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Treating Addiction: Unraveling the Relationship Between *N*-acetylcysteine, Glial Glutamate Transport, and Behavior

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The study by Ducret *et al*. (1) in this issue of *Biological Psychiatry* is an important contribution to our understanding of the impact of glial glutamate transport restoration in addiction-related behaviors and offers insight into treatment of substance use disorders (SUDs) using *N*-acetylcysteine (NAC). Specifically, the authors found that NAC restored expression of the glial glutamate transporter (GLT-1), as well as increased sensitivity to punishment in animals given extended access to cocaine self-administration. Of note, the typical reduction in nucleus accumbens core GLT-1 after self-administered cocaine was found after "self-imposed abstinence" from cocaine in this study, rather than after experimenter-induced withdrawal, and this effect was access dependent. A reduction in GLT-1 also was found in the dorsolateral striatum. The NAC treatment regimen used to restore GLT-1 and reduce cocaine-related behaviors in this study was chronic (administered over the course of 23 sessions), and the dose used was lower (60 mg/kg) than that of some other preclinical studies [e.g., 100 mg/kg (2)], perhaps leading to biological levels more akin those that found in humans, given the poor bioavailability of NAC (3). The authors conclude that NAC aids in restoration of control over intake of cocaine after it is paired with a negative consequence (foot shock) by aiding in glutamatergic reorganization. Given the shift from ventral to dorsal striatum that has been found to underlie the development of compulsive drug seeking, the logical progression from the conclusions of this study is that NAC treatment may aid in the reversal of this shift to allow control over drug seeking to be re-established.

Despite some recent developments in the treatment of SUDs, a significant number of individuals fail to maintain long-term abstinence, and relapse rates remain high. NAC has become a promising pharmacotherapy in the treatment of many psychiatric disorders, including bipolar disorder, SUDs, Alzheimer's disease, and trichotillomania, among others (4). This compound has shown translational relevance in the treatment of addiction at both the clinical and preclinical levels of analysis across different drug classes. Importantly, NAC is Food and Drug Administration-approved for use in acetaminophen overdoses and has antioxidant properties attributed to its impact on glutathione (5,6). These aspects of NAC increase its viability as a useful pharmacotherapy because it has proven to be a safe, well-tolerated compound in the treatment of various disorders. The popularity of NAC as a

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pharmacotherapy to treat several aspects of SUDs has grown because it presents a somewhat novel approach in treating SUDs (restoration of drug-induced neuroadaptations rather than replacement therapy), and the effects of NAC on reinstatement of drug seeking seem to be long lasting (7). In addition, and perhaps most importantly, the mechanisms by which NAC exerts its antirelapse effects has been shown to be through reversal of drug-induced neurobiological changes that underlie drug use and craving.

Although NAC has shown promise and its mechanisms of action as an addiction therapeutic have begun to be uncovered, this compound has shown somewhat checkered success clinically (8). Interestingly, there seems to be a parallel between the preclinical study by Ducret *et al.* (1) and the clinical trial reported by LaRowe *et al.* (8). Although NAC shows efficacy in reducing drug seeking after extended periods of withdrawal [a number of preclinical studies have examined the impact of NAC on reinstatement of drug seeking and the underlying neurobiology after two weeks of withdrawal with extinction training (2,9)], it seems that treatment with NAC while individuals are not abstaining from drug use (or in the case of Ducret *et al.*, "self-imposed abstinence" for a few sessions when paired with punishment) may not be an effective treatment strategy for maintaining long-term drug abstinence. In the study by Ducret *et al.*, animals were administered NAC chronically while self-administering cocaine, which did not decrease cocaine intake. In fact, animals escalated drug use, which has been argued to be a model of dysregulated drug intake. Thus, this study showed that NAC treatment does not inhibit the progression from acquisition to dysregulation of drug use thought to underlie the transition to addiction, despite their results showing that NAC impacted neurobiological outcomes. Assuming that the extended access model of addiction is a valid mime of the transition from regulated to dysregulated drug use in SUDs and that this transition does indeed lead to a neurobiological shift from ventral to dorsal striatum, it seems that NAC does not inhibit this neurobehavioral transition, despite being administered concurrently with escalated drug use.

An interesting finding in the Ducret *et al.* (1) study is that long-term administration of NAC can augment cocaine intake while punishment is delivered concurrently with the drug. It should be noted, however, that animals in the long access group did resume prepunishment cocaine-taking behavior after the punishment sessions, and a trend appears in the short access group as well. Despite the ability of NAC to decrease drug taking when paired with punishment, it remains unclear if these results actually indicate that NAC restored control over cocaine self-administration or if NAC-treated animals were slower to learn that lever pressing no longer led to punishment. As well, Ducret *et al.* report the characteristic reduction in nucleus accumbens core GLT-1 after cocaine and the ability of NAC to restore it. Interestingly, the results in this study indicate that GLT-1 is restored via NAC while cocaine taking is ongoing. Recently, nucleus accumbens core GLT-1 has been shown to underlie the ability of NAC to reduce reinstatement of cocaine seeking after withdrawal with extinction (2). Despite the NAC-induced restoration of GLT-1 reported in Ducret *et al.*, however, NAC-treated animals still resumed prepunishment levels of cocaine taking. In combination with studies showing inconsistent efficacy of NAC in the treatment of SUDs clinically, these results lead to questions regarding the relationship between NAC and GLT-1 and whether restoration of GLT-1 can treat all aspects of drug addiction. Perhaps GLT-1 is not the mechanism by which NAC exerted its ability to augment cocaine-taking behavior

while in the presence of a punisher, even though it was upregulated in these animals compared with vehicle treatment. Indeed, although the mechanisms by which NAC inhibits drug-seeking behavior currently are a subject of intense study and GLT-1 seems to be a primary candidate as its neural substrate, it remains unclear how NAC restores glial expression of GLT-1 given that it interacts with the glial cystine-glutamate exchanger as a cystine prodrug (10). GLT-1 is downregulated after chronic use of cocaine and is reversed by NAC at both early and late withdrawal points. However, in late withdrawal, the restoration seems to impact addiction-related behaviors more readily. Although NAC holds promise as an effective pharmacotherapy in the treatment of addiction, both clinical and preclinical studies indicate that caution should be taken when designing a treatment protocol, because it may impact drug use cessation outcomes. Although these findings indicate that treatment regimen may play an important role in promoting drug use cessation, the study by Ducret *et al.* indicates that the behavioral relevance of the relationship between GLT-1 and NAC remains elusive. Thus, the results reported in this study are an important step toward our understanding of NAC as an effective pharmacotherapy in the treatment of SUDs and clarifies the necessity of future work to characterize more fully the biological and behavioral impacts of this therapeutic to better promote drug use cessation.

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