

Raising Endogenous Brain Levels of Kynurenic Acid May Produce Anti-Reward and Enhance Suicide Ideation

Kenneth Blum^{1,3-5*}, Marlene-Oscar-Berman², Eric R Braverman^{1,3} and Mark S Gold¹

¹Department of Psychiatry, Mcknight Brain Institute, University of Florida, Gainesville, Florida, USA

²Department of Psychiatry and Neurobiology, Boston University School of Medicine and Veterans Administration Administration System, Boston, Massachusetts, USA

³Department of Clinical Neurology, Path Foundation, New York, USA

⁴Department of Addiction Research and Therapy, Malibu Beach Recovery Center, Malibu Beach, California, USA

⁵Dominion Diagnostics, LLC, North Kingstown, Rhode Island, USA

While we applaud the elegant research in animals by our NIDA colleagues and their arduous attempt to find a novel treatment for Cannabis abuse, unfortunately we disagree with their suggestion to raise brain kynurenic acid. However, we do agree with their premise that raising kynurenic acid will indeed reduce neuronal release of dopamine at mesolimbic sites [1]. There are a number of reports showing that kynurenic acid (KYNA) is an endogenous negative allosteric modulator of $\alpha 7$ nAChRs [1,2]. In fact it is known that KYNA levels can be enhanced in the brain by even dietary tryptophan. Essentially, the neuro-inhibitory tryptophan metabolite kynurenic acid (KYNA) is a preferential antagonist of the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR). Interestingly, it was found that administration of 1.5% tryptophan added diet reduced the extracellular DA level to 60%, and increased the extracellular KYNA to 320% in the striatum of rodents [3]. Certainly, as reported by Justinova et al. [1] the kynurenine 3-monooxygenase (KMO) inhibitor Ro 61-8048 increases brain KYNA levels and attenuates cannabinoid-induced increases in extracellular dopamine in reward-related brain areas. Morales et al. [4] revealed the mechanism by which blocking the $\alpha 7$ nAChRs with KYNA results in reduced activity of cannabis. These investigators provided clear evidence that due to co-expression between $\alpha 7$ nAChRs and the cannabinoid receptor 1 (CB1), these $\alpha 7$ nACh/CB1 interneurons are the major subpopulation of hippocampal interneurons expressing CB1 mRNA. With this brief background it becomes quite obvious that one-way to block cannabis induced euphoria is to raise brain levels of KYNA. However, we must caution this approach and remind the field of an equally feasible method as we have seen with the CB1 antagonist rimonabant (Acomplia) [5]. In fact, the United States Food and Drug Administration (FDA) fortunately rejected the application of Acomplia due to known changes in mood as well as suicide ideation [6].

We are cognizant that potentially in a short-term the therapeutic approach of blocking the euphoric effects of cannabinoids could be useful in terms of extinction, but this must be avoided in the long-term [7]. Clinically, there is enough evidence to caution us against this proposed method because it is becoming increasingly important to activate dopaminergic type receptors (e.g. D2 type) rather than blocking or reducing neuronal dopamine release at the Nucleus Accumbens (NAc) [8]. In fact, Volkow's group showed the profound effects of drugs of abuse (e.g. chronic cocaine) on inducing unbalances between D1 and D2 receptor signaling leading to dopaminergic deficiency [9]. In light of these findings, it may be parsimonious to consider dopamine agonist rather than antagonistic therapy for long term maintenance as observed now in many clinical trials utilizing a natural D2 agonist such as KB220Z [10].

Acknowledgements

The writing of this paper was supported in part by funds from the National Institutes of Health, NIAAA (RO1-AA07112 and K05-AA00219) and the Medical

Research Service of the US Department of Veterans Affairs (MOB). Kenneth Blum AND Eric R Braverman are the recipients of a grant from Life Extension Foundation, Ft. Lauderdale, Florida awarded to Path Foundation NY.

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*Corresponding author: Kenneth Blum, Department of Psychiatry, Mcknight Brain Institute, University of Florida, Gainesville, Florida, USA, Tel: 619-890-2167; E-mail: drd2gene@gmail.com

Received January 26, 2014; Accepted February 17, 2014; Published February 20, 2014

Citation: Blum K, Berman MO, Braverman ER, Gold MS (2014) Raising Endogenous Brain Levels of Kynurenic Acid May Produce Anti-Reward and Enhance Suicide Ideation. *J Alcohol Drug Depend* 2: 151. doi:10.4172/2329-6488.1000151

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