

Are Metabotropic Glutamate Receptors Promising Targets for the Treatment of Alcoholism?

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For several years pharmaceutical companies have been conducting research programs on the involvement of metabotropic glutamate receptors (mGluRs) in various psychopathological conditions, including drug addiction and alcoholism. These drug development programs have yielded interesting new compounds that selectively target the different groups of mGluRs. Some of these compounds might have promising potential for the treatment of alcohol-dependent patients—the hope is that they will reduce harmful alcohol drinking and assist in prolonging the duration of abstinence and thus decrease the likelihood of relapse. But whether the rationale for the efficacy of compounds targeting various mGluRs in alcohol-dependent patients is compelling and this hope is justified is uncertain.

A variety of ethanol's effects on the brain are inarguably mediated via the glutamate system, and thus *N*-methyl-D-aspartate (NMDA) receptors are one of the primary targets of ethanol (1). Due to this direct interaction of ethanol with the glutamate system, adaptive changes occur with repeated intermittent alcohol exposure. Some of these adaptive changes might even become persistent, and an allostatic shift toward augmented function of glutamatergic components might ultimately contribute to the transition into an addicted state. These assumptions have led to the formulation of the glutamate hypothesis of alcohol addiction, which suggests that enhanced glutamate-mediated neuronal excitability during withdrawal and protracted abstinence contributes to craving and relapse (1,2). However, on the basis of an examination of the facts contributing to this hypothesis, it remains unclear how glutamate and its associated components, such as transporters and receptors, function in the course of the transition into an addicted state. Furthermore, it is not known whether some of these components do in fact undergo persistent change and whether these potential changes are causally linked to craving and relapse. Hopefully, longitudinal human neuroimaging/genetics studies using within-subject designs in young people at risk for alcohol use disorders, such as that conducted by the IMAGEN consortium (3), or multimodal neuroimaging studies in small rodents undergoing drinking procedures that eventually result in compulsive alcohol-seeking and drinking behavior (4) will provide answers to these urgent questions. But, assuming that the glutamate hypothesis turns out to be true, it still remains to be determined whether the pharmacological targeting of mGluRs is a useful approach to developing clinically effective medications.

The mGluRs have evolved to regulate glutamate-mediated neuronal excitability (5), and the high expression patterns of Group I mGluR5 receptors (but not GluR1) and group II receptors (mGluR2 and mGluR3; note: expression levels are lower

compared with mGluR5) within the mesocorticolimbic system in fact make them ideal candidate targets to restore normal glutamatergic activity in the alcohol-addicted brain. Neuropharmacological studies have indeed provided substantial evidence that the activation of predominantly presynaptically located mGluR2/3 by various selective agonists (e.g., LY379268) attenuates ethanol-seeking behavior elicited by either stress or conditioned cues in the reinstatement paradigm (6) and reduces relapse-like drinking behavior in the alcohol deprivation model (V. Vengeliene, personal communication). Blockade of mGluR5—predominantly located postsynaptically—by the reference compound 2-methyl-6-(phenylethynyl)pyridine (MPEP) reduces ethanol-seeking in the reinstatement paradigm and relapse-like drinking behavior in the alcohol deprivation model (7).

Two reports in the current issue of *Biological Psychiatry* now support these initial findings and provide a deeper insight into the neuroanatomical substrates mediating mGluR2/3/5 effects on excessive alcohol consumption. Besheer *et al.* (8) did pharmacological mapping studies in alcohol-preferring P-rats—a well-defined genetic model of excessive alcohol consumption—by microinjecting MPEP and LY379268 into different brain sites (i.e., nucleus accumbens [NAC], dorsomedial caudate putamen, and the medial prefrontal cortex). Intra-NAC infusion of MPEP reduced operant ethanol self-administration in P-rats, whereas intracaudate or medial prefrontal cortex infusions were without effect. Intra-accumbal administration of LY379268 produced only nonspecific effects in the NAC, but this compound was not tested in the other brain sites. In conclusion, mGluR5 within the NAC should be seen as a critical anatomical locus for modulating excessive alcohol consumption. Furthermore, it is interesting to speculate that mGluR5 on medium spiny neurons (MSNs), which integrate mesoaccumbal dopamine and glutamatergic signals from cortical and limbic regions, might be the cellular correlate of this action. The MSNs can be divided into two functionally distinct populations—expressing either dopamine D1 or D2 receptors—and mGluR5 is densely expressed on both MSN populations. Examining animal models with selective deletion of mGluR5 in D1- or D2-MSNs will finally provide an indication of the precise cellular location of mGluR5-mediated effects on excessive alcohol drinking.

In another study, from the laboratory of Friedbert Weiss, the effects of LY379268 and MPEP on ethanol-seeking behavior in postdependent rats were examined (9). To describe the state of alcohol dependence-induced behavioral changes and neuroadaptations in experimental animals, the term postdependent state was introduced by Markus Heilig and George Koob. Importantly, one of the key characteristics of the postdependent state is its persistence even in the absence of the drug. As such, postdependent animals comprise a well-defined model for the clinical state of remission from or sequelae of alcohol dependence (10). In the current study by the Weiss laboratory, a leftward shift in the dose-response curve after LY379268 treatment but not after MPEP administration in the postdependent state was found. Thus, when postdependent rats were subsequently tested in the reinstatement paradigm, lower doses of the mGluR2/3 agonist

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LY379268 were already effective in reducing ethanol-seeking behavior when compared with nondependent animals.

The latter results favor mGluR2/3 activation as a treatment strategy for alcohol-dependent patients, because mGluR5 antagonism seems to be less potent. In addition, the primary reasons for dropping mGluR5 antagonists as potential therapeutics are the cognitive deficits repeatedly reported under mGluR5 blockade (2) as well as new findings by Thomas Tzschenke *et al.* They showed in rats that MPEP potentiated conditioned place preference induced by various addictive drugs (11) and was readily self-administered (12). The underlying mechanisms of the reinforcing effect of MPEP and its potentiating effect on drugs of abuse in the conditioned place preference paradigm are not fully understood, but pure selectivity for mGluR5 is not given—MPEP also acts on NMDA receptors (13). Interestingly, mGluR5 antagonists have properties similar to NMDA receptor antagonists, and it is therefore possible that the interaction with NMDA receptors might contribute to the observed rewarding and potentiating effects of MPEP. Whether this is a substance-specific interaction of MPEP with NMDA receptors or a direct physical mGluR5/NMDA receptor coupling as described previously (14) remains to be clarified. However, recent combined genetic analysis of variants of the NMDA receptor subunit NR2A and mGluR5 in alcohol-dependent subjects showed a synergistic effect, arguing for the latter explanation (15). Translating these assumptions into the clinical condition could mean that mGluR5 antagonism might yield alcohol substitution effects along with many unwanted side effects. Thus, only mGluR2/3 agonists likely have a promising therapeutic potential for the treatment of alcoholism, and the new findings by Markus Heilig *et al.* that alcohol-induced neurodegeneration and cognitive impairment in rats was prevented by LY379268 gives further support (16). In summary, these preclinical findings are clearly convincing enough to pursue clinical testing of an appropriate Group II mGluR agonist.

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