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Gender, BDNF Val66Met, and Methamphetamine Use Frequency

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Abstract

Pre-treatment methamphetamine (MA) use frequency is an important predictor of outcomes of treatment for MA dependence. Preclinical studies suggest females self-administer more MA than males but few clinical studies have examined potential sex differences in MA use frequency. Estrogen increases expression of brain-derived neurotrophic factor (BDNF) which has effects on MA-induced striatal dopamine release and protects against MA-induced neurotoxicity. Therefore, we examined potential effects of sex, the Val66Met polymorphism in BDNF, and their interaction, on MA use frequency among 60 Caucasian MA dependent volunteers screening for a clinical trial. Females reported significantly more pre-treatment days with methamphetamine use in the past 30 than males. There was a significant interaction between sex and BDNF Val66Met with the highest frequency of MA use among females with Val/Val genotype. These results, although preliminary, add to the literature documenting sexual dimorphism in response to stimulants including methamphetamine and suggest a potential biological mechanism involving BDNF that may contribute to these differences. Additional research characterizing the biological basis of altered response to methamphetamine among females is warranted.

Keywords

BDNF Val66Met; Brain-derived neurotrophic factor; Gender; Methamphetamine

Introduction

Pre-treatment methamphetamine (MA) use frequency is an important predictor of treatment outcomes for MA dependence. More days in the past 30 with MA use at baseline was associated with lower rates of MA abstinence and treatment retention with standard behavioral therapy for MA dependence [1] while lower pre-treatment MA use frequency is a predictor of response to bupropion for MA dependence [2, 3]. As a result, the identification of factors associated with pre-treatment MA use frequency would have important implications for the design of more effective treatments for MA dependence.

Multiple studies have described gender differences in response to psychostimulants including cocaine and amphetamines [4, 5] that may influence frequency of MA use. In preclinical studies, female rats achieve acquisition of MA self-administration faster and self-administer significantly more MA than male rats [6]. Male mice release more dopamine in

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striatum following MA treatment than female mice [7], estrogen co-infused with MA reduces MA-induced striatal dopamine release [8], and female mice have higher density/activity of the dopamine transporter (DAT) and VMAT2 [9] all of which may contribute to the sex differences observed in MA self-administration. Female mice also exhibit lesser magnitude and duration of striatal dopamine depletion following a neurotoxic dose of MA relative to male mice [10, 11] and treatment of gonadectomized female mice with estrogen protects against MA-induced striatal dopamine depletion [12, 13], suggesting that estrogen may protect females from MA-induced neurotoxicity. Together, these findings suggest that females self-administer more MA, possibly due to increased sensitivity of the striatal dopaminergic systems to the reinforcing effects of MA and/or decreased susceptibility to MA-induced neurotoxicity.

Clinical studies have also found sex differences in response to amphetamines. Similar to preclinical findings, healthy males have greater amphetamine-induced striatal dopamine release [14, 15] and lower striatal dopamine transporter density [16-18] relative to healthy females in imaging studies. Men report greater amphetamine subjective effects than women [19, 20], but amphetamine discriminative-stimulus effects do not differ by sex [20]. Similar to results of human cocaine studies [5], amphetamine subjective effects vary throughout the menstrual cycle. Females report lower subjective effects relative to males during the luteal but not follicular phase [19] suggesting that progesterone may attenuate amphetamine subjective effects, although both estradiol and progesterone increased amphetamine subjective effects among women in experimental studies [21-23] suggesting that non-hormonal factors are also important. Few studies have examined potential sex differences in amphetamine self-administration. In a community sample, women amphetamine users reported higher frequency of amphetamine use and greater emotional effects from amphetamine than men [24] while in human lab studies, women self-administered more low (8 to 10 mg) dose amphetamine capsules but males self-administered more high (16 to 20 mg) dose amphetamine capsules [25, 26]. Higher MA self-administration for women in most but not all clinical and preclinical studies suggest that women may also have higher pre-treatment MA use frequency, but studies examining this are lacking.

In addition to sex differences, brain-derived neurotrophic factor (BDNF), a neurotrophin important for the development and survival of striatal dopaminergic neurons [27], may also influence MA use frequency. Intra-nucleus accumbens infusion of BDNF reduced MA-induced dopamine release and MA-related behaviors in rats [28] while heterozygous BDNF knockout mice exhibit prolonged amphetamine-induced locomotor stimulation [29] suggesting that BDNF may influence MA use frequency via affecting response of striatal dopaminergic systems to amphetamine. BDNF also has neurotrophic effects that may influence MA use frequency by protecting against MA-induced neurotoxicity as use frequency escalates. Both amphetamine [29] and MA [30, 31] increase striatal BDNF expression and MA dependent volunteers have higher plasma BDNF levels relative to health controls [32] which are inversely correlated with length of MA abstinence [33]. BDNF dose-dependently blocked MA-induced neuronal cell death *in vitro* [34] and altered BDNF expression reduced MA-induced striatal dopamine depletion in mice [35] but intra-cerebral injection of BDNF failed to protect against MA-induced neurotoxicity in rats [36] possibly due to species or methodological differences between studies. Together, these results suggest that increased BDNF following MA may be a protective response against subsequent MA-induced neurotoxicity.

The Val66Met single nucleotide polymorphism in the BDNF gene affects intra-neuronal BDNF trafficking and secretion [37], with lower activity-dependent BDNF secretion with the Met allele [38] and as a result, Vall66Met may influence MA use frequency via altered BDNF secretion. The Val allele (higher BDNF secretion) is associated with MA dependence in

Chinese males [39, 40] but not Caucasian males [41] or in a predominantly male Japanese sample [42] but whether BDNF Val66Met is associated with MA dependence in females is not known. In a human lab study among healthy adults, Val/Val homozygotes reported greater amphetamine subjective effects (arousal and energy) relative to Met carriers [43] while we previously reported better outcomes of treatment for MA dependence among Caucasians with Val/Val genotype [44]. But no studies have examined whether Val66Met is associated with frequency of MA use.

In addition to potential main effects of sex and BDNF Val66Met on MA use frequency, preclinical studies suggest that sex and Val66Met may interact to influence MA use frequency. The BDNF gene includes a sequence similar to the estrogen response element [45] and estrogen increases brain BDNF expression [46, 47] while BDNF expression is reduced in estrogen receptor-α knockout mice [48]. These results suggest that the effect of BDNF Val66Met on MA use frequency may differ by sex due to estrogen-mediated increases in BDNF expression in females. Therefore, we performed an exploratory study examining the effect of sex and BDNF Val66Met, as well as their interaction, on pre-treatment MA use frequency among a sample of MA dependent participants entering a MA pharmacotherapy clinical trial.

Methods

Data for this study is taken from a MA dependence pharmacotherapy trial and details regarding the methods of the main trial have been published previously [49]. Inclusion/exclusion criteria were those for the clinical trial. Inclusion criteria were: (1) 18 years of age or older; (2) current MA dependence; (3) willing and able to comply with trial procedures; (4) willing and able to provide written informed consent; and (5) not pregnant or lactating if female. Exclusion criteria were: (1) any unstable medical condition, such as active tuberculosis, unstable cardiac, renal, or liver disease, unstable diabetes, or elevated liver enzymes (SGOT or SGPT) greater than four times the upper limit of normal; (2) a current neurological disorder (e.g., organic brain disease, dementia) or major Axis-I psychiatric disorder not due to substance abuse or past 30 days history of suicide attempts and/or current serious suicidal intention or plan; (3) currently taking prescription medication that is contraindicated for use with modafinil; (4) current dependence on cocaine, opiates, alcohol, or benzodiazepines; (5) alcohol dependence within the past 3 years; (6) mitral valve prolapse, left ventricular hypertrophy, cardiac arrhythmias, angina, myocardial infarction, acute coronary syndrome (unstable angina), cardiac syncope or presyncope, or any EKG abnormalities that suggests the presence of one of these conditions due to cardiac effects of modafinil; (7) a systolic blood pressure greater than 160, or a diastolic blood pressure greater than 100 or a heart rate greater than 70% of the maximum heart rate expected for their age at any screening visit; (8) a history of narcolepsy; (9) a history of sensitivity to modafinil; or (10) any other circumstances that, in the opinion of the investigators, would compromise participant safety.

A total of 207 participants were screened for the trial of which 71 were eligible and were enrolled. Of the 71 participants, 60 Hispanic and non-Hispanic Caucasians are included in the current analysis. Four African American and 2 Asian participants were excluded to avoid issues related to population stratification, 4 participants did not consent to DNA collection, and one participant did not have data for MA use frequency.

Participants were genotyped for the BDNF Val66Met polymorphism using the TaqMan method and the ABI PRISM 7900 Sequence Detection System (ABI, Foster City, CA, USA) at the UCLA Genotyping Core Laboratory. Demographic and clinical information, including days with methamphetamine use in the past 30 and lifetime years of methamphetamine use,

were collected during the clinical trial screening period, prior to initiating treatment, via administration of the Addiction Severity Index (ASI). Demographics, lifetime MA use, ASI scores, and BDNF Val66Met genotype were compared for males versus females using t tests for continuous variables and chi square tests for categorical variables. An ANOVA model including the main effect of sex and BDNF Val66Met genotype, and their interaction, on days with MA use in the past 30 pre-treatment was run. The mean MA use days for males versus females and for BDNF Val66Met among males and females were then compared using t tests. Due to the low frequency of Met homozygotes, Val/Met and Met/Met genotypes were combined for the analysis and are referred to as Met carriers. All analyses were performed using SPSS. The study was approved by the UCLA Institutional Review Board.

Results

There were no significant differences in demographics, lifetime years of MA use, or ASI scores for males versus females other than significantly higher scores on the Family domain of the ASI for females (Table 1). Genotype frequencies for BDNF Val66Met (Table 1) did not differ significantly from those expected from Hardy-Weinberg equilibrium among males ($\chi^2 = 1.32$, d.f. = 1, p = 0.25) or females ($\chi^2 = 1.28$, d.f. = 1, p = 0.26).

In a two-way analysis of variance model, the main effect of gender (F = 8.7, d.f. = 1, p = 0.005) and the interaction between gender and BDNF Val66Met genotype (F = 7.8, d.f. = 1, p = 0.007) were significantly associated with mean number of days with MA use in the past 30 but the main effect of BDNF Val66Met (F = 0.2, d.f. = 2, p = 0.817) was not significant (overall model F = 5.4, d.f. = 4, p = 0.001, R squared = 0.28). Females reported more days with MA use in the past 30 compared to males (Table 2; t = -3.5, d.f. = 58, p = 0.001). Among females, mean number of days with MA use was significantly higher for Val/Val homozygotes relative to Met carriers (t = 2.3, d.f. = 14, p = 0.036) while among males, MA use days were lower for Val/Val homozygotes relative to Met carriers, but the difference was not statistically significant (t = -1.9, d.f. = 42, p = 0.064; Table 2).

Discussion

In a sample of treatment-seeking MA dependent participants entering a pharmacotherapy trial, females reported significantly more days with MA use in the 30 days pre-treatment than males. Pre-treatment MA use days is an important predictor of treatment outcomes with behavioral therapy [1] and pharmacotherapy [2, 3] for MA dependence and therefore if confirmed, these results would have important clinical implications.

The higher MA use frequency among women in this sample of treatment seeking MA-dependent volunteers is similar to results of preclinical studies which have found that females self-administer more MA than males [6]. Few clinical studies have examined sex differences in MA use frequency or self-administration. Women reported more frequent amphetamine use than men in a community sample of amphetamine users [24] and women self-administered more low, but not high, doses of amphetamine in a human lab study [25]. Results of these studies and the current study suggest that women use MA more frequently than men but additional clinical studies attempting to replicate this result are needed before any conclusions can be made.

If future studies confirm more frequent MA use in females, it may result from sex differences in sensitivity of striatal dopaminergic systems to amphetamine, including lower amphetamine-induced dopamine release and greater density/activity of DAT and VMAT2 in females [7, 9, 14, 16] and reductions in MA-induced striatal dopamine release with estrogen [8].

Estrogen also has neuroprotective effects [13] and females may be able to use MA more frequently due to a greater resistance to MA-induced neurotoxic effects. Alternately, differences in MA pharmacokinetics [50] or social/environmental influences may contribute to sex differences in MA use frequency. The current study does not include data to identify the mechanism underlying potential sex differences in MA use frequency and therefore additional studies are needed.

In addition to the main effect for sex, there was also a significant interaction between sex and BDNF Val66Met genotype with females with Val/Val genotype reporting greater MA use frequency relative to female Met carriers. To our knowledge, this is the first study to examine BDNF Val66Met and MA use frequency. Previous studies have found an association between the Val allele and MA dependence in Chinese males [39, 40] but not in Caucasian or Japanese samples [41, 42] and Val/Val homozygotes reported greater amphetamine subjective effects than Met carriers in a human lab study [43] but none of these studies examined MA use frequency or self-administration.

Although speculative, previous studies do suggest several possible mechanisms to explain the observed interaction between sex and BDNF Val66Met on MA use frequency. First, the Val66Met Met allele is associated with lower activity-dependent neuronal BDNF secretion relative to Val [38] while estrogen increases BDNF expression [47] suggesting that the effect of the Val allele on BDNF secretion may be enhanced in females due to estrogen-mediated increases in BDNF expression. Second, both BDNF [28] and estrogen [8] reduce MA-induced striatal dopamine release and the more frequent MA use observed in Val/Val females may be the result of blunted striatal dopaminergic response to MA prompting more frequent MA self-administration. Finally, both estrogen and BDNF have neuroprotective effects [13, 34] and Val/Val females may therefore be most resistant to neurotoxic effects of frequent MA use. Future studies examining these potential mechanisms for interactions between sex and BDNF on MA self-administration are also warranted.

There are several limitations to this study that render the results preliminary. This is an exploratory study and *post-hoc* analysis with a small sample size, especially among females, which could result in findings due to chance. Replication of the results in a prospective study are required. Furthermore, our results would not survive a Bonferroni correction for multiple comparisons nor a genome-wide level of significance. The sample includes both Hispanic and non-Hispanic Caucasians and the results may be confounded by genetic admixture that is not accounted for in the sample. Participants were a highly selected group of treatment-seeking volunteers with MA dependence entering a pharmacotherapy trial and therefore results are not generalizable to other MA using populations. It is possible that participants may have altered their MA use prior to assessment in anticipation of entering treatment but this is unlikely to explain observed differences by sex or genotype. We did not have data on amount of MA used, only days with MA use, and therefore we cannot exclude the possibility that males administered higher doses on MA but on fewer days than females. Still, results of the study suggest a direction for future studies examining MA use frequency and self-administration.

Conclusions

Our findings, although preliminary, add to a body of literature documenting sexual dimorphism in response to stimulants including MA and point to a potential biological mechanism involving BDNF that may contribute to these differences. Additional research characterizing the biological basis of altered response to MA among females is warranted.

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Table 1

Demographics, lifetime methamphetamine use, Addiction Severity Index Scores, and BDNF Val66Met genotype for methamphetamine dependent participants by sex.

	Mean (S.D.) or % (N)				
	Male (N=44)	**Female (N=16)**	***t* or χ^2**	**d.f.**	***p* value**
Demographics					
Age, years *	38.5 (10.8)	36.3 (9.7)	0.7	57	0.478
Ethnicity					
White, Non-Hispanic	52% (23)	56% (9)	0.1	1	0.785
White, Hispanic	48% (21)	44% (7)			
Education, years	13.4 (2.1)	13.1 (2.5)	0.5	58	0.596
Income, US $	1,634 (3,718)	1,619 (2,680)	0.1	58	0.988
Marital Status					
Married	21% (9)	44% (7)	3.4	2	0.185
Divorced/Separated	23% (10)	12% (2)			
Never Married	56% (25)	44% (7)			
Lifetime methamphetamine use, years	9.4 (6.9)	11.2 (7.0)	-0.9	58	0.383
Addiction Severity Index Score					
Drug	0.21 (0.10)	0.24 (0.07)	-1.0	58	0.302
Alcohol	0.11 (0.14)	0.06 (0.12)	1.0	58	0.307
Employment	0.44 (0.31)	0.45 (0.35)	-0.1	58	0.907
Family	0.17 (0.21)	0.31 (0.26)	-2.1	58	0.039
Legal	0.05 (0.11)	0.08 (0.13)	-0.7	58	0.464
Medical	0.20 (0.28)	0.15 (0.29)	0.6	58	0.576
Psychiatric	0.20 (0.21)	0.17 (0.21)	0.5	58	0.621
BDNF Val66Met Genotype					
Val/Val	73% (32)	50% (8)	4.5	2	0.103
Val/Met	23% (10)	50% (8)			
Met/Met	4% (2)	0% (0)			

* Age missing for one participant

Table 2

Days with methamphetamine (MA) use in the past 30 among MA dependent participants by sex and BDNF Val66Met genotype

	Days with MA Use, mean (S.D.)	*t*	d.f.	*p* value
Males (N = 44)	11.5 (10.3)	-3.5	58	0.001
Females (N = 16)	22.0 (10.0)			
Males *				
Val/Val (N = 32)	9.8 (9.8)	-1.9	42	0.064
Val/Met (N = 10)	16.4 (11.1)			
Met/Met (N = 2)	15.0 (7.1)			
Females *				
Val/Val (N = 8)	27.1 (5.8)	2.3	14	0.036
Val/Met (N = 8)	16.9 (11.0)			
Met/Met (N = 0)	N/A			

* Note: means are shown for each genotype but analyses were performed with Val/Met and Met/Met groups collapsed due to small number of Met/Met genotype.