Dopamine D3 receptor gene deletion or D3 pharmacological antagonism counteracts alcohol intake in mice

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Mesolimbic dopamine controls drug and alcohol seeking behavior. Stimulation of dopamine D_3 autoreceptor reduces extracellular levels of dopamine. We tested the hypothesis that dopamine D_3 receptor (D_3R) gene deletion or its pharmacological blockade counteracts alcohol preference and intake in a long-term voluntary ethanol intake paradigm. Mice $D_3R^{-/-}$ and their wild type (WT) littermates, treated or not with the D_3R antagonists U99194A and SB277011A, were tested. The selectivity of the D_3R antagonists was further assessed by molecular modeling. Activation of dopamine (DA) transmission and D_3R expression was assessed at the end of the experiment. After 8 days, daily ethanol intake was negligible in $D_3R^{-/-}$ and robust in WT; this behavior was stably maintained for 44 days. Treatment with D_3R antagonists counteracted ethanol intake in WT and was associated to increased DA transmission (assessed as phosphorylation of DARPP-32 and GSK3β) in striatum and prefrontal cortex. Forced ethanol intake increased the expression of RACK1 and BDNF in both WT and $D_3R^{-/-}$; in WT there was also a robust overexpression of D_3R. Thus, increased expression of D_3R associated with activation of RACK1/BDNF seems to operate as a reinforcing mechanism in voluntary ethanol intake. Taking into account that ethanol intake increases mesolimbic DA, low levels of extracellular DA resulting from D_3R overexpression would facilitate ethanol intake, and high levels of extracellular DA, from either gene deletion of D_3R blockade, would inhibit ethanol intake. Thus, modulation of DA mesolimbic pathway by selective targeting of D_3 receptor might provide a basis for novel weaning treatments in alcoholism.