Dopamine D$_2$ Receptor Availability is Associated with Subjective Responses to Alcohol

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Background: The mesolimbic dopaminergic system is thought to mediate alcohol abuse and dependence. Determining the relationship between in vivo dopamine and the subjective response to alcohol could improve understanding of the mechanisms that lead to alcohol abuse and dependence. Here, we examined the relationship between dopamine D$_2$ receptors in the nucleus accumbens and scores of perceived "high" and "intoxication" during an intravenous (IV) alcohol infusion.

Methods: Nine healthy control subjects received [^{11}C]raclopride PET scanning at baseline. Eight subjects received a second [^{11}C]raclopride scan during a pharmacodynamically modeled and controlled rise of IV alcohol, followed by steady state (60 mg% ± 5 mg%) alcohol infusion. Numerical ratings of "high" and "intoxication" were tested for correlations with measures of dopaminergic function.

Results: Baseline D$_2$ receptor availability in the left nucleus accumbens was significantly correlated with peak perceived "intoxication" ($p = 0.02$) and marginally correlated with peak perceived "high" ($p = 0.07$).

Conclusions: Resting D$_2$ receptor availability may predict healthy subject responses to alcohol exposure.

Key Words: Alcohol, D$_2$ Receptor, Subjective Perceptions, Raclopride, Positron Emission Tomography.

A COMMON FEATURE OF alcohol and other drugs of abuse is their ability to elicit both primary and secondarily conditioned increases in dopamine concentration in the nucleus accumbens (Grace, 2000). Thus, the mesolimbic dopaminergic system is a commonly targeted area when studying the initiation and maintenance of addictive behaviors. However, addiction is a complex process, and it remains unclear how the components of the dopaminergic reward system are involved in the biological substrates of both the psychological and physiological aspects of alcohol abuse and dependence. For instance, the subjective experiences associated with brain exposure to alcohol could be mediated by postsynaptic receptor number, and/or by the amount of dopamine released in response to alcohol. Moreover, there are very few studies of dopamine function in humans as it relates to alcohol intoxication.

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Decreased D$_2$ receptor availability is associated with chronic drug dependence (Heinz et al., 2004; Hietala et al., 1994; Martinez et al., 2004; Volkow et al., 2001; Volkow et al., 1993; Volkow et al., 1990; Volkow et al., 1996; Volkow et al., 2002b; Wang et al., 1997), and it is possible that the density of D$_2$ receptors predicts an individual's response to drugs *before* the development of dependence. For example, healthy controls' D$_2$ receptor availability has been negatively correlated with positive affective responses to IV methylphenidate (Volkow et al., 1999b; Volkow et al., 2002a). D$_2$ receptors may also mediate the severity of symptoms in addicted individuals and predict treatment relapse (Guardia et al., 2000). Heinz et al. (2004) also reported a negative correlation between the severity of alcohol craving and D$_2$ receptor availability in alcoholics. However, no relationship was detected between D$_2$ levels and the perceived positive effects of cocaine in cocaine-dependent individuals (Martinez et al., 2004).

Although quantifying the number of D$_2$ receptors gives an indication of how postsynaptic signaling may be involved in the generation and maintenance of addictive processes, it is also instructive to understand how the functional effects of alcohol and other drugs of abuse contribute to substance dependence. In healthy humans, relative increases in dopamine induced by methylphenidate and amphetamine are correlated with the perceived positive reinforcing effects of these drugs (Abi-Dargham et al., 2003; Volkow et al., 1999c).

Animal studies with microdialysis and voltammetry provide evidence that alcohol increases DA in the nucleus

accumbens via direct and indirect stimulation of dopaminergic neurons in the ventral tegmental area (Grace, 2000). However, the literature is lacking in investigations of the responses of the human mesolimbic dopaminergic system to alcohol, as well as its involvement in the perceptions generated by alcohol intake. In healthy controls, Boileau et al. (2003) found that alcohol increased DA release in the ventral striatum/nucleus accumbens. There was no relationship with subjects' perceived subjective responses to alcohol, although the personality trait of impulsiveness and the increase in heart rate in response to alcohol both correlated with DA release (Boileau et al., 2003). Salonen et al. (1997) reported no striatal DA response to alcohol, but the data sampling in this study may have precluded observation of any alcohol-induced DA release occurring specifically in the nucleus accumbens. Furthermore, both of these studies administered alcohol orally, a technique known to cause substantial variability in the time course of breath alcohol concentration (BrAC) between subjects, caused by the intersubject variability in consumption, absorption, first-pass metabolism, distribution and elimination kinetics of alcohol. Oral administration of alcohol yields a threefold range of the concentrations of alcohol that neurons are exposed to at any moment, probably resulting in highly variable neuronal responses (e.g., differential patterns and/or magnitude of DA release). Here, we used pharmacodynamically modeled intravenous (IV) alcohol administration (the "Indiana Alcohol Clamp") to precisely control the delivery and concentration of alcohol in each subject (O'Connor et al., 1998; O'Connor et al., 2000; Ramchandani et al., 1999). With the clamp, the effects of variable consumption, absorption and first-pass kinetics are minimized by using an IV infusion of alcohol. In addition, the time course of the infusion is computed using a physiologically based pharmacokinetic model of alcohol distribution and elimination with parameters tailored to each individual subject. The method results in nearly the same time course of brain exposure to alcohol in all subjects.

The first goal of this study was to examine the relationship of baseline D_2 receptor availability with subjectively perceived feelings of "high" and "intoxication" during IV alcohol administration. Secondly, we sought to characterize the relative magnitude of change in D_2 receptor availability (representative of dopamine release) caused by IV alcohol infusion, and to determine if this change is associated with change in subjective perceptions as a function of alcohol. To study dopaminergic mechanisms involved in the subjective effects of alcohol, we used PET with the tracer [^{11}C]raclopride ([^{11}C]RAC), a competitive dopamine D_2 receptor antagonist that can be displaced by increases in endogenous dopamine (Seeman et al., 1989; Young et al., 1991).

MATERIALS AND METHODS

Nine healthy normal subjects (eight male, one female, average age 25 ± 5.3 years) participated in this protocol. Subjects were screened for neurological and psychiatric conditions via self-report. A semistructured interview (approximately 2 hr) was performed to assess habitual drinking [Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, IV (SCID) or the Semi-Structured Assessment for the Genetics of Alcoholism-II (SSAGA-II)] and to rule out alcoholism. Family history of alcoholism was determined using the Family History Assessment Module (FHAM) of the SSAGA interview of the subject. Six subjects were negative for a family history of alcoholism (FHN), and three subjects were family history positive (FHP), defined by having ≥2 first- or second-degree relatives affected by alcoholism.

The study had ethical approval from the Indiana University Institutional Review Board (IU IRB). All procedures were explained to the subjects and written consent was obtained, in accordance with the requirements of the IU IRB. Subjects received a T1-weighted magnetic resonance imaging scan (MR) to rule out neurological abnormalities and for coregistration to facilitate region of interest (ROI) placement. Subjects received two [^{11}C]raclopride ([^{11}C]RAC) scans on the same day with the EXACT HR+ (CTI, Knoxville, TN). FWHM was 9 mm when reconstructed with a 5 mm Hanning filter. [^{11}C]RAC was synthesized as reported previously (Fei et al., 2004). Scans were initiated with the IV injection of 14.3 ± 2.39 mCi of [^{11}C]RAC. Average specific activity at injection was 0.91 ± 0.48 Ci/μmol. The first scan was conducted in the morning while subjects rested quietly. The second scan was conducted in the afternoon. During the second scan, subjects were exposed to visual (via mirror goggles) and olfactory alcohol cues (using an air-dilution olfactometer, Kareken et al., 2004) of their two most-preferred alcoholic beverages for 10 min. Subjects had been instructed that the presence of alcoholic cues would predict with certainty whether they would be infused with alcohol (although for the purposes of this study, no subjects were exposed to 'neutral' cues which would have signaled what subjects were told would be a neutral saline infusion). Five minutes after the initiation of cue exposure, the infusion of alcohol began, achieving a linear ascension to a target BrAC of 60 mg% over ten minutes, and then clamped at this target concentration (± 5 mg%, O'Connor et al., 2000) for 30 min. Scan order was not randomized because persisting effects of alcohol given during the first scan would confound the subsequent afternoon measurement of baseline D_2 receptor levels. Technical reasons caused the timing of the start of the alcohol clamp to vary across subjects (clamp initiation at 3 min post-[^{11}C]RAC injection in 4 subjects with other start times being 2, 5, 7.5, and 17 min). One subject did not receive alcohol during the second scan, but received the infusion clamp at another time while positioned and supine in the scanner, and with the same cue exposures. A modification of the Subjective High Assessment Scale (SHAS; a visual analog scale from 0 to 100, with the subject voicing a whole number) was used to record perceived *high* ("stimulated, up, feeling good") and *intoxication* ("feeling drunk, affected by alcohol") periodically during the second scan (Judd et al., 1977; Morzorati et al., 2002; Schuckit, 1980). SHAS scores were taken at baseline (preinfusion), at 5 min after the beginning of infusion, and at 10 min intervals thereafter until the end of the clamp session. SHAS subscale scores reported by each subject were recorded for analysis. After scanning, subjects were observed by nursing staff at the IU General Clinical Research Center and were not released until their breath alcohol was below 20 mg%, as verified by a breath alcohol meter.

MRs were coregistered with the PET images. All images (PET and MR) were oriented coronally to allow visualization of the nucleus accumbens, which was the ROI we hypothesized a priori would be most likely to exhibit alcohol-induced effects on dopamine release. ROIs were placed on the MR images, and were transferred to the dynamic PET images. Dynamic data (time-activity curves, TACs) from the coronally oriented PET images were generated by MEDx (Medical Numerics, Inc., Sterling, VA). Dopamine D_2 receptor availability for each ROI during the baseline and alcohol conditions was measured using the index of binding potential (BP ≡ B'_{max}/K_D), which was calculated according to a multilinear reformulation of the Logan plot (Ichise et al., 2002; Logan et al., 1996). Other striatal regions of interest (ROI) included the caudate, the anterior putamen, and the posterior putamen. No effect of alcohol on dopamine release was anticipated in these regions, and they were considered to be "negative control" ROIs. TACs were produced for

each region in both hemispheres, and were derived from circles (diameter, 4 pixels; 1 pixel = 2.06 mm x 2.06 mm) placed on each region over 3 - 11 slices (slice thickness, 2.06 mm), depending on the structure (Fig. 1). TACs from the right and left cerebellum (D_2 receptor-free "reference regions") were used for calculation of BP in lieu of a plasma input function. This avoided the possible confound that blood flow in the left and right hemispheres was differentially affected by alcohol. The reference region ROIs were circles 8 pixels in diameter, and were placed on 5 slices of the posterior cerebellar cortex. Change in binding potential (ΔBP) was calculated as ($BP_{baseline}$ - $BP_{alcohol}$)/($BP_{baseline}$).

As data were normally distributed, differences in D_2 receptor availability between scan conditions ($BP_{baseline}$, $BP_{alcohol}$) were tested using parametric paired t-tests. Paired t-tests were also used to examine differences in baseline BP between left and right regions. Pearson's correlation coefficients were calculated to test for relationships between variables. Given the exploratory nature of this study, and to avoid Type II error, corrections for multiple region comparisons were not applied. Statistical significance was set at $p < 0.05$. Trend-level significance was defined as $0.05 < p < 0.1$.

RESULTS

Baseline [^{11}C]raclopride binding potential (BP) values for each region of interest are presented in Table 1. There were no differences in baseline (BP) values between hemispheres for nucleus accumbens ($p = 0.1$), dorsal caudate ($p = 0.82$), and anterior putamen ($p = 0.24$). BP values between the left and right posterior putamen reached the upper limit of trend-level significance ($p = 0.09$).

Baseline D_2 receptor availability in the left nucleus accumbens was significantly positively correlated with peak intoxication score, and reached trend-level significance with peak high score (Fig. 2). No other area had an association with either peak intoxication or peak high scores reported during the alcohol clamp.

There were no differences in D_2 receptor availability between baseline and alcohol conditions for any of the regions tested (Table 1).

In the left anterior putamen, ΔBP (an index of relative dopamine release) was significantly positively correlated with peak intoxication score ($r = 0.72, p = 0.04$, Fig. 3) but
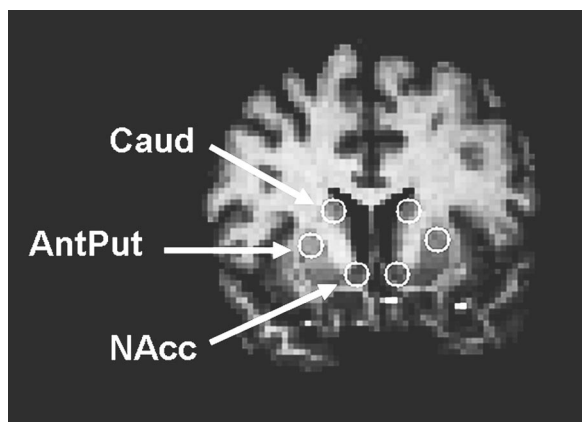

Fig. 1. Coronal MR slice containing representative ROI placement for the caudate (Caud), anterior putamen (AntPut), and nucleus accumbens (NAcc). Posterior putamen ROI placement is not shown, but is similar to the anterior putamen and was defined anatomically as being posterior to the decussation of the anterior commissure.

not with peak high ($r = 0.39, p = 0.34$). However, if the negative ΔBP values are excluded, the correlation becomes insignificant ($r = 0.53, p = 0.48$). ΔBP did not correlate with either subjective measure within any other ROI.

Timing of a stimulus that induces neurotransmitter release can affect ΔBP (Yoder et al., 2004). ΔBP in the left nucleus accumbens was significantly correlated with the timing of initiation of the alcohol clamp ($r = 0.73, p = 0.04$, Fig. 4). A similar trend-level relationship between ΔBP and timing of the alcohol infusion was detected in the left caudate ($r = 0.70, p = 0.05$). Again, if the negative ΔBP values are eliminated, both correlations become insignificant ($r = 0.81, p = 0.19$ for LNAcc versus infusion start time; $r = 0.76, p = 0.24$ for LCaud versus infusion start time). ΔBP results from other regions were not associated with timing of alcohol infusion.

DISCUSSION

We found that baseline D_2 receptor availability in healthy subjects is positively correlated with perception of intoxication during an IV infusion of alcohol designed to achieve a steady state BrAC of 60 mg% in all subjects. Baseline D_2 binding potential measurements also reached a trend-level correlation with subjective reports of feelings of being "high" from alcohol. Thus, the more D_2 receptors available for binding in the sober state, the more likely is the subject to feel "intoxicated" and "high" from alcohol exposure. This suggests that dopamine D_2 receptors may be directly involved in mediating these subjective responses to alcohol in healthy, nonalcoholic subjects. The study did not address the extent to which these effects were "pleasurable" to subjects, which may be a strong indicator of the addictive liability of a drug to an individual. However, the pleasurable effects of methylphenidate (which also increases dopamine in the striatum) have been shown to have a negative correlation with basal D_2 availability (Volkow et al., 1999b; Volkow et al., 2002a).

The correlation between D_2 availability and subjective effects are compatible with the theory that lower D_2 availability may predispose people to addiction. The alcohol dose given in this study (60 mg%) is below the legal definition of intoxication. Thus, subjects who were more sensitive (more easily intoxicated) at a low dose of alcohol had greater receptor availability. Individuals with less available receptors may require more alcohol to perceive a subjective effect. These data are also in line with those of Volkow et al. (1996; 2002b), who documented that alcoholics have lower D_2 receptor availability than control subjects, and suggested that this may result in increased alcohol consumption to activate a deficient dopaminergic reward pathway.

The association of relative D_2 levels with subjective intoxication and high were found only in the left nucleus accumbens. Although we had no a priori reason to expect a differential relationship between alcohol-induced sensa-

Table 1. [¹¹C]raclopride D_2 Receptor Binding Potential Values for Baseline Scan, Alcohol Infusion Scan, and the Average Change in Binding Potential, by Region (n=8)

Region	BP₁	BP₂	ΔBP	t	p
Left nucleus accumbens	1.52 ± 0.29	1.46 ± 0.33	0.02 ± 0.23	0.43	0.68
Right nucleus accumbens	1.65 ± 0.22	1.76 ± 0.46	−0.09 ± 0.34	−0.61	0.56
Left dorsal caudate	2.05 ± 0.42	2.04 ± 0.33	−0.01 ± 0.10	0.15	0.88
Right dorsal caudate	2.05 ± 0.29	2.14 ± 0.35	−0.06 ± 0.17	−0.79	0.46
Left anterior putamen	2.78 ± 0.40	2.79 ± 0.41	−0.01 ± 0.06	−0.22	0.83
Right anterior putamen	2.52 ± 0.28	2.73 ± 0.35	−0.10 ± 0.18	−1.43	0.20
Left posterior putamen	2.61 ± 0.62	2.68 ± 0.30	−0.06 ± 0.13	−0.63	0.55
Right posterior putamen	2.31 ± 0.33	2.61 ± 0.50	−0.15 ± 0.28	−1.59	0.16

BP₁, baseline scan; BP₂, alcohol infusion scan; ΔBP, average change in binding potential.
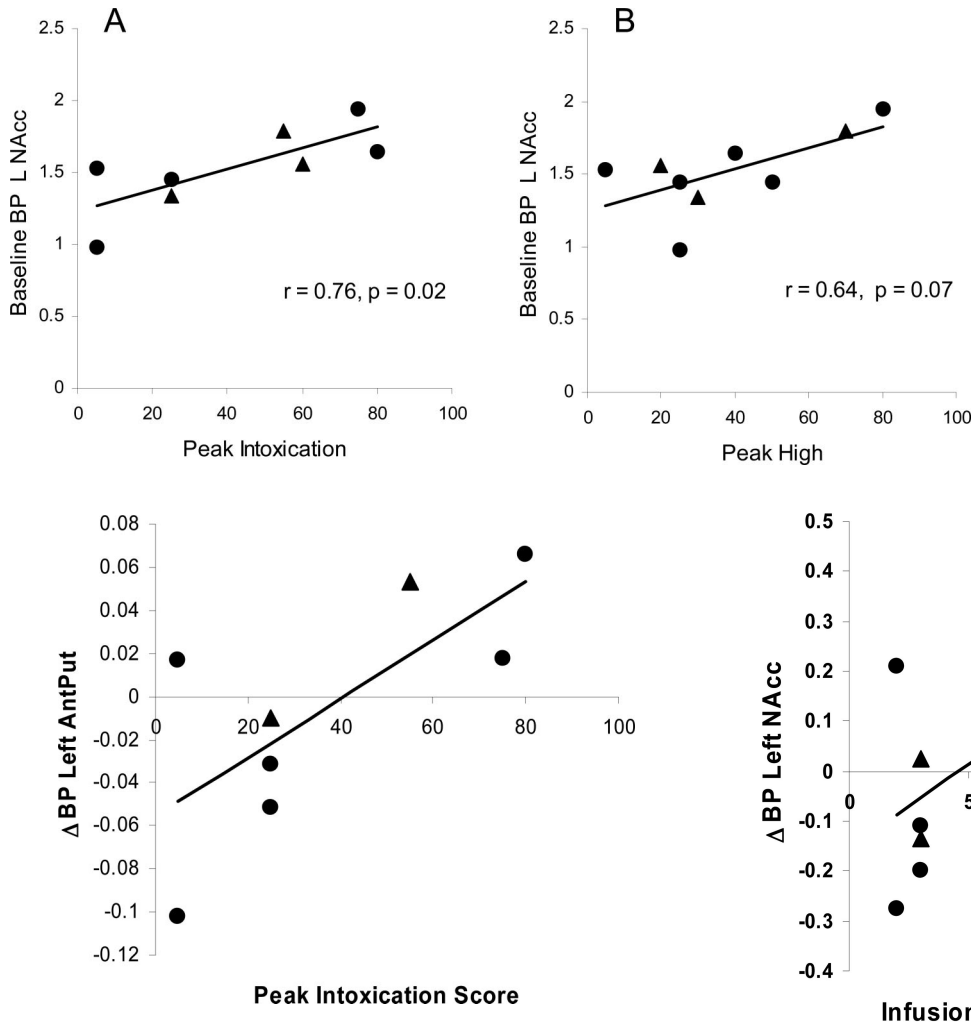The t statistics and p-values for the paired t-tests of differences in BP between scan conditions are also presented.

Fig. 2. Correlations of baseline [¹¹C]raclopride D_2 binding potential (BP) in the left nucleus accumbens (L NAcc) with (A) peak intoxication, and (B) peak high scores reported during IV alcohol infusion. n = 9 in both plots. In (A), there are two points that overlap at (25, 1.448295) and at (25, 1.449356). The three family history positive subjects are denoted by triangles.
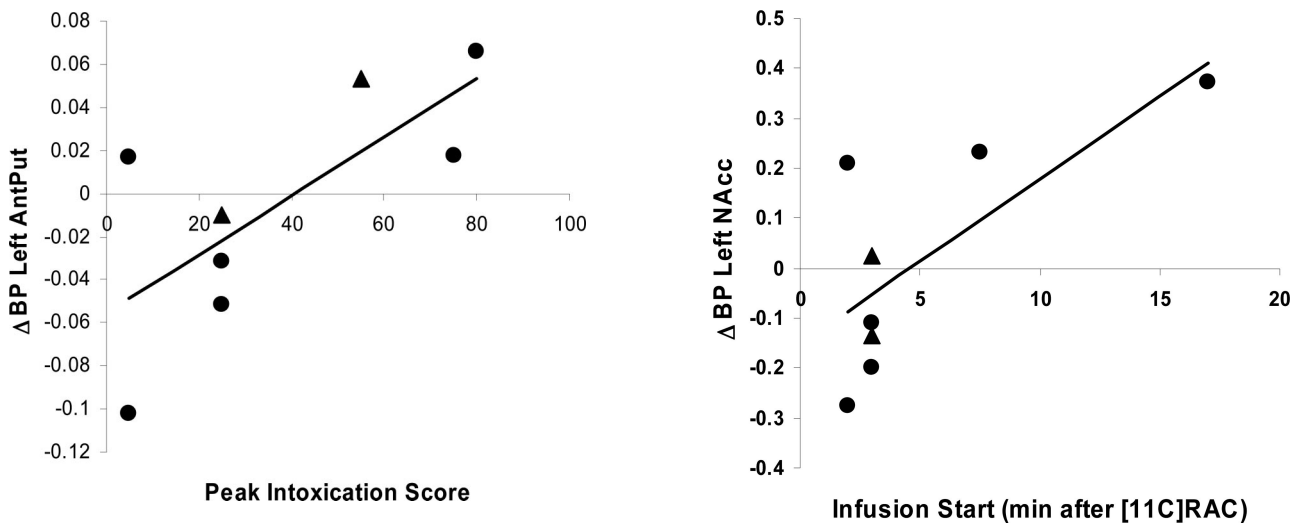

Fig. 3. Change in binding potential (ΔBP) in the left anterior putamen (AntPut) is correlated with peak intoxication score. The two family history positive subjects who received alcohol infusions during scanning are denoted by triangles.
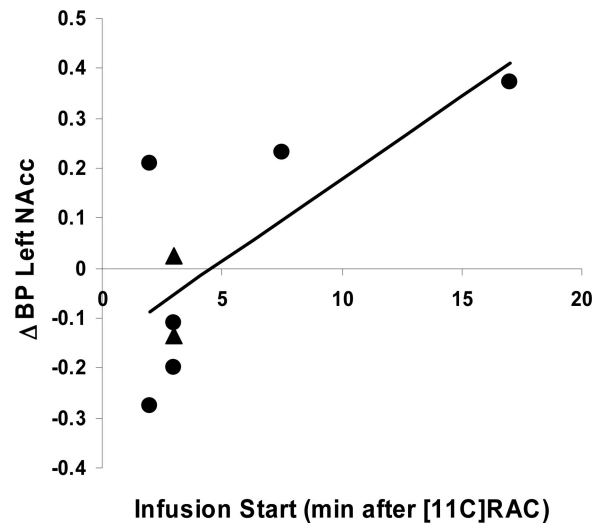

Fig. 4. Change in binding potential (ΔBP) in the left nucleus accumbens is correlated with timing of the alcohol infusion after the start of the [¹¹C]raclopride ([¹¹C]RAC) scan. The two family history positive subjects who received alcohol infusions during scanning are denoted by triangles.

tions in either the left or right nucleus accumbens, several studies suggest that some perceptual responses involving alcohol and other drugs of abuse may be hemisphere-specific (Breiter et al., 1997; Mathew et al., 1997; Modell and Mountz, 1995; Volkow et al., 1999a).

Significant and trend-level associations between ΔBP and intoxication score and between ΔBP and timing of alcohol infusion were found in some regions. It should be noted that these correlations were driven mostly by nega-

tive ΔBP values, which, by definition, imply a decrease in endogenous dopamine in response to alcohol - a response opposite to that which we would anticipate. These data should be interpreted with caution, although it is not unusual for other groups to report correlations that include similar negative ΔBP data points (Abi-Dargham et al., 2003; Barrett et al., 2004; Volkow et al., 1999c). Thus, we cannot rule out the possibility that some individuals expe-

rience a reduction in endogenous dopamine in response to alcohol exposure.

A surprising finding of this study was the lack of a consistent dopaminergic response to alcohol (measured by ΔBP), although this is consistent with previously reported results (Salonen et al., 1997). Certain limitations of the present study could have contributed to this result. First, the timing of the alcohol infusion (and, presumably, the dopaminergic response) was not consistent across all subjects, which can lead to a high variability in ΔBPs across subjects (Yoder et al., 2004). Second, the target alcohol clamp dose was 60 mg%, which may not have been strong enough to elicit a consistently measurable response across all subjects. Finally, we cannot exclude the possibility that the heterogeneous nature of the sample (with respect to gender and family of history of alcoholism) obscured some effects of alcohol on DA release.

Future studies are needed to examine the effect of family history of alcoholism on baseline D_2 availability and the influence of family history on the relationship of D_2 levels and the subjective response to alcohol. Subjects who have a family history of alcoholism are more sensitive to the effects of intravenously infused alcohol, and develop a more acute tolerance to the effects of "clamped" alcohol concentration over time (Morzorati et al., 2002). Given the differences in subjective responses in FHP and FHN subjects and the results of the current study, it would be of interest to explore the differences of D_2 receptor availability in FHN and FHP subjects as well as the relationships between D_2 levels and subjective responses in both groups.

In summary, this work continues to support the idea that D_2 receptors are related to subjective experiences from alcohol. Further studies are needed to understand how this is relevant to the development of alcohol abuse and alcoholism.

ACKNOWLEDGEMENTS

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