krupitsky et al., 2007; Krishnan-Sarin et al., 2015) in individuals with a family history of alcoholism. However, memantine does not appear to be effective in reducing alcohol consumption in alcohol-dependent patients (Evans et al., 2007; Krishnan-Sarin et al., 2015).

The Walsh et al. study chose a narrow and dichotomous criterion for distinguishing their subjects with and without a family history of alcoholism, i.e., the presence of an alcohol use disorder in one or more parents. It is challenging to quantify the true heritable risk for developing an alcohol use disorder within an individual. Estimates suggest that alcohol dependence has approximately 40% to 60% heritability (Kaprio et al., 1987; Dick and Bierut, 2006). Thus, in the Walsh et al. study, it is possible that the child of a parent with an alcohol use disorder history might drink heavily for reasons other than their inherited risk. Two common research strategies are employed to strengthen the association between inherited risk and various informative traits. The first approach is to study individuals from families where both a parent and one other first- or second-degree relative have an alcohol use disorder (Petrakis et al., 2004), building on the assumption that higher rates of alcohol use disorders within a family reflect a more potent heritable risk. The second approach is to recruit subjects from families with an array of alcohol use disorder densities and to examine the relationship between increasing familial risk, based on the number of first-degree and second-degree relatives with alcohol use disorder histories, and various dependent measures (Johnson and Pickens, 2001). From this perspective, the Walsh et al. study used a limited measure of family history, a parent with an alcohol use disorder, which did not enable them to identify people with the highest familial risk in their "family history positive" sample. This criterion also allowed individuals with other familial risks for alcohol use disorders to be included in their "family history negative" sample. Thus, the extent of the group differences in this study may underestimate the true magnitude of the impact of alcoholism family history on nitrous oxide response. Inadvertently, allowing individuals with mothers with alcohol use disorders into their study may have introduced another potential confound. Fetal exposure to alcohol produces an array of alterations in brain development that maybe related to impaired NMDA-R function some of which alterations in NMDA-R function (Toso et al., 2005; Goodfellow et al., 2016).

In summary, Walsh et al. have found evidence of increased euphoric responses and reduced dysphoric responses to nitrous oxide in individuals with a family history of alcohol dependence. These new data adds to evidence of altered NMDA-R function associated with the familial risk for developing alcohol use disorders. Further, these data may provide support for further exploration of roles that NMDA-R antagonists might play in the prevention of alcohol use disorders.

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