How much alcohol is in ketamine`s antidepressant response?

The rapid and robust antidepressant action following a single intravenous sub-narcotic ketamine infusion (usually 0.5 mg/kg over 40 minutes) in the treatment of resistant major depression is unique and encouraging, albeit short-lasting (up to 7 days). Increasing clinical trials have addressed this disadvantage by investigating the effects of repeated ketamine-applications and different dosing-regimes. As yet, these studies and follow-ups are still too short-lasting to get useful information about the abuse and neurotoxicity liabilities of ketamine which itself has driven several waves of abuse since the late 1960ies. Thus, it is unclear whether ketamine can be addictive also in depressive patients without a substance abuse history.

At this juncture, we can look at a couple of pharmacological features ketamine is sharing with alcohol. All of which are parts of a cascade that precipitates enhanced synaptogenesis and connectivity in cortico-limbic networks and are assumed to be involved in the mechanism of ketamine`s rapid antidepressant response (AR): i) non-competitive antagonism of glutamatergic NMDA-receptors, ii) disinhibition of pyramidal cells producing an extracellular glutamate surge iii) amplification of glutamate non-NMDA receptor- and downstream mTORC1-signaling pathways (notably responding to most sorts of biological stresses), iv) increase of neurotrophins (BDNF, NGF). When ethanol vapor is repeatedly applied to rodents, their prefrontal pyramidal neurons develop an increase in dendritic spine density in the first abstinence days, which may resemble the synaptic remodeling observed after a single sub-anesthetic ketamine pulse. While the first is interpreted to reflect plasticity changes of burgeoning addiction, is the second shown to reverse chronic-stress-mediated decreases in spine density and assumed to represent the morphologically of AR. Do a few ethanol pulses work similarly `refreshing´ (rebalancing) on stressed spines of a non-addicted brain? Notably, low ethanol doses are followed by antidepressant-like effects in Porsolt`s swim test on mice. Theoretically, ethanol`s AR might have been weaker than that of ketamine considering ethanol´s weaker antagonism of NMDA-receptors and stronger stimulation of GABA-A-receptors. In this vein, primarily depressed alcohol dependents had reported an improvement of their depressive state after a few glasses of beer or wine, which then lasted for some abstinent days (ethanol`s AR?), however, only in the beginning of their drinking career. To cope with depression sustainably, these patients gradually increased the frequency and amount of alcohol intake, which resulted in hangover and tolerance to ethanol`s putative AR. Once addicted, aversive withdrawal symptoms, craving and alcohol seeking behavior occurred in these patients, which worsened their depression and fueled more frequent or continuous drinking. Is this a negative scenario for ketamine, too?

Abstaining alcohol dependents have lower limbic brain glutamate concentrations than normal controls, suggesting a long-term adaptation to too many glutamate surges alongside harmful drinking. Can this also happen to the brain when ketamine is frequently applied, thus, arousing an aberrant learning process, such as addiction? Moreover, prolonged intake of either ethanol or

ketamine is associated with gene expression of specific NMDA-receptor subunits, sustained inhibition of synaptic long-term potentiation and decreasing levels of neurotrophins, all of which related to an addicted brain and precursors to neurotoxicity.

Ketamine and ethanol are good examples for psychoactive drugs, whose wanted, even therapeutic effects (e.g. AR) may silently turn to adverse effects (e.g. addiction, neurotoxicity) after exceeding an individual critical amount and duration of intake. This seems to be based on their ability to use the same pathway to trigger cortico-limbic plasticity, which may drive the AR, but also tolerance and addiction. If at all possible, finding the optimal route of administration and dosing of ketamine to produce a sustained AR without inducing tolerance (even to ketamine`s AR) or addiction remains a big challenge.

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