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Striking Similarities between Clinical and Biological Properties of Ketamine and Ethanol: Linking Antidepressant-After Effect and Burgeoning Addiction?

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Abstract

Ketamine is an old drug of abuse showing currently a new wave in its spread. Also, ketamine`s therapeutic quality is currently under strong observation, especially in terms of its value in the treatment of depression and suicidality. It`s a potential revolution in understanding the mechanisms of antidepressant treatment that single and repeated therapeutic administrations of sub-anesthetic ketamine doses are associated with a rapid and robust but transient antidepressant after-effect (ADE) in patients with treatment resistant major depression. There is increasing evidence that this ADE might result primarily from ketamine`s feature of being a non-competitive antagonist of glutamatergic N-methyl-D-aspartate (NMDA)-receptors embedded in synaptic membranes of neuronal cortico-limbic networks promoting an extracellular glutamate surge, thereby mediating changes in synaptic and cellular plasticity via local glutamate non-NMDA-receptors. Here, we focus on a couple of striking clinical and biological overlaps with ketamine and ethanol being a non-competitive antagonist of NMDA-receptors, too. Among them, a good portion is currently assumed to be specifically involved in both, the mechanisms of ADE (in the case of ketamine) and the development of addiction (in the case of ethanol). These overlaps are mainly addressed here in more detail, what may draw the reader in terms of the treatment of mood disorders to both, the possibility of a progressing transfer from ADE to addiction when repeatedly using therapeutic ketamine pulses, and on the other hand, a hypothesized therapeutic `antidepressant window´ of modest and cautious ethanol use in depressives, who are (still?) not addicted to ethanol. Of course, more frequent and intense use of ethanol or ketamine would prepare the brain to tolerance and dependence possibly using the same pathways.

Keywords: Ethanol; Major depression; Glutamate; Antidepressant ethanol after-effect; Antidepressant ketamine after-effect; Addiction; Neurotoxicity

Introduction

Ketamine is approved to start and maintain anaesthesia or analgesia and known as an old drug of abuse showing currently a new wave in its spread [1-3]. Also, ketamine`s therapeutic quality is currently under strong observation, especially in terms of its value in the treatment of depression and suicidality [4-6]. A growing number of studies demonstrated a rapid and rigorous but transient anti-anhedonistic and antidepressant after-effect (ADE) occurring subsequent to sub-anesthetic parenteral ketamine doses (usually a single ketamine infusion of 0.5 mg/kg over 40 minutes) in 50-80% of the cases when applied the first time to patients with treatment resistant unipolar or bipolar major depression [4-6]. ADE emerged within the first hours after a single ketamine administration, peaked in the next 24 to 48 hours and dissipated within the following 3 to 7 days [4-6]. The onset and duration of ketamine`s ADE was highly inter-individual and increased with repeated or serial ketamine-infusions in those subjects, who did not respond on the infusions before [7] reminiscent of well-known observations of early and delayed improvements using typical antidepressants. Adverse effects (mostly dissociation, dry mouth, tachycardia and elevated blood pressure) were mild, transient and dose dependent [4-6]. Recently, intramuscular, intranasal and oral routes of sub-anesthetic ketamine administration were demonstrated to be also followed by an ADE [4-9].

There are several speculations about sub-anesthetic ketamine`s ADE, including epigenetic mechanisms [6]. The most convincing hypothesis starts with an extracellular glutamate surge in cortico-limbic brain regions due to disinhibited glutamatergic pyramidal neurons by an inhibition of tonic firing of GABAergic interneurons via inactivation of its NMDA-receptors by ketamine [10]. In this regard, increased glutamate activities were found in the medial prefrontal cortex of rats subsequent to the administration of sub-anesthetic but not anesthetic doses of ketamine [11]. Thereby, postsynaptic glutamatergic non-NMDA-receptors can be activated and sensitized, which should drive changes in cellular and synaptic plasticity assumed to be involved in ADE [12,13]. More specifically, an activation of mammalian target of rapamycin function (mTOR) should play a key role in remodeling synapses, thus mediating ADE [12-14]. Additionally, dopaminergic pyramidal neurons were assumed to be disinhibited or facilitated by ketamine [15] leading to dopamine surge in cortico-limbic areas [16,17], which was assumed to be responsible for stimulating and psychotomimetic effects of ketamine [15].

Similarities between Ethanol and Ketamine

At this juncture, elevated glutamate concentrations were found

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recently i) in the blood of ethanol intoxicated patients, which declined during detoxification [18] and ii) in limbic brain regions of detoxifying alcoholics [19]. This is intriguing on the background that ethanol in physiological doses was demonstrated to antagonize NMDA-receptors non-competitively [20-22], just like ketamine. Of note, low doses of ethanol were found to be associated with antidepressant-like effects in Porsolt`s swim test on mice [23]. We can recall a few primary depressive ethanol-dependents [24], who reported in their early untreated history from `feeling better´, notably improved mood, more energy and better concentration (ADE?), after a few glasses of beer or wine, initially persisting over a few days before decaying. Assuming to better cope with their depression the frequency of ethanol-intake had been increased over time resulting in a tolerance towards their `feeling better´. In addition, aversive withdrawal symptoms had occurred that worsened their depression and promoted more frequent or continuous drinking (own unpublished observations).

Of note, chronic ethanol-dependents were described to have lower brain glutamate concentrations in sustained abstinence than normal controls [25,26], eventually pointing to long-term adaptation due to former repeated or prolonged glutamate-surge of regular drinking. Is this what can happen as a consequence of more frequent ketamine infusions, thus giving birth to an aberrant learning process, such as addiction [27]?

In mammalian animals, ketamine was found (i) to reduce ethanol-seeking behavior and (ii) to substitute for ethanol in drug discrimination tasks [28,29]. In the late 1990ies, Krystal et al. had demonstrated that ketamine produced dose-related ethanol-like effects in detoxified alcoholics [30]. In healthy subjects, a usual sub-anesthetic intravenous ketamine dose was estimated to produce subjective effects similar to 5 standard drinks [31]; approximately three quarters a bottle of wine.

Addressing these substantial similarities between ketamine and ethanol, the question arises whether `sub-anesthetic´ ethanol is able to evoke ADE when applied modestly `with caution´ in low frequent pulses, i.e. no more than once to thrice a week, to depressives being not addicted to ethanol. Ethanol`s ADE might be less pronounced than ketamine`s ADE due to ethanol`s somewhat weaker antagonism of NMDA-receptors [20-22,32]. Subsequent to more frequent ethanol intake, ethanol`s ADE might be blurred by hangover and the development of tolerance and abstinence symptoms, which could partially result from ethanol`s stronger agonistic action on GABA-A-receptors and up-regulation of NMDA-receptors [20-22,32]. There are some further intriguing clinical and biological characteristics, that ethanol shares with ketamine:

i) Increasing doses were associated with sedation, anesthesia, amnesia and more pain relief [6,31,32] - perhaps via increasing agonistic and activating actions on cortical, subcortical and brain-stem GABA-A-receptors and voltage-gated ion-channels [20,21,32-35].

ii) Modulation of cortico-limbic dopamine [17,21,35-38] and opioid pathways [31,32,39] potentially involved in rewarding [40,41] and affect regulation [42,43].

iii) Increased neurotrophin (BDNF, NGF) levels after acute administration [44,45] and decreased neurotrophin levels during prolonged intake [14,46].

iv) Inhibition of synaptic long-term potentiation (LTP) of rodent hippocampal neurons which persisted after washout of the respective drug, promoting the discussion about drug-induced meta-plastic synaptic changes [47-49].

v) Activation of mTOR-signaling pathways [12,13,50,51].

vi) Synaptic adaptations, such as increasing number and size of dendritic spines in rodent hippocampal and prefrontal neurons [13,52,53].

vii) Repeated administration induced tolerance in euphoriant and stimulating actions [21,54] as well as in ADE [55-57], own unpublished observations].

viii) Repeated administration induced gene expression of specific NMDA receptor subunits in cortico-limbic brain regions [20,32,58-60].

ix) Down-regulation of cerebellum following repeated drug administration [59].

x) Chronic or regular intake was associated with the development of addiction and neurotoxic effects that could lead to brain atrophy [32,34,54,61].

xi) Bioavailability of oral ketamine is low (20%) [34] and that of ethanol decreased from about 85% in young people down to 40% in the elderly [62].

Among them, a good portion (ii-vi) is currently discussed to be specifically involved in both, the mechanisms of ADE (in case of ketamine) [6,12-14,45,52] and the development of addiction (in the case of ethanol) [21,44,47,50,51,53,58,59,63,64]. Other similarities (vii, viii) were more plainly associated with adverse effects, such as addiction and neurotoxicity [20,32,34,54,55-61]. Especially, an altered gene expression of specific NMDA-receptors (viii) due to repeated administrations of both agents might be crucial in attenuating ADE and augmenting the adverse effects of ketamine and ethanol. Most recently, further evidence was found that an overexpression of NMDA-receptor subunit epsilon-1 (NR2A) might promote vulnerability for major depression [65] perhaps contributing to a tolerance in ADE [55-57]. Frequent and regular ethanol ingestion was associated with an overexpression of NR1- and NR2B-subunit containing NMDA-receptors in cortico-limbic synapses, including the dorsomedial striatum, assumed to be involved in the development of addiction and abstinence syndrome [20,31,66]. However, both might be simply result from a weakened stress defense being characteristic for both, major depression and addiction [52,65]. In this context, chronic stress is associated with a loss of synaptic spines of rodent hippocampal and prefrontal neurons supposed to reflect an impaired synaptic plasticity there [52]. Intriguingly, a single and low dose of ketamine was demonstrated to increase spine density and reverse stress-induced deficits in synaptic function of prefrontal pyramidal neurons [52] hypothesized to contribute to ketamine`s ADE [52].

It is emphasized that chronic intermittent ethanol exposure to rats was also associated with an increase in dendritic spine density in prefrontal pyramidal neurons that occurred precisely within one week after ethanol cessation [63,64] and that seems to be similar to alterations in spine morphology found after a single, low dose of ketamine [13,52]. It`s a challenge to differentiate whether those dynamics in morphological plasticity of excitatory glutamatergic neurotransmission [52] are assigned to therapeutic, e.g. antidepressant actions [13] of the drugs, or simply to the development of substance dependence [53,63,64], unless being two clinical sides of the same coin generally reflecting the neurobiological trace of plasticity (cellular learning) in stress-regulation.

Differences between Ethanol and Ketamine

On the other hand, there are some ketamine-specific effects that differentiate from ethanol, such as short elimination half-live [21,32], minor potency in activating postsynaptic GABA-A-receptors [21,32,34,67] and augmentation of tau-phosphorylation in animal cortices [59] as well as producing genitourinary toxicology [34] and negligible physical withdrawal symptoms in humans [34,54,68,69]. Moreover, ketamine administration is associated with dose-dependent psychedelic, dissociative, hallucinogenic and psychotomimetic perceptions [4-6,54], which are not characteristic for ethanol-intoxication.

Dissociation, ADE and Glutamate Surge

Recently, dissociative symptoms were found to be positively related to ketamine`s ADE [70]. But one should bear in mind that depersonalization is clinically overlapping with dissociation and was found to be related to ethanol ingestion [71,72] and was hypothesized to be associated with increased brain glutamate [73] – just like ketamine [4-6,70]. Ambiguously, dissociative symptoms were found to be not unusual in substance abusers [74] and were assigned to co-morbidity of alcoholism [75]. However, both dissociation and glutamate activity were demonstrated to be not related to ketamine`s ADE in ten patients with major depression – unfortunately, the glutamate measurements were made in their occipital cortices and not in their cortico-limbic areas [76]. In healthy volunteers, sub-anesthetic ketamine was inconsistently associated with a glutamate surge in the prefrontal cortex [77-79], and in patients with major depression a glutamate sink was documented there, which normalized with clinical recovery [79]. In aggregate, further clarifying studies on the effects of both, ketamine and ethanol pulses on glutamate activities in cortico-limbic pathways of patients with mood disorders and its relation to ADE or `feeling better´ are warranted.

Discussion

The explanation that ketamine exerts its ADE via antagonism of glutamate NMDA-receptor is called into question considering a lacking ADE of memantine being an uncompetitive antagonist of this receptor, too [80]. Nevertheless, there is new evidence that memantine has antimanic and mood stabilizing properties in the treatment of bipolar disorder [81]. Further support for the `glutamate-hypothesis´ of ADE comes from nitrous oxide - exerting also antagonizing actions on NMDA-receptors -, as this narcotic agent was also demonstrated to evoke a rapid and robust ADE in treatment resistant major depression subsequent to a sub-anesthetic dose [82], just like ketamine does [4-6].

The presented overview about the clinical and biological overlaps of ketamine and ethanol should draw the readers` attention in terms of the treatment of major depression to both, the possibility of a progressing transfer from ADE to addiction when using repeated ketamine pulses, and on the other hand, a hypothesized therapeutic `antidepressant window´ of low frequent and modest ethanol pulses in depressives, who are (still?) not addicted to ethanol.

More frequent and intense use of ethanol or ketamine would prepare the brain to tolerance and dependence upon in the same sophisticated neurobiological pathways considering aberrant cellular learning in cortico-limbic networks [83,84]. Recent epidemiological findings from a survey of a nationally representative sample of the population in the USA underlined the risky role of ethanol in affect-regulation as it confirms that drinking to mitigate mood symptoms was associated with the development of ethanol dependence [85]. And without a doubt, at risk drinking of patients with major depression is reliably accompanied by a worsening of depression, social functioning, suicide risk and increasing health care utilization [86]. Nevertheless, the authors are not aware of any study that specifically assessed ethanol after-effects on mood and energy in individuals with affective disorders being or not being addicted to ethanol. Although the use of ethanol to relieve affective symptoms is common among patients with mood disorders [87] and despite the fact that ethanol has some mechanistic characteristics in common with antidepressants, such as enhancing monoaminergic neurotransmission [42], there is merely insufficient evidence of the self-medication hypothesis in mood disorders up to date [88-90]. To the contrary, there is increasing evidence attributing the nucleus accumbens with its projections to the prefrontal cortex to be a key circuit in both, regulating of antidepressant actions [91] and burgeoning as well as maintaining addiction [83,84].

The mood changes of acute mild ethanol intoxication (transient euphoria) and chronic alcohol intake (ongoing dysphoria) is commonly thought to be largely due to the mediation of central dopamine system, e.g. by indirectly increasing and decreasing the synaptic dopamine efflux in cortico-limbic dopamine circuits implicated in the learning of goal-directed and rewarding behaviors [21,37,38,40,41,92,93], respectively. However, one might speculate on the possibility of longer lasting favorable ethanol after-effects, just like ADE, due to sustained modifications in cortico-limbic glutamatargic synapses, notably being discussed to be also involved in the progression of adverse effects, such as addiction and neurotoxicity [20-22,53,58,59,61,83].

Conclusion

There are striking similarities between ketamine and ethanol, particularly in terms of modulating dopaminergic and glutamatergic pathways in cortico-limbic brain areas, evidently being involved in learning and affect regulation, thereby probably mediating ADE, as well as the development of addiction. Exceeding an individual threshold with ingesting a critical amount or using a critical frequency of administration of these drugs would turn its favorable, therapeutic effect (ADE) more likely to adverse effects (addiction, neurotoxicity).

Conflict of Interest

U.B. received fees for lectures and the organization of training courses by the following pharmaceutical companies: Actelion, Boehringer-Ingelheim, Bristol-Myers Squibb, esparma, GlaxoSmithKline, Janssen-Cilag, Lilly, Lundbeck, Merz, and Servier. N.S. received fees for lectures, development of educational presentations and board memberships from Lundbeck, Jassen-Cilag, Reckitt-Benckiser and a grant from Roche.

References

1. Jansen KL, Darracot-Cankovic R (2001) The nonmedical use of ketamine, part two: A review of problem use and dependence. J Psychoactive Drugs 33: 151-158.
2. Marland S, Ellerton J, Andolfatto G, Strapazzon G, Thomassen O, et al. (2013) Ketamine: use in anesthesia. CNS Neurosci Ther 19: 381-389.
3. UNDOC. World Drug Report 2014 – amphetamine-type substances (ATS) and new psychoactive substances (NPS) Accessed April 4, 2015.
4. Fond G, Loundou A, Rabu C, Macgregor A, Lançon C, et al. (2014) Ketamine administration in depressive disorders: a systematic review and meta-analysis. Psychopharmacology (Berl) 231: 3663-3676.
5. Naughton M, Clarke G, O'Leary OF, Cryan JF, Dinan TG (2014) A review of ketamine in affective disorders: current evidence of clinical efficacy, limitations of use and pre-clinical evidence on proposed mechanisms of action. J Affect Disord 156: 24-35.

6. Potter DE, Choudhury M (2014) Ketamine: repurposing and redefining a multifaceted drug. Drug Discov Today 19: 1848-1854.

7. Shiroma PR, Johns B, Kuskowski M, Wels J, Thuras P, et al. (2014) Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression. J Affect Disord 155: 123-129.

8. Irwin SA, Iglewicz A, Nelesen RA, Lo JY, Carr CH, et al. (2013) Daily oral ketamine for the treatment of depression and anxiety in patients receiving hospice care: a 28-day open-label proof-of-concept trial. J Palliat Med 16: 958-965.

9. Lapidus KA, Levitch CF, Perez AM, Brallier JW, Parides MK, et al. (2014) A randomized controlled trial of intranasal ketamine in major depressive disorder. Biol Psychiatry 76: 970-976.

10. Homayoun H, Moghaddam B (2007) NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. J Neurosci 27: 11496-11500.

11. Choudhury GM, Behar KL, Cho W, Thomas MA, Rothman DL, Sanacora G (2012). ^{1}H-[^{13}C]-nuclear magnetic resonance spectroscopy measures of ketamine's effect on amino acid neurotransmitter metabolism. Biol Psychiatry 71: 1022-1025.

12. Maeng S, Zarate CA Jr, Du J, Schloesser RJ, McCammon J, et al. (2008) Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. Biol Psychiatry 63: 349-352.

13. Duman RS, Li N, Liu RJ, Duric V, Aghajanian G (2012) Signaling pathways underlying the rapid antidepressant actions of ketamine. Neuropharmacology 62: 35-41.

14. Zhou W, Wang N, Yang C, Li XM, Zhou ZQ, et al. (2014) Ketamine-induced antidepressant effects are associated with AMPA receptors-mediated upregulation of mTOR and BDNF in rat hippocampus and prefrontal cortex. Eur Psychiatry 29: 419-423.

15. Kegeles LS, Abi-Dargham A, Zea-Ponce Y, Rodenhiser-Hill J, Mann JJ, et al. (2000) Modulation of amphetamine-induced striatal dopamine release by ketamine in humans: implications for schizophrenia. Biol Psychiatry 48: 627-640.

16. Lindefors N, Barati S, O'Connor WT (1997) Differential effects of single and repeated ketamine administration on dopamine, serotonin and GABA transmission in rat medial prefrontal cortex. Brain Res 759: 205-212.

17. Moghaddam B, Adams B, Verma A, Daly D (1997) Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. J Neurosci 17: 2921-2927.

18. Brousse G, Arnaud B, Vorspan F, Richard D, Dissard A, et al. (2012) Alteration of glutamate/GABA balance during acute alcohol withdrawal in emergency department: a prospective analysis. Alcohol Alcohol 47: 501-508.

19. Bauer J, Pedersen A, Scherbaum N, Bening J, Patschke J, et al. (2013) Craving in ethanol-dependent patients after detoxification is related to glutamatergic dysfunction in the nucleus accumbens and the anterior cingulate cortex. Neuropsychopharmacology 38: 1401-1408.

20. Woodward JJ (2000) Ethanol and NMDA receptor signaling. Crit Rev Neurobiol 14: 69-89.

21. Tabakoff B, Hoffman PL (2013) The neurobiology of alcohol consumption and alcoholism: an integrative history. Pharmacol Biochem Behav 113: 20-37.

22. Chandrasekar R (2013) Alcohol and NMDA receptor: current research and future direction. Front Mol Neurosci 6: 14.

23. Hilakivi LA, Durcan MJ, Lister RG (1989) Effects of ethanol on fight- or swim-stressed mice in Porsolt's swim test. Neuropsychopharmacology 2: 293-298.

24. Brown SA, Inaba RK, Gillin JC, Schuckit MA, Stewart MA, et al. (1995) Alcoholism and affective disorder: clinical course of depressive symptoms. Am J Psychiatry 152: 45-52.

25. Mon A, Durazzo TC, Meyerhoff DJ (2012) Glutamate, GABA, and other cortical metabolite concentrations during early abstinence from ethanol and their associations with neurocognitive changes. Drug. Ethanol Depend 125: 27-36.

26. Thoma R, Mullins P, Ruhl D, Monnig M, Yeo RA, et al. (2011) Perturbation of the glutamate-glutamine system in alcohol dependence and remission. Neuropsychopharmacology 36: 1359-1365.

27. Hillemacher T, Bleich S, Demling J, Kornhuber J (2007) Ketamine for the treatment of depression: what about the addictive potential? Aust N Z J Psychiatry 41: 772-773.

28. Grant KA, Knisely JS, Tabakoff B, Barrett JE, Balster RL (1991) Ethanol-like discriminative stimulus effects of non-competitive n-methyl-d-aspartate antagonists. Behav Pharmacol 2: 87-95.

29. Vivian JA, Waters CA, Szeliga KT, Jordan K, Grant KA (2002) Characterization of the discriminative stimulus effects of N-methyl- D-aspartate ligands under different ethanol training conditions in the cynomolgus monkey (Macaca fascicularis). Psychopharmacology (Berl) 162: 273-281.

30. Krystal JH, Petrakis IL, Webb E, Cooney NL, Karper LP, et al. (1998) Dose-related ethanol-like effects of the NMDA antagonist, ketamine, in recently detoxified alcoholics. Arch Gen Psychiatry 55: 354-360.

31. Krystal JH, Madonick S, Perry E, Gueorguieva R, Brush L, et al. (2006) Potentiation of low dose ketamine effects by naltrexone: potential implications for the pharmacotherapy of alcoholism. Neuropsychopharmacology 31: 1793-1800.

32. Mion G, Villevieille T (2013) Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther 19: 370-380.

33. Irifune M, Sato T, Kamata Y, Nishikawa T, Dohi T, et al. (2000) Evidence for GABA(A) receptor agonistic properties of ketamine: convulsive and anesthetic behavioral models in mice. Anesth Analg 91: 230-236.

34. Li JH, Vicknasingam B, Cheung YW, Zhou W, Nurhidayat AW, et al. (2011) To use or not to use: an update on licit and illicit ketamine use. Subst Abuse Rehabil 2: 11-20.

35. Lindefors N, Barati S, O'Connor WT (1997) Differential effects of single and repeated ketamine administration on dopamine, serotonin and GABA transmission in rat medial prefrontal cortex. Brain Res 759: 205-212.

36. Vollenweider FX, Geyer MA (2001) A systems model of altered consciousness: integrating natural and drug-induced psychoses. Brain Res Bull 56: 495-507.

37. Kapur S, Seeman P (2002) NMDA receptor antagonists ketamine and PCP have direct effects on the dopamine D(2) and serotonin 5-HT(2)receptors-implications for models of schizophrenia. Mol Psychiatry 7: 837-844.

38. Tan S, Lam WP, Wai MS, Yu WH, Yew DT (2012) Chronic ketamine administration modulates midbrain dopamine system in mice. PLoS One 7: e43947.

39. Shenoda BBK (2014) The potential role of endogenous opioid system in the antidepressant effect of ketamine. Research in Neurology: An International Journal 2014: 11.

40. Berridge KC, Robinson TE, Aldridge JW (2009) Dissecting components of reward: 'liking', 'wanting', and learning. Curr Opin Pharmacol 9: 65-73.

41. Salamone JD, Correa M (2012) The mysterious motivational functions of mesolimbic dopamine. Neuron 76: 470-485.

42. Markou A, Kosten TR, Koob GF (1998) Neurobiological similarities in depression and drug dependence: a self-medication hypothesis. Neuropsychopharmacology 18: 135-174.

43. Rose EJ, Simonotto E, Ebmeier KP (2006) Limbic over-activity in depression during preserved performance on the n-back task. Neuroimage 29: 203-215.

44. Logrip ML, Janak PH, Ron D (2009) Escalating ethanol intake is associated with altered corticostriatal BDNF expression. J Neurochem 109: 1459-1468.

45. Kavalali ET, Monteggia LM (2012) Synaptic mechanisms underlying rapid antidepressant action of ketamine. Am J Psychiatry 169: 1150-1156.

46. Ke X, Ding Y, Xu K, He H, Zhang M, et al. (2014). Serum brain-derived neurotrophic factor and nerve growth factor decreased in chronic ketamine abusers. Drug Ethanol Depend 142: 290-294.

47. Zorumski CF, Mennerick S, Izumi Y (2014) Acute and chronic effects of ethanol on learning-related synaptic plasticity. Alcohol 48: 1-17.

48. Izumi Y, Zorumski CF (2014) Metaplastic effects of subanesthetic ketamine on CA1 hippocampal function. Neuropharmacology 86: 273-281.

49. Ribeiro PO, Tomé AR, Silva HB, Cunha RA, Antunes LM, et al. (2014). Clinically relevant concentrations of ketamine mainly affect long-term potentiation rather than basal excitatory synaptic transmission and do not change paired-pulse facilitation in mouse hippocampal slices. Brain Res 1560: 10-17.

50. Sabino V, Narayan AR, Zeric T, Steardo L, Cottone P (2013) mTOR activation is required for the anti-alcohol effect of ketamine, but not memantine, in alcohol-preferring rats. Behav Brain Res 247: 9-16.

51. Neasta J, Barak S, Hamida SB, Ron D (2014) mTOR complex 1: a key player in neuroadaptations induced by drugs of abuse. J Neurochem 130: 172-184.

52. Duman CH, Duman RS2 (2015) Spine synapse remodeling in the pathophysiology and treatment of depression. Neurosci Lett .

53. Carpenter-Hyland EP, Chandler J (2007) Adaptive plasticity of NMDA receptors and dendritic spines: implications for enhanced vulnerability of the adolescent brain to ethanol addiction. Pharmacol Biochem Behav 86: 200–208.

54. Wolff K, Winstock AR (2006) Ketamine : from medicine to misuse. CNS Drugs 20: 199-218.

55. Liebrenz M, Stohler R, Borgeat A (2009) Repeated intravenous ketamine therapy in a patient with treatment-resistant major depression. World J Biol Psychiatry 10: 640-643.

56. Cusin C, Hilton GQ, Nierenberg AA, Fava M (2012) Long-term maintenance with intramuscular ketamine for treatment-resistant bipolar II depression. Am J Psychiatry 169: 868-869.

57. Harihar C, Dasari P, Srinivas JS (2013) Intramuscular ketamine in acute depression: A report on two cases. Indian J Psychiatry 55: 186-188.

58. Kroener S, Mulholland PJ, New NN, Gass JT, Becker HC, et al. (2012) Chronic alcohol exposure alters behavioral and synaptic plasticity of the rodent prefrontal cortex. PLoS One 7: e37541.

59. Wai MS, Luan P, Jiang Y, Chan WM, Tsui TY, et al. (2013) Long term ketamine and ketamine plus alcohol toxicity - what can we learn from animal models? Mini Rev Med Chem 13: 273-279.

60. Xu K, Lipsky RH (2015) Repeated ketamine administration alters N-methyl-D-aspartic acid receptor subunit gene expression: implication of genetic vulnerability for ketamine abuse and ketamine psychosis in humans. Exp Biol Med (Maywood) 240: 145-155.

61. Wang C, Zheng D, Xu J, Lam W, Yew DT (2013) Brain damages in ketamine addicts as revealed by magnetic resonance imaging. Front Neuroanat 7: 23.

62. Oneta CM, Pedrosa M, Rüttimann S, Russell RM, Seitz HK (2001) Age and bioavailability of alcohol. Z Gastroenterol 39: 783-788.

63. Kim A, Zamora-Martinez ER, Edwards S, Mandyam CD (2014) Structural reorganization of pyramidal neurons in the medial prefrontal cortex of ethanol dependent rats is associated with altered glial plasticity. Brain Struct Funct Mar 26.

64. McGuier NS, Padula AE, Lopez MF, Woodward JJ, Mulholland PJ (2015) Withdrawal from chronic intermittent alcohol exposure increases dendritic spine density in the lateral orbitofrontal cortex of mice. Alcohol 49: 21-27.

65. Kaut O1, Schmitt I, Hofmann A, Hoffmann P, Schlaepfer TE, et al. (2015) Aberrant NMDA receptor DNA methylation detected by epigenome-wide analysis of hippocampus and prefrontal cortex in major depression. Eur Arch Psychiatry Clin Neurosci .

66. Wang J, Lanfranco MF, Gibb SL, Yowell QV, Carnicella S, et al. (2010) Long-lasting adaptations of the NR2B-containing NMDA receptors in the dorsomedial striatum play a crucial role in alcohol consumption and relapse. J Neurosci 30: 10187-10198.

67. Foster AC, Kemp JA (2006) Glutamate- and GABA-based CNS therapeutics. Curr Opin Pharmacol 6: 7-17.

68. Goyal S, Ambekar A, Ray R (2014) Ketamine dependence in an anesthesiologist: an occupational hazard? Indian J Psychol Med 36: 335-337.

69. Liu JX, Zerbo E, Ross S (2015) Intensive ketamine use for multiple years: A case report. Am J Addict 24: 7-9.

70. Luckenbaugh DA, Niciu MJ, Ionescu DF, Nolan NM, Richards EM, et al. (2014) Do the dissociative side effects of ketamine mediate its antidepressant effects? J Affect Disord 159: 56-61.

71. Davison k (1964) Episodic Depersonalization; Observations on 7 Patients. Br J Psychiatry 110: 505-513.

72. Raimo EB, Roemer RA, Moster M, Shan Y (1999) Alcohol-induced depersonalization. Biol Psychiatry 45: 1523-1526.

73. Pikwer A (2011) Depersonalization disorder may be related to glutamate receptor activation imbalance. Med Hypotheses 77: 593-594.

74. Dunn GE, Paolo AM, Ryan JJ, Van Fleet J (1993) Dissociative symptoms in a substance abuse population. Am J Psychiatry 150: 1043-1047.

75. Evren C, Sar V, Karadag F, Tamar Gurol D, Karagoz M (2007) Dissociative disorders among alcohol-dependent inpatients. Psychiatry Res 152: 233-241.

76. Valentine GW, Mason GF, Gomez R, Fasula M, Watzl J, et al. (2011) The antidepressant effect of ketamine is not associated with changes in occipital amino acid neurotransmitter content as measured by [(1)H]-MRS. Psychiatry Res 191: 122-127.

77. Rowland LM, Bustillo JR, Mullins PG, Jung RE, Lenroot R, et al. (2005) Effects of ketamine on anterior cingulate glutamate metabolism in healthy humans: a 4-T proton MRS study. Am J Psychiatry 162: 394-396.

78. Stone JM, Dietrich C, Edden R, Mehta MA, De Simoni S, et al. (2012) Ketamine effects on brain GABA and glutamate levels with 1H-MRS: relationship to ketamine-induced psychopathology. Mol Psychiatry 17: 664-665.

79. Taylor MJ, Tiangga ER, Mhuircheartaigh RN, Cowen PJ (2012) Lack of effect of ketamine on cortical glutamate and glutamine in healthy volunteers: a proton magnetic resonance spectroscopy study. J Psychopharmacol 26: 733-737.

80. Drewniany E, Han J, Hancock C, Jones RL, Lim J, et al. (2015) Rapid-onset antidepressant action of ketamine: potential revolution in understanding and future pharmacologic treatment of depression. J Clin Pharm Ther 40: 125-130.

81. Serra G, Koukopoulos A, De Chiara L, Koukopoulos AE, Tondo L, et al. (2015) Three-year, naturalistic, mirror-image assessment of adding memantine to the treatment of 30 treatment-resistant patients with bipolar disorder. J Clin Psychiatry 76: e91-97.

82. Nagele P, Duma A, Kopec M, Gebara MA, Parsoei A, et al. (2014) Nitrous Oxide for Treatment-Resistant Major Depression: A Proof-of-Concept Trial. Biol Psychiatry .

83. Quintero GC (2013) Role of nucleus accumbens glutamatergic plasticity in drug addiction. Neuropsychiatr Dis Treat 9: 1499-1512.

84. Spiga S, Mulas G, Piras F, Diana M (2014) The “addicted” spine. Front Neuroanat 8: 110.

85. Crum RM, Mojtabai R, Lazareck S, Bolton JM, Robinson J, et al. (2013) A prospective assessment of reports of drinking to self-medicate mood symptoms with the incidence and persistence of ethanol dependence. JAMA Psychiatry 70: 718-726.

86. Sullivan LE, Fiellin DA, O’Connor PG (2005) The prevalence and impact of alcohol problems in major depression: a systematic review. Am J Med 118: 330-341.

87. Bolton JM, Robinson J, Sareen J (2009) Self-medication of mood disorders with alcohol and drugs in the National Epidemiologic Survey on Alcohol and Related Conditions. J Affect Disord 115: 367-375.

88. Raimo EB, Schuckit MA (1998) Alcohol dependence and mood disorders. Addict Behav 23: 933-946.

89. Boden JM, Fergusson DM (2011) Alcohol and depression. Addiction 106: 906-914.

90. Lembke A (2012) Time to abandon the self-medication hypothesis in patients with psychiatric disorders. Am J Drug Alcohol Abuse 38: 524-529.

91. Chang CH, Chen MC, Lu J (2015) Effect of antidepressant drugs on the vmPFC-limbic circuitry. Neuropharmacology 92: 116-124.

92. Narendran R, Mason NS, Paris J, Himes ML, Douaihy AB, et al. (2014) Decreased prefrontal cortical dopamine transmission in alcoholism. Am J Psychiatry 171: 881-888.

93. Vena AA, Gonzales RA (2015) Temporal profiles dissociate regional extracellular ethanol versus dopamine concentrations. ACS Chem Neurosci 6: 37-47.

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