Drug and Alcohol Dependence 160 (2016) 163–169

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Differences in IV alcohol-induced dopamine release in the ventral striatum of social drinkers and nontreatment-seeking alcoholics

Karmen K. Yoder[a,b,c,d,*], Daniel S. Albrecht[a,b,c,1], Mario Dzemidzic[a,b,e], Marc D. Normandin[a,2], Lauren M. Federici[a,b], Tammy Graves[a,f], Christine M. Herring[a,b], Karen L. Hile[a,b], James W. Walters[a,b], Tiebing Liang[f], Martin H. Plawecki[g], Sean O'Connor[g,h], David A. Kareken[a,b,e,g]

[a] Department of Radiology and Imaging Sciences, Indiana University School of Medicine (IUSM), R2-E124, 950 W. Walnut St., Indianapolis, IN, USA
[b] Center for Neuroimaging, IUSM, GH Ste. 4100, 355 W. 16th St., Indianapolis, IN 46202, USA
[c] Stark Neurosciences Research Institute, IUSM, NB Ste. 414, 320 W. 16th St., Indianapolis, IN 46202, USA
[d] Department of Psychology, Indiana University—Purdue University at Indianapolis, 402 N. Blackford St., Indianapolis, IN 46202, USA
[e] Department of Neurology, IUSM, GH Ste. 4700, 355 W. 16th St., Indianapolis, IN 46202, USA
[f] Department of Medicine, IUSM, 340 W. 10th St., Ste. 6200, Indianapolis, IN 46202, USA
[g] Department of Psychiatry, IUSM, GH Ste. 4800, 355 W. 16th St., Indianapolis, IN 46202, USA
[h] Roudebush Veteran's Administration Medical Center, 1481 W. 10th St., Indianapolis, IN 46202, USA

ARTICLE INFO

Article history:
Received 4 November 2015
Received in revised form
15 December 2015
Accepted 3 January 2016
Available online 13 January 2016

Keywords:
Dopamine
Raclopride
Alcohol
Positron emission tomography
Ventral striatum

ABSTRACT

Background: Striatal dopamine (DA) has been implicated in alcohol use disorders, but it is still unclear whether or not alcohol can induce dopamine release in social drinkers. Furthermore, no data exist on dopamine responses to alcohol in dependent drinkers. We sought to characterize the DA responses to alcohol intoxication in moderately large samples of social drinkers (SD) and nontreatment-seeking alcoholics (NTS).
Methods: Twenty-four SD and twenty-one NTS received two [^{11}C]raclopride (RAC) PET scans; one at rest, and one during an intravenous alcohol infusion, with a prescribed ascent to a target breath alcohol concentration (BrAC), at which it was then "clamped." The alcohol clamp was started 5 min after scan start, with a linear increase in BrAC over 15 min to the target of 80 mg%, the legal threshold for intoxication. Target BrAC was maintained for 30 min. Voxel-wise binding potential (BP_{ND}) was estimated with MRTM2.
Results: IV EtOH induced significant increases in DA in the right ventral striatum in NTS, but not SD. No decreases in DA were observed in either group.
Conclusions: Alcohol intoxication results in distinct anatomic profiles of DA responses in SD and NTS, suggesting that in NTS, the striatal DA system may process effects of alcohol intoxication differently than in SD.

1. Introduction

There is strong evidence that the neurotransmitter dopamine (DA) plays multiple roles in alcoholism and other addictions (Berridge, 2007; Horvitz, 2000; O'Tousa and Grahame, 2014; Redgrave et al., 1999; Salamone et al., 2005). Despite the wealth of preclinical literature, the functions of DA in human alcohol use disorders (AUD) remain poorly understood. Thus, determining how striatal DA responds to alcohol continues to be pivotal for developing preventative and therapeutic approaches.

Several groups have used positron emission tomography (PET) with the D_2/D_3 radioligand [^{11}C]raclopride (RAC) to study the effects of alcohol ingestion on striatal DA. Oral alcohol appears

* Corresponding author at: Associate Professor of Radiology and Imaging Sciences, Center for Neuroimaging, Indiana University School of Medicine, Goodman Hall Ste 4100, 355 W. 16th St Indianapolis, IN 46202, USA. Fax: +1 317 963 7547.
E-mail address: kkyoder@iupui.edu (K.K. Yoder).
[1] Current address: Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, 149 Thirteenth Street, Room 2301, Charlestown, MA 02129, USA.
[2] Current address: Gordon Center for Medical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, 55 Fruit St., Boston, MA 02114, USA.

http://dx.doi.org/10.1016/j.drugalcdep.2016.01.001
0376-8716/

to cause modest increases in dopamine in the ventral striatum of healthy subjects (Boileau et al., 2003; Setiawan et al., 2014; Urban et al., 2010), with more notable effects in men (Urban et al., 2010) and in subjects with traits that may increase risk for AUD (Setiawan et al., 2014). However, there are properties of oral alcohol intake that complicate interpretation of these studies. First, the chemosensory (smell, taste) and somatosensory (oral sensations) characteristics of alcohol have powerful Pavlovian associations with intoxication. In rodents, these conditioned cues are believed to mediate the acute increases in striatal DA observed in oral alcohol self-administration studies (Doyon et al., 2005). We have shown in humans that beer flavor provokes DA release in the ventral striatum (Oberlin et al., 2015). Additionally, even with well-controlled dosing, oral ingestion of alcohol results in highly variable rates and concentrations of brain alcohol exposure because of inter-subject differences in stomach pH, volume of stomach contents, age, gender, and first-pass metabolism (Ramchandani et al., 2009). Different brain exposure timecourses, such as those induced by different peak breath alcohol concentrations (BrACs) and/or differing rates of BrAC increase, are likely to induce variation in the timing and magnitude of DA responses across subjects. In turn, variability in DA release profiles can cause unwanted variance in the outcome measure of RAC binding potential (Endres and Carson, 1998; Yoder et al., 2004).

Intravenous (IV) alcohol infusion avoids these potential confounds. The physiologically-based pharmacokinetic (PBPK) model-based IV alcohol clamp (O'Connor et al., 2000) precisely controls alcohol infusion rates using PBPK model parameters customized for each individual (Plawecki et al., 2007). This permits control over the timing of alcohol delivery, minimizes experimental variation in the brain's exposure to alcohol across subjects, and allows the maintenance ("clamping") of a target breath alcohol concentration (BrAC). Our initial RAC PET studies with the PBPK-IV

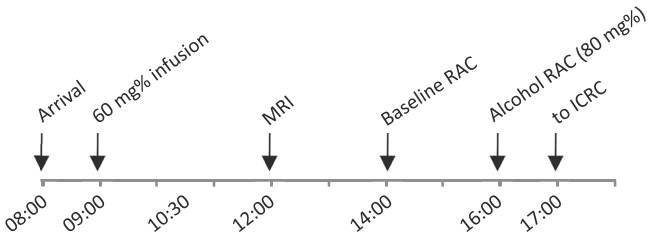

Fig. 1. Typical study day timeline. RAC = [^{11}C]raclopride PET scan; ICRC = Indiana Clinical Research Center.

alcohol clamp did not show alcohol-induced DA release at either 60 mg% or 80 mg% (the latter being the legal definition of intoxication; Yoder et al., 2007, 2005). However, these were relatively small samples, and there was variable timing of initiation of alcohol administration, leading to different brain alcohol exposures across subjects. Using similar IV clamping methods, Ramchandani et al. (2011) found that only social drinkers with the minor (and statistically rare) G allele of the functional μ-opioid receptor polymorphism (*OPRM1* A118G) had measurable IV alcohol-induced DA release. In contrast, there were no apparent effects in subjects homozygous for the major 118A allele. More recently, Aalto et al. (2015) reported striatal DA release from a bolus IV alcohol infusion in a small group of social drinkers, although imaging during this non-PBPK paradigm may have captured both ascending and descending limbs of brain alcohol exposure. Taken together, the PBPK-IV clamp data seem to suggest that IV alcohol may not produce a robust DA response in social drinkers; however, Type II error cannot be ruled out, given the sample sizes of all three PBPK-based infusion studies.

Although evidence suggests that alcoholics have functional alteration of the DA system (Martinez et al., 2005; Narendran

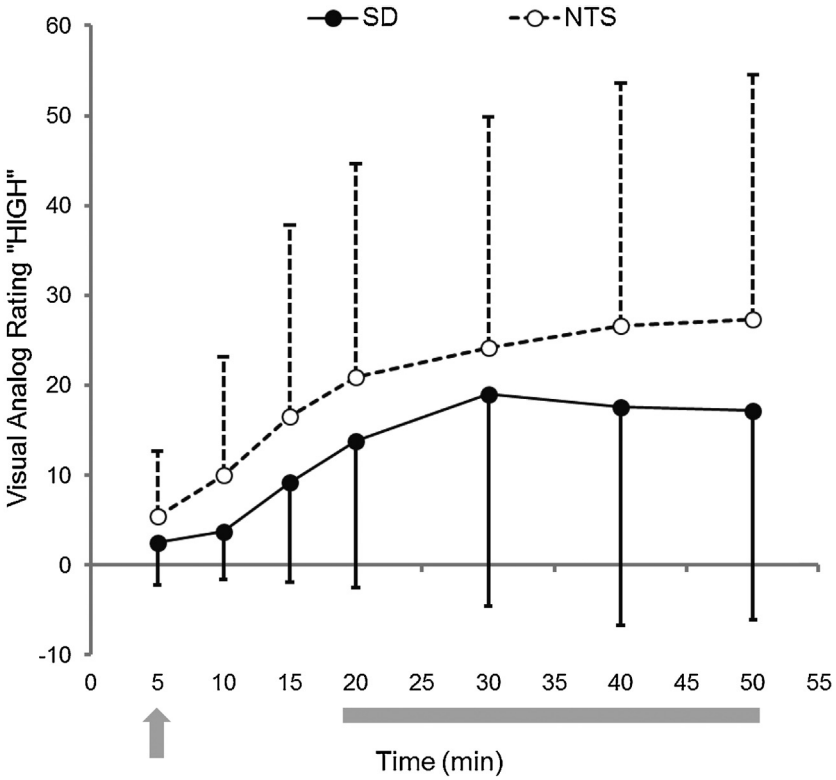

Fig. 2. Subjective ratings for "high" during the alcohol RAC PET scan. Left *y*-axis, visual analog ratings for "high" for SD (filled circles, black line) and NTS (open circles, dotted line). Data are mean ± SD. Data were not available for one NTS subject. Alcohol infusion was started (gray arrow) 5 min after the RAC injection ($t = 0$). The BrAC target for the 30 min IV alcohol clamp (gray bar) was 80 mg%. See text for details.