SY12-2
METABOTROPIC GLUTAMATE RECEPTOR SUBTYPE 2 AS A TARGET FOR RESEARCH AND TREATMENT OF ALCOHOLISM
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Excessive glutamatergic neurotransmission has long been implicated in the pathogenesis of alcohol use disorders but the neural mechanisms underlying the emergence and maintenance of addictive responses remain unknown. Here we review findings from multilevel analysis in both alcohol dependent patients and animal models that resulted in new insight into the molecular basis by which repeated alcohol intoxication causes a substantial and long-lasting reorganization of the medial prefrontal cortex, a structure that participates in executive functions.

Specifically, our research identified the infralimbic cortex as particularly sensitive to the long-term consequences of repeated alcohol intoxications. Alcohol dependent subjects lack metabotropic glutamate receptors of the mGluR2 type. We can directly link this deficit to escalated alcohol seeking because restoring mGluR2 levels in infralimbic projection neurons by focal virus-mediated gene transfer was sufficient to completely abolish the excessive seeking response. Loss of infralimbic mGluR2 also partially accounts for executive deficits. The translational value of the findings from experimental animals is supported by data from human postmortem brains showing a reduction in mGluR2 expression in a corresponding PFC region of alcoholics.

Thus, our translational studies suggest that mGluR2 loss in rodent and human neural circuits may be a major consequence of alcohol dependence causing failure in inhibitory self-control and thereby increased propensity to relapse. Normalization of mGluR2 function within this brain circuit may be of therapeutic value.