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Review article

How much alcohol is in ketamine's antidepressant action?

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ABSTRACT

Ketamine is approved to start and maintain anaesthesia or analgesia. Ketamine is also known to be neurotoxic and an old drug of abuse. Numerous studies have proven a rapid and strong antidepressant response (AR) following parenteral sub-anaesthetic ketamine doses when applied the first time to patients with treatment resistant unipolar or bipolar major depression. This rapid and robust AR is encouraging, though short-lived (usually up to seven days). There is growing evidence that repeated und escalating ketamine administrations exert longer-lasting AR than single infusions. Yet, the clinical studies and follow-ups are still too short-lasting to get useful information about ketamine's liability to be addictive and neurotoxic after repeated or even prolonged administrations to severely depressed patients. In this vein, it could be worth to have a look at a couple of pharmacological features that ketamine shares with alcohol being presented here. In essence, there are striking similarities between ketamine and alcohol particularly in terms of modulating glutamatergic and dopaminergic signaling in cortico-limbic brain areas involved in learning, reward and mood regulation, thereby, probably mediating both, AR as well as the development of addiction. Moreover, moderate amounts of both drugs have comparable immunoinhibitory effects hypothesized to be involved in AR, too.

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1. Introduction

Ketamine is approved to start and maintain anaesthesia or analgesia [1]. Ketamine is also known to have psychotomimetic and neurotoxic (e.g. cortical atrophy) [2] properties and an old drug of abuse just undergoing a new wave in its spread [3,4]. Currently, ketamine's therapeutic quality is under careful observation, especially in terms of its value in the treatment of depression and suicidality [5,6]. A growing number of studies have verified a rapid and rigorous but transient antianhedonistic and antidepressant response (AR) occurring subsequent to sub-anaesthetic parenteral ketamine doses (usually a single ketamine infusion of 0.5 mg/kg over 40 min) in 50–80% of the cases when applied the first time to patients with treatment resistant unipolar or bipolar major depression [5,6]. However, there are also reports of response rates lower than 10% after the first infusion against treatment resistant depression [7]. Characteristically, AR emerged within the first hours after a single ketamine administration, peaked in the next 24 to 48 h and dissipated within the following 3 to 7 days [5,6]. Patients with anxious depression or a positive family history of an alcohol use disorder

Abbreviations: AR, antidepressant response; NMDA, *N*-methyl-D-aspartat; mTORC1, mechanistic target of rampamycin complex 1; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; GABA, gamma-amino-butyric acid; Na, natrium; Ca, calcium.

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were recently shown to have a somewhat longer lasting AR [8]. The rapid AR following one single intravenous sub-anaesthetic ketamine pulse against treatment resistant major depression is encouraging, even though short-lived, not free from bias [7] and most likely hazardous for patients with co-morbid substance use disorder [9,10]. There is some evidence that repeated and escalating ketamine administrations are more effective than single infusions and can be followed by a sustained AR, at least up to two weeks [7,11,12]. Twice- and thrice-weekly ketamine administrations were recently shown to be equally effective and well tolerated by treatment resistant depressed patients [13]. At this juncture, there is preliminary evidence of oppositional tolerance in AR after repeated ketamine administrations [14,15]. Yet, the clinical studies and follow-ups are still too short-lasting to get useful information about the liabilities of ketamine to be addictive and neurotoxic [3,4], even in severely depressed and not substance-abusing patients.

2. Similarities and differences between ketamine and alcohol effects

In this context, it could be worth to have a look at a couple of pharmacological features that ketamine shares with alcohol (ethanol). Some of which comprise the activation of parts of a cascade that precipitates enhanced synaptogenesis and connectivity in cortico-limbic networks, thus, being assumed to be crucially involved in the mechanism of ketamine's AR: [16,17] 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-signaling and downstream translational signaling pathways mediated by mechanistic target of rampamycin complex 1 (mTORC1), iv) increase of neurotrophins (brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF)) (c.f. [15,18]). In support, inhibition of mTORC1-dependent signaling e.g. by sirolimus being used for immunosuppression in transplant recipients is associated with the occurrence of depression or depressed mood [19]. Moreover, moderate intake of either alcohol or ketamine reduced the production of pro-inflammatory cytokines in humans [20,21] which have been related to AR in case of ketamine [22]. Increasing drinking can turn the immunoinhibitory effect of alcohol to its opposite [21,23] which awaits further study in case of escalating, repeated or prolonged ketamine dosing. However, there is a paucity of in depth studies that examine dose-dependent effects of alcohol and ketamine in depressed humans.

When ethanol vapor is repeatedly applied to rodents, their prefrontal pyramidal neurons develop an increase in dendritic spine density in the first abstinence days [24], which may resemble the synaptic remodeling observed after a single sub-anaesthetic ketamine pulse [16,17]. While the first is interpreted to reflect plasticity of burgeoning addiction [24], is the second shown to reverse chronic-stress-mediated decreases in spine density and assumed to represent the morphological expression of AR [16]. Would a few ethanol pulses work similarly 'refreshing' on stressed spines of a non-addicted brain? Remarkably, low ethanol doses are followed by antidepressant-like effects in Porsolt's swim test on mice [25]. Occasionally, depressed patients reported an improvement of their unrelenting state after a few glasses of beer or wine, which lasted for some abstinent days (alcohol's AR?), however, effectively only in the beginning of their drinking career [15,18]. To cope with depression more sustainably, these patients deemed to have gradually increased the frequency and amount of their alcohol intake which have increased the probability of hangover and tolerance against alcohol's putative AR, too [15,18]. One may speculate that alcohol's putative AR is weaker than that of ketamine as a result of alcohol's weaker antagonism of NMDA-receptors and stronger stimulation of GABA-A-receptors [1,26,27]. This could also account for the weaker dissociative potential of alcohol. Once addicted, aversive withdrawal symptoms, craving and alcohol seeking behavior occurred, which worsened the patients' depression and fueled more frequent or continuous drinking [15,18]. Increasing ketamine administrations against depression have been presumed to be burdened with a similar scenario [10].

On the other hand, there are some ketamine-specific effects that differentiate from alcohol, such as short elimination half-live [1,27], augmentation of tau-phosphorylation in animal cortices [28] as well as urinary tract toxicity [3], minor toxicity of metabolites and minor physical withdrawal symptoms in humans [3,29,30]. Characteristically, sub-anaesthetic ketamine administration is associated with dose-dependent sympathomimetic, psychedelic, dissociative, hallucinogenic and further psychotomimetic perceptions, which are not typical for alcohol intoxication [1,27]. On the other hand, healthy volunteers evaluated a usual sub-anaesthetic ketamine infusion to have subjective effects similar to 5 standard drinks [31], which are approximately three quarters a bottle of wine.

Abstaining alcohol dependents have lower limbic brain glutamate concentrations than normal controls [32], 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 giving birth to an aberrant learning process, such as addiction? Moreover, prolonged intake of either alcohol or ketamine is associated with gene expression of specific NMDA-receptor subunits, sustained inhibition of synaptic long-term potentiation and decreasing levels of neurotrophins (BDNF, NGF), all of which related to an addicted brain and being precursors to neurotoxicity (c.f. [15,18]). Both, alcohol and ketamine were also shown to modulate directly some ionic channel receptors (e.g. Na^+, Ca^{2+}) as well as opioid, cholinergic and especially dopamine neurotransmission in a similar vein, which are pivotally involved in learning, rewarding and mood regulation [1,15,18,27,33–37]. Notably, catecholamine populations including midbrain dopamine neurons were shown to co-release dopamine and glutamate [38] pointing to a close interaction of glutamatergic and dopaminergic cortico-limbic signaling.

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 their usage. Most likely, this is based on both drug's ability to use the same pathway to elicit cortico-limbic plasticity, which may drive the AR by network rewiring, but tolerance and addiction, too. If at all possible, finding the optimal dose, frequency and route of administration to evoke a sustained AR without inducing tolerance (even to ketamine's AR) and neurotoxicity remains a big challenge. Following a single pulse of ketamine, the profiles of gene expression alterations in the striatum and hippocampus of mice were found to be most similar to those after the administration of monoaminergic antidepressants or drugs of abuse, such as alcohol [39]. Nevertheless, some differences between the acute effects of sub-narcotic alcohol and sub-anaesthetic ketamine appear to exist in the functional connectivity of limbic and cognitive control networks [40,41]. For instance, the resting state connectivity of healthy subjects was found to be enhanced and decreased in parts of cortico-limbic pathways [40–42] measured within 0.5 h of ketamine and alcohol challenge, respectively. Notably, in case of ketamine, a preliminary study on patients with major depression found that this drug appeared to generally reduce connectivity at times removed from its acute effects (e.g. dissociation), regardless of whether the connectivity was abnormally high or low compared to controls at baseline [43]. A human study directly comparing the effects of acute and repeated ketamine and acute and repeated alcohol on the connectivity of cortico-limbic networks of depressed and non-substance abusing patients would be further enlightening.

Unquestionably, frequent at-risk drinking of patients with depression is reliably associated with worse clinical and functional outcomes [44,45]. This can apply for ketamine, too, when this drug's therapeutic actions have been already overridden by its adverse effects [15,18]. A simple and cautious 'real-world'-strategy would be to try to speed up the action of ongoing, but ineffective antidepressant treatment by only a few ketamine applications. In depth studies on this subject are on the way. Preliminary data, however, suggest that the combination of antidepressants, atypical antipsychotics and/or mood stabilizers did not