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Under the influence

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We all know that consumption of alcohol can lead to changes in mood, cognition and motor behaviour, but how ethanol affects neuronal function is not so well understood. A new study shows that ethanol inhibits clearance of the neurotransmitter serotonin (5-HT) from the extracellular fluid in the mouse hippocampus, and that, surprisingly, this occurs through a mechanism that is independent of the serotonin transporter (5-HTT).

Ethanol increases extracellular levels of 5-HT in the forebrain, including the hippocampus, but whether this occurs through stimulation of 5-HT release or inhibition of its clearance was previously unknown. Growing evidence of abnormal 5-HTT function in cases of alcoholism has led to the suggestion that ethanol might act as an antagonist of the 5-HTT, thereby elevating levels of extracellular serotonin through inhibition of its clearance. Moreover, both 5-HT and the hippocampus have been implicated in mediating the behaviours that are altered following alcohol consumption.

By directly measuring 5-HT clearance from the extracellular space in the CA3 area of the hippocampus, Daws *et al.* show for the first time that physiologically relevant (moderately intoxicating) doses of ethanol — either locally applied or systemically administered — produce a concentration-dependent inhibition of this process.

If this effect of ethanol is mediated by antagonism of the 5-HTT, then inactivation of the 5-HTT, which normally leads to inhibition of 5-HT clearance, should prevent any additional effect due to ethanol. To their surprise, the authors found the opposite: genetic inactivation of *5-HTT* exacerbated the clearance-inhibiting effect of ethanol in a *5-HTT* genotype-dependent manner, with inhibition occuring at lower doses of ethanol and extracellular 5-HT levels taking longer to return to baseline in *5-HTT*-knockout mice compared with wild-type mice.

When both ethanol and the 5-HTT antagonist fluvoxamine were administered to wild-type mice, either locally or systemically, the inhibition of extracellular 5-HT clearance was greater than with either drug alone. Together with the genetic findings, these data led the authors to suggest that the 5-HTT can partially compensate for the clearance-inhibiting effect of ethanol, but that another site of action is primarily responsible for mediating this effect.

This work clearly establishes that blocking the removal of 5-HT underlies, at least in part, the effects of ethanol in the brain. It remains to be determined exactly how ethanol inhibits 5-HT removal from the extracellular fluid. The noradrenaline transporter, which also transports serotonin and is expressed in the hippocampus, is one candidate site of action. However, more work will be required to confirm a role for this transporter in the influence of alcohol on neuronal function and behaviour. These findings could help to explain the positive association between a polymorphism in the promoter region of human *5-HTT*, which confers low-expression of *5-HTT*, and alcoholism.

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ORIGINAL RESEARCH PAPER Daws, L. C. *et al.* Ethanol inhibits clearance of brain serotonin by a serotonin transporter-independent mechanism *J. Neurosci.* **26**, 6431–6438 (2006)