P.712 Ketamine reduces alcohol consumption in hazardous drinkers by interfering with the reconsolidation of drinking memories: Preliminary findings

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Background: In harmful drinking and alcohol use disorders, maladaptive reward memories linking environmental cues and the availability/effects of alcohol imbue alcohol-associated cues with the ability to trigger craving, motivated alcohol seeking and ultimately relapse [1]. A new translational treatment paradigm aims to reduce harmful drinking by directly weakening these during their reconsolidation [2]. During reconsolidation, consolidated memories briefly destabilise or reactivate following retrieval in order to update before restabilising or reconsolidating. It is well established that restabilisation requires NMDAR signalling [3] and that NMDAR antagonists can weaken reactivated reward memories by preventing their reconsolidation. However to date there has been no applied assessment of this approach in humans. We therefore examined whether a single-dose of NMDAR antagonist ketamine, following reactivation of drinking memories, could reduce alcohol consumption in hazardous drinkers.
Methods: Ninety hazardous beer drinkers (regularly consuming >40 UK units/weeks, scoring >10 on the Alcohol Use Disorders Identification Test, but not seeking treatment for AUD) were randomised to one of three conditions: Retrieval of drinking memories with ketamine (**RET+KET**), or placebo (**RET+PBO**), or ketamine without alcohol memory retrieval (**No RET +KET**). Participants completed assessments of alcohol use (Timeline Follow-Back) On Day 1 (baseline). On Day 2 (manipulation), participants retrieved alcohol memories (**RET**) or control memories (**No RET**) prior to a 30 minute infusion of racemic ketamine (**KET**) or matched saline (**PBO**), double-blind, at a blood concentration of 0.35mg/ml for 30 minutes. On Day 3 (test; Day 2 + 1 week) participants re-completed baseline assessments. Remote follow-up assessments of drinking were performed at 1 and 3 months following manipulation.
Results: Between the baseline and test periods, a highly significant decrease in number of drinking days was seen in the **RET+KET** group only [$F(1.86) = 10.585$, $p = 0.002$, $np2 = 0.11$], with a significant Group x Time interaction [$F(2.86) = 3.689$, $p = 0.029$, $\eta p2 = 0.08$.] Correspondingly, large decrease in total alcohol consumption was seen in **RET+KET** [$F(1.86) = 23.269$, $p < 0.001$, $np2 = 0.213$]. A significant, but smaller reduction was seen in **No RET + KET** [$F(1.86) = 8.67$, $p = 0.004$, $np2 = 0.092$] and a no significant change was seen in **RET + PBO** [$F(1.86) = 2.904$, $p = 0.092$, $np2 = 0.033$]. The Group x Time interaction was at trend level [$F(2.86) = 2.729$, $p = 0.071$, $np2 = 0.06$]. The reductions in alcohol consumption were maintained at the 1 and 3 month follow-up time points.
Conclusions: This preliminary evidence is the first, to our knowledge, to show that single-dose ketamine following the retrieval of alcohol memories, produces lasting reductions in alcohol consumption in hazardous drinkers. In the current and previous studies [4] ketamine alone was found to reduce drinking levels, the simple retrieval of alcohol memories prior to ketamine infusion greatly potentiated these effects. These findings are commensurate with successful blockade of alcohol memory reconsolidation and are highly encouraging for the clinical development of this approach in alcohol use disorders.

References

[1] Hyman, S.E., Malenka, R.C., Nestler, E.J., 2006. Neural mechanisms of addiction: the role of reward-related learning and memory. Annu Rev Neurosci 29, 565–598.
[2] Kamboj, S.K., Das, R.K., 2017. Behavioral and pharmacological strategies for weakening maladaptive reward memories: A new approach to treating a core disease mechanism in tobacco use disorder. JAMA Psychiatry 74. doi: 10.1001/jamapsychiatry.2016.3937.
[3] Milton, A., Schramm, M.W., Wawrzynski, J., Gore, F., Oikonomou-Mpegeti, F., Wang, N., et al., 2012. Antagonism at NMDA receptors, but not β-adrenergic receptors, disrupts the reconsolidation of pavlovian conditioned approach and instrumental transfer for ethanol-associated conditioned stimuli. Psychopharmacology (Berl) 219, 751–761.
[4] Krupitsky, E.M., Grinenko, A.Y., 1997. Ketamine psychedelic therapy (KPT): A review of the results of ten years of research. J Psychoactive Drugs 29, 165–183.

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P.713 Fatal overdose in recently detoxified Russian HIV-positive persons with opioid use disorder: The role of naltrexone in prevention

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Background: Detoxification and abstinence from opioids increase the risk of opioid overdose due to the loss of tolerance. Long-term naltrexone treatment also leads to