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Short communication

Effects of methamphetamine on the noradrenergic activity biomarker salivary alpha-amylase

Colin N. Haile*, Richard De La Garza II, James J. Mahoney III, Thomas F. Newton

Baylor College of Medicine, Menninger Department of Psychiatry & Behavioral Sciences, Michael E. DeBakey VA Medical Center, Houston, TX 77030, USA

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ABSTRACT

Background: Methamphetamine (METH) potently activates the sympathetic nervous system (SNS) by increasing central and peripheral norepinephrine (NE). Salivary α-amylase (sAA) is a biomarker of SNS activation that correlates with plasma NE levels. The purpose of this study was to determine the impact of METH on sAA activity and whether changes in sAA activity were correlated with subjective effects ratings.

Methods: Non-treatment seeking METH-dependent volunteers ($N = 8$) participated in this within-subjects laboratory-based study. Volunteers received randomly administered intravenous METH (0 mg, 30 mg) and sAA activity, cardiovascular measures and subjective ratings were assessed at baseline (−15 min) and five post-METH time points (10, 20, 30, 45, and 60 min).

Results: METH (30 mg) increased sAA activity over time. sAA activity significantly correlated with diastolic blood pressure following 0 mg METH and systolic blood pressure following 30 mg METH. Subjective ratings (ANY EFFECT, HIGH, GOOD, STIMULATED, LIKE, WLLING TO PAY) highly correlated with sAA over five post-METH time points ($N = 40$; r's = 0.543–0.684, p's < 0.001). Age, body mass index and METH amount received on a mg/kg basis were significantly associated with sAA activity. Multiple linear regression analysis indicated sAA activity remained a significant predictor of subjective ratings following METH after controlling for these factors.

Conclusions: The NE peripheral biomarker sAA activity is associated with METH's subjective effects.

1. Introduction

Methamphetamine (METH) rapidly increases central dopamine (DA) and norepinephrine (NE) neurotransmission by acting as a substrate for presynaptic and vesicular monoamine transporters, reversing their action and increasing cytosolic and synaptic transmitter levels (Sulzer, 2011). Increases in synaptic catecholamine levels within specific brain mesocorticolimbic circuitry are thought to mediate METH's reinforcing effects (Vollm et al., 2004). Although most research has focused on DA, accumulating evidence indicates NE may play an important role in mediating METH's effects (Weinshenker and Schroeder, 2007). Indeed, METH induces NE release more potently than DA and medications that target NE attenuate stimulant-induced positive subjective drug effects and decrease drug use (Colfax et al., 2011; Haile et al., 2012; Newton et al., 2012).

Salivary α-amylase (sAA) is better known as the enzyme responsible for the digestion of starch but has been shown to be a biomarker of stress-induced activation of the sympathetic nervous system (SNS; Nater and Rohleder, 2009). Stress-induced increases in plasma NE correlate with sAA activity (Thoma et al., 2012). Similar to stress, adrenergic agonists and medications that facilitate the release of NE also increase sAA activity whereas adrenergic antagonists reduce sAA activity (Andrews and Pruessner, 2013; Ehlert et al., 2006; van Stegeren et al., 2006).

To our knowledge, there are no studies assessing the impact of acute METH administration on sAA activity. Therefore, we conducted the present study in non-treatment seeking METH-dependent volunteers to determine if METH administration would alter sAA activity and if sAA activity was related to METH's cardiovascular and subjective effects.

2. Methods

2.1. Subjects

Data included in this study were obtained from eight non-treatment seeking METH-dependent individuals who were taking part in other studies in our laboratory. This study was conducted at the Baylor College of Medicine (BCM) and the Michael E. DeBakey Veteran's Administration Medical Center (MEDVAMC). Subjects

* Corresponding author at: Baylor College of Medicine and Michael E. DeBakey VA Medical Center, 2002 Holcombe Blvd., Houston, TX 77030, United States. Tel.: +1 713 791 1414x6019.
E-mail address: chaile@bcm.edu (C.N. Haile).

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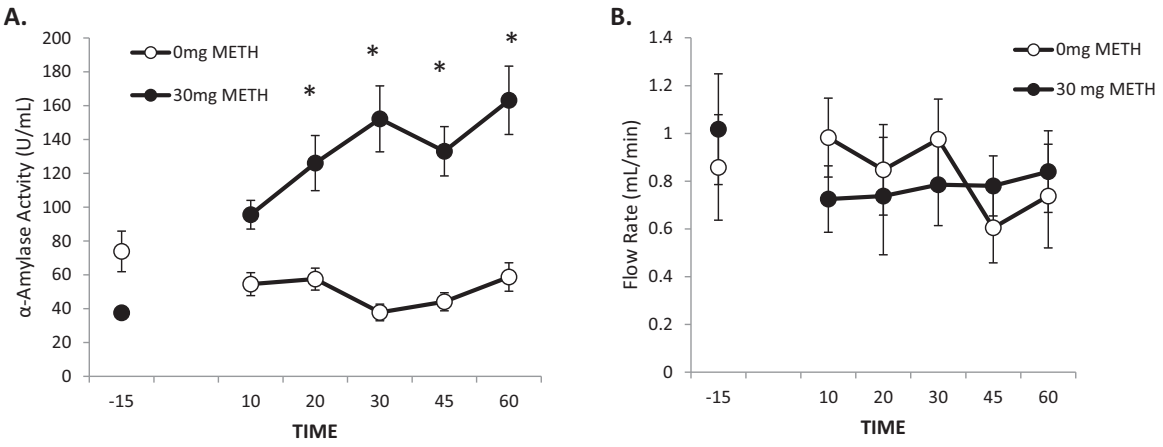

Fig. 1. Impact of METH (0 mg and 30 mg) administration on salivary α-amylase activity (A) and salivary flow rate (B) over time. Time in minutes is relative to the administration of METH. Data is presented as mean ± SEM. Significance is denoted by * ($p < 0.05$).

were paid for their participation. All gave consent after being fully informed about the study protocol.

All subjects (7 male, 1 female; African American-2, Caucasian-5, Hispanic-1) met DSM-IV-TR criteria for METH-dependence. Additional inclusion criteria were age between 18 and 55 years (mean age, 38.13 ± 2.92 yrs), a history of METH use (mean yrs METH use, 19 ± 2.31; last 30 days, 18.06 ± 2.25) by smoking or intravenous routes (smoke-2, IV-1, all routes-5), being in good health, confirmed by a physician and clinical laboratory blood chemistry tests. Subjects were excluded if criteria were met for dependence on other drugs except for nicotine (mean yrs use, 19 ± 4.04; last 30 days, 26.25 ± 3.75) and cannabis (mean yrs use, 13.29 ± 5.11; last 30 days, 3.88 ± 3.73). All subjects had used alcohol in the past but did not meet criteria for dependence (mean yrs use, 15.88 ± 3.82; last 30 days, 2.50 ± 1.83).

2.2. Study design

This study was conducted using a double-blind, placebo controlled, randomized within-subjects design. The study protocol consisted of a single test day with two sessions (AM and PM) where the participant randomly received 0 mg (saline) or 30 mg METH. Infusions were administered with the participant resting in a hospital bed. Subjective ratings were obtained using visual analog scales (0 and 100). Cardiovascular measures (HR, systolic, SBP, diastolic, DBP) and electrocardiograms (ECG) were collected at baseline (−15 min) and five time points throughout each session (10, 20, 30, 45, and 60 min) following infusion. Participants were allowed to smoke cigarettes up to 30 min prior to each infusion session only. Sterile METH for human use was provided by NIDA's medication supply program (RTI International, Research Triangle Park, NC) and prepared by the MEDVAMC Research Pharmacy.

2.3. Salivary α-amylase activity (sAA)

Salivary α-amylase activity was determined using a commercially available kit (Salimetrics, State College, PA, USA). Saliva samples were obtained using the Salimetrics Oral Swab which was placed under the tongue for 30 s at the same time participants provided subjective effects ratings. Samples were then stored at −80° C until assayed in our laboratory.

2.4. Data analysis

Data analysis was performed using SigmaStat 12.0 (SYSTAT Software Inc., San Jose, CA, USA). Normality (Shapiro–Wilk) and equal variance tests revealed the sAA data was found to be highly skewed so log-transformed values were used in the analysis. Untransformed values were used to generate Fig. 1A Cardiovascular measures, subjective ratings, sAA activity and salivary flow rate were assessed using a two-way repeated measures analysis of variance (METH dose: 0 mg and 30 mg; time: −15–60 min) with time as the repeated factor. Significant main effects were followed with pair-wise multiple comparison procedures (Bonferroni *t*-test). Regression analysis (Pearson's and Spearman Rank Order) was used to determine possible relationships between sAA activity, cardiovascular measures and subjective ratings over all time points within the session except baseline ($N = 40$, 10–60 min). Body mass index (BMI), diurnal rhythms, gender and age may influence sAA activity (Rohleder and Nater, 2009). Therefore, factors that showed a significant relationship with sAA activity were included in a Multiple Regression Analysis model assessing their ability to predict a given dependent variable (e.g. ANY EFFECT, HIGH). An additional Multiple Regression Analysis model that included the time (AM/PM) in which a participant randomly received METH was used to ascertain whether diurnal or order effects influenced sAA. Extra diagnostic tests were employed to assess the potential impact of each individual data point ($DFFITS_i$ statistic, leverage and Cooke's Distance). Significance was set at $p < 0.05$ and all data are presented as mean ± standard error.

3. Results

3.1. Effects of METH on subjective ratings and cardiovascular measures

Infusion of 30 mg METH significantly increased HR (METH dose × time interaction, $F_{5,95} = 3.64$, $p < 0.05$), SBP and DBP (F's > 2.8, p's < 0.05) over time compared to 0 mg METH. Post hoc pair-wise multiple comparisons revealed significant differences from 0 mg METH at all time points except baseline (−15 min) following METH (p's < 0.05). Main effects and interactions (F's > 3.19, p's < 0.05) were found for ratings of ANY EFFECT, HIGH, GOOD, LIKE, STIMULATED, $ WILLING TO PAY. Post hoc pair-wise multiple comparisons following significant main effects revealed differences between METH doses and subjective measures at all time points except baseline (p's < 0.05).

3.2. Effects of METH on salivary alpha-amylase activity

As shown in Fig. 1A, sAA activity differed over time and was dependent upon METH dose. This statement is supported by a significant main effect for METH dose ($F_{1,95} = 40.30$, $p < 0.001$) and time ($F_{5,95} = 2.97$, $p < 0.05$) and a METH dose × time interaction ($F_{5,95} = 3.95$, $p < 0.05$). Post hoc comparisons indicated significant differences in sAA activity at time points 20–60 min (p's < 0.05). There were no main effects found for METH dose or time and no interactions for salivary flow rate, a potential confound (Fig. 1B, F's < 1.80, p's > 0.05).

3.3. Association between salivary alpha-amylase activity and cardiovascular measures and subjective ratings over all time points

For these analyses, we included measures from each time point following infusion, so the sample sizes were 40 (5 time points and 8 participants). Regression analysis revealed that DBP ($N = 40$, $r = 0.431$; $p < 0.006$) was positively correlated with sAA activity following 0 mg METH and SBP ($N = 40$, $r = 0.689$; $p < 0.001$) following 30 mg METH (see Supplementary Material for additional analysis).

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2013.07.029.