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Gender Differences in the Effect of Tobacco Use on Brain Phosphocreatine Levels in Methamphetamine Dependent Subjects

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Abstract

Background—A high prevalence of tobacco smoking has been observed in methamphetamine users, but there have been no *in vivo* brain neurochemistry studies addressing gender effects of tobacco smoking in methamphetamine users. Methamphetamine addiction is associated with increased risk of depression and anxiety in females. There is increasing evidence that selective analogues of nicotine, a principal active component of tobacco smoking, may improve depression and cognitive performance in animals and humans.

Objectives—To investigate the effects of tobacco smoking and gender on brain phosphocreatine (PCr) levels, a marker of brain energy metabolism reported to be reduced in methamphetamine-dependent subjects.

Methods—Thirty female and twenty-seven male methamphetamine-dependent subjects were evaluated with phosphorus-31 magnetic resonance spectroscopy (³¹P-MRS) to measure PCr levels within the pregenual anterior cingulate, which has been implicated in methamphetamine neurotoxicity.

Results—Analysis of covariance revealed that there were statistically significant slope (PCr versus lifetime amount of tobacco smoking) differences between female and male methamphetamine-dependent subjects ($p=0.03$). In females, there was also a statistically significant interaction between lifetime amounts of tobacco smoking and methamphetamine in regard to PCr levels ($p=0.01$), which suggests that tobacco smoking may have a more significant positive impact on brain PCr levels in heavy, as opposed to light to moderate, methamphetamine-dependent females.

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Declaration of interest

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Conclusion—These results indicate that tobacco smoking has gender-specific effects in terms of increased anterior cingulate high energy PCr levels in methamphetamine-dependent subjects. Cigarette smoking in methamphetamine-dependent women, particularly those with heavy methamphetamine use, may have a potentially protective effect upon neuronal metabolism.

1. Introduction

1.1 Effects of Methamphetamine and Tobacco Smoking

Methamphetamine use is associated with significant neuroimaging alterations as well as psychiatric symptoms and cognitive impairments (1-3). Methamphetamine-induced toxicity is associated with derangement of dopaminergic systems (4-6) and many other neuronal and molecular systems (7), including toxicity of monoamine and biochemical processes (8-11). Although substantial neurotoxicity is associated with chronic methamphetamine use (2), at this time there are no FDA-approved pharmacotherapies, and psychosocial interventions are the mainstay of treatment (12).

In methamphetamine abusers, tobacco (*Nicotiana tabacum*) smoking is highly prevalent (13, 14). Tobacco smoking is well known to have adverse effects on the human body, such as increased incidence of malignancy (15), cerebrovascular disease, coronary heart disease and pulmonary obstructive disease mediated by atherosclerotic processes, oxidative stress and inflammation (16). The impact of tobacco smoking on cognition has been a point of debate. For example in some reports chronic and heavy tobacco smoking is associated with decreased performance in cognitive domains such as executive function (17), visual search speed and verbal memory (18), and mini-mental state examination scores (19). On the other hand, there is increasing evidence that nicotine may improve cognitive performance overall or selectively in rats, monkeys and humans (20). In humans, positive attentional and non-attentional cognitive effects of nicotine have been reported (21). Tobacco smoking has also been associated with positive effects in some clinical conditions (22). For example, a reduced incidence of Parkinson's disease is associated with tobacco smoking (23, 24). Nicotine, a principal psychoactive component of tobacco smoke, binds to nicotinic acetylcholine receptors, and eventually induces increased dopamine activity in the brain (25, 26), which may be related to the decreased risk of Parkinson's disease. Nicotine and nicotinic acetylcholine receptor agonists also have neuroprotective effects in reducing apoptosis induced by ischemia, and excitotoxicity in brain cortical neurons (27, 28). Thus it has been proposed that the cognitive benefits of nicotine may serve as a form of self-medication, by counteracting methamphetamine-induced neurotoxicity when considering the high prevalence of tobacco smoking in methamphetamine users (13, 14).

1.2 Sex differences in Effects of Methamphetamine and Tobacco Smoking

Females are more sensitive to the reinforcing effects of methamphetamine than are male users (29, 30). Female methamphetamine users also have more severe depressive symptoms, and a higher incidence of depression than male methamphetamine users (31-33). Interestingly, females also appear to be more vulnerable to methamphetamine-induced bioenergetic compromise than males: recently it was reported that women

methamphetamine users had significantly lower phosphocreatine (PCr) levels than men, despite lesser daily usage (11).

The rate of tobacco smoking in subjects with depression has been found to be increased (34, 35). Also, it is known that women are more likely to experience depressive symptoms during tobacco smoking cessation (36-38), and depression serves as a risk factor for tobacco smoking relapse during abstinence (35, 39). Animal and *in vitro* studies have suggested that components of tobacco smoke significantly inhibit monoamine oxidase (MAO) (40-42) despite the mixed reports for the effect of nicotine itself (40, 43). Human studies using positron emission tomography have confirmed that tobacco smoke significantly inhibits MAO-A (44, 45), which is known to result in antidepressant-like effects (46).

1.3 Magnetic Resonance Spectroscopy for Neurochemistry

In vivo magnetic resonance spectroscopy (MRS) can be used to investigate neurochemical changes associated with drug-induced neurotoxicity. Our recent methamphetamine study utilized phosphorus-31 MRS (^{31}P -MRS), a unique method for evaluating the *in vivo* concentrations of high-energy phosphorus-bearing neurometabolites, to find that methamphetamine users had decreased PCr levels in the frontal lobe compared with healthy control subjects (11). PCr is the substrate reservoir for the creatine kinase reaction (47). In brain mitochondria, this reaction reversibly converts PCr and adenosine diphosphate (ADP) into creatine and adenosine triphosphate (ATP) in a 1:1 molar ratio (48). Neuronal energy demands are met through a shift in reaction equilibrium, which is designed to maintain the ATP concentration constant (49). Since ATP is maintained at the sacrifice of PCr levels, PCr levels are more vulnerable to neuronal alterations in brain energy metabolism than ATP levels (50).

1.4 Study Aims

Despite the frequent observation of a high prevalence of tobacco smoking and several differences between females and males with regard to substance use behavior, few published studies have addressed the interaction of “tobacco smoking” $\times$ “gender” on neurochemistry in methamphetamine dependence. Specifically, there have been no reports of the ^{31}P -MRS metabolite levels that are associated with methamphetamine and tobacco smoking.

Therefore the present study aimed to examine the differential effect of tobacco smoking on brain PCr levels in male and female methamphetamine dependent subjects, as a function of subjects’ lifetime quantity of tobacco smoking and methamphetamine. It was hypothesized that there would be significant gender differences in the association between brain PCr levels and lifetime amount of tobacco smoking in methamphetamine dependent subjects.

2. Methods

2.1 Subjects

We enrolled and studied fifty seven adults meeting DSM-IV diagnostic criteria for current methamphetamine dependence, who endorsed methamphetamine as their preferred substance of abuse. Thirty females (mean age 32.8 ± 1.5 yrs) and twenty seven males (35.2 ± 1.1 yrs) met lifetime methamphetamine dependence, as diagnosed with DSM-IV criteria.

Following written informed consent, the Structured Clinical Interview for DSM-IV (SCID-IV), medical history, and physical examination were administered to each participant. Exclusion criteria included: presence of a major medical or neurological disorder, schizophrenia, bipolar disorder, and preferred drug of abuse other than methamphetamine. Subjects were also excluded for HIV seropositivity, full scale intelligence quotient < 70 or a learning disability. The study was conducted in accordance with the policy of the Institutional Review Board of the University of Utah and the Department of Human Services of the State of Utah. Written informed consent was obtained from all participants.

2.2 Neuroimaging Acquisition and Data Analysis

Structural MRI and two dimensional phosphorus magnetic resonance spectroscopic imaging (2D ^{31}P -MRSI) were acquired on a 3 Tesla Siemens scanner (Trio, Siemens AG, Erlangen, Germany) using a $^{31}\text{P}/^1\text{H}$ double-tuned volume head coil (Clinical MR Solutions LLC, Brookfield, WI). Methamphetamine users had been abstinent for at least two weeks at the time of scanning. Three dimensional magnetization prepared rapid acquisition gradient echo (MPRAGE) acquisitions were performed, to obtain high resolution T1-weighted whole-brain volumes for positioning of MRS grids and tissue segmentation of the ^{31}P -MRS data. 2D ^{31}P -MRSI was acquired with chemical shift imaging free induction decay pulse sequence (TR = 3000 ms, TE = 2.3 ms, flip angle = 90° , number of average = 36, vector size = 1024, acquisition matrix 8×8 , field of view = 200 mm $\times$ 200 mm, slice thickness = 2.5 cm, sampling bandwidth = 2.5 kHz, and nominal voxel dimension = 2.5 cm $\times$ 2.5 cm). The MRSI slab was positioned to cover an *a priori* region of interest (ROI), the pregenual anterior cingulate. Bilateral voxels were averaged in order to increase spectral signal to noise ratios. Slabs in axial, coronal, and sagittal orientations of MRSI grid are illustrated in Figure 1. Anatomical MPRAGE data were segmented in each voxel using freely-available FMRIB's Software Library (FSL) (51) into gray matter, white matter, and cerebrospinal fluid. Gray matter tissue fraction was calculated as the ratio to total brain tissue, i.e., gray matter / (white matter + gray matter). Abnormal structural findings were grounds for exclusion, but no subjects were excluded for this reason in the present study.

2D ^{31}P -MRSI data were preprocessed with a Hamming filter to reduce the effect of the point-spread-function, and line-broadened with 10 Hz of apodization. Frequency shift correction, zero-/first-order phase correction and baseline correction were applied after Fourier transformation of the preprocessed data. The ^{31}P -MRSI data were post-processed using the advanced method for accurate, robust and efficient spectral (AMARES) fitting algorithm (52) provided within jMRUI software package (53). The metabolite of interest was PCr (Figure 1) and metabolite integral values were expressed as the fraction of the total phosphorus integral (TP) in the spectrum (54).

Analysis of covariance was performed to compare two regression slopes. A significant "categorical by continuous interaction" meant that the slope of the continuous variables (dependent variable: PCr levels, and independent variable: lifetime amount of tobacco smoking) is different for the levels of the categorical factor (gender group) in methamphetamine dependent subjects. Pearson correlation coefficients (r) were reported. Partial correlation coefficients were also calculated with age, other drug use, and voxel

tissue composition as covariates in the models. As we had an *a priori* hypothesis, adjustments for multiple comparisons were not performed for the exploratory statistical analyses. Fisher's Exact Test was used for categorical demographic variables. Stata for Linux, version 13 (StataCorp, College Station, TX) was used for statistical computations.

3. Results

The female and male methamphetamine groups did slightly differ in mean age, but the difference was small and not significant (i.e., ~2.4 years) ($p = 0.21$). In the methamphetamine dependent subjects, the number of lifetime tobacco smokers versus non-smokers was not significantly different between the groups (29 vs. 1 for females and 24 vs. 3 in males, respectively, $p = 0.34$). Average daily tobacco consumption was 9.7 ± 7.6 and 9.9 ± 7.4 cigarettes for females and males, respectively. Education, handedness, and ethnicity were similar between the groups. Table 1 presents study subject characteristics, including detailed drug use history.

3.1 Relationship between PCr levels and lifetime tobacco smoking amount

Analysis of covariance revealed that there was a statistically significant interaction effect, $F(1, 53) = 5.31$, $p = 0.03$, between gender and lifetime amount of tobacco smoking with regard to brain PCr levels. Post-hoc analysis showed that females had a significant correlation coefficient ($r = 0.58$, $p < 0.01$) between PCr levels and lifetime tobacco smoking, but not male ($r = 0.09$, $p = 0.67$) methamphetamine dependent subjects (Figure 2). To reduce heteroscedastic errors and potential outliers, the robust variance estimation (55) was also performed, which indicated even a higher significance of the interaction term, $F(1, 53) = 5.82$, $p = 0.02$. The relationship between PCr and tobacco smoking in methamphetamine dependent females remained significant, after controlling for demographic variables such as age ($r = 0.52$, $p = 0.01$), education level ($r = 0.47$, $p = 0.02$) and other potentially confounding variables such as cannabis use ($r = 0.52$, $p = 0.01$). The mean gray matter tissue fractions for our anterior cingulate ROI were similar between groups ($43.9 \pm 7\%$ for female and $43.6 \pm 4\%$ for male groups, respectively, $F(1, 55) = 0.04$, $p = 0.84$). When the gray matter tissue fraction was entered as a covariate in the model, the interaction term remained significant $F(1, 52) = 4.89$, $p = 0.03$. Usage of other drugs of abuse including alcohol ($r = -0.13$, $p = 0.52$), cocaine ($r = -0.28$, $p = 0.15$), opioids ($r = -0.15$, $p = 0.44$) and cannabis ($r = -0.21$, $p = 0.29$) did not have a significant association with PCr levels.

3.2 Interaction effects between methamphetamine and tobacco smoking on PCr levels

Female methamphetamine dependent subjects demonstrated a significant continuous by continuous interaction, i.e., lifetime methamphetamine use $\times$ lifetime tobacco smoking, $F(1, 26) = 7.0$, $p = 0.01$ (see Figure 3 for graphic illustration). This finding suggests that lifetime tobacco use may have a more significant impact on brain PCr levels in heavy, as opposed to light to moderate methamphetamine users.

3.3 Other exploratory findings

There were no group differences in gray matter tissue fraction in the voxels of anterior cingulate, $F(1, 55) = 0.04$, $p = 0.84$, temporoparietal lobe, $F(1, 55) < 0.01$, $p = 0.95$, and

occipital lobe, $F(1, 55) = 0.81$, $p = 0.37$. PCr and other phosphorus metabolites such as phosphomonoester, phosphodiester, inorganic phosphate and nucleoside triphosphate did not reveal gender differences (see Table 2). There were no methamphetamine $\times$ lifetime tobacco smoking interactions in metabolites other than PCr. In other brain regions, our gender-based analyses did not reveal significant interactions between lifetime amount of tobacco smoking and gender with regard to PCr levels (temporoparietal lobe, $F(1, 53) = 2.15$, $p = 0.15$; occipital lobe, $F(1, 53) = 2.10$, $p = 0.15$).

4. Discussion

The present study is the first to report a significant positive correlation between lifetime tobacco smoking and high energy phosphate metabolism, specifically PCr concentration, in female methamphetamine dependent subjects. This finding of a positive tobacco smoking effect in methamphetamine users is consistent with evidence from studies of neurodegenerative conditions. For instance, significantly lower rates of dementia have been reported in smokers (56, 57). *Ex vivo* experiments have reported that nicotine has protective effects against beta-amyloid and senile plaques in cultured cells (58-60). Preclinical studies have also shown that acute nicotine administration produces alterations in brain phospholipid and high-energy phosphate metabolism. As a further clinical example, epidemiological studies have demonstrated that the incidence of Parkinson's disease is less than half in tobacco smokers compared to that in non-smokers, even after accounting for tobacco smoking-related mortality (22, 24). Also, an animal model of rotenone-induced Parkinson's disease showed reduced dopaminergic neuronal cell loss in the substantia nigra, following simultaneous subcutaneous injection of nicotine and rotenone (61). Another study reported that nicotine pretreatment produced a significant protection in methamphetamine-induced Parkinsonian-like neurodegeneration in wild-type mice (62). The authors suggested that the $\alpha 4$ nicotinic subtype receptor may be required for this protection, because $\alpha 4$ knockout mice did not display this neuroprotective effect (62). Since the risk of Parkinson's disease is significantly higher in methamphetamine users (hazard ratio = 1.76) as compared to control subjects or cocaine users (63, 64), it is of interest that tobacco smoking was associated with increased brain PCr levels in the present study.

The exact neural and molecular mechanisms responsible for this relationship have yet to be elucidated, but there are several potential explanations. First, nicotine could provide neuroprotection as an antioxidant due to its free radical chain-breaking properties, thus reducing free radical generation. Since estrogens have been reported to have similar neuroprotective effects (65, 66), it is possible that synergistic benefits may exist, contributing to the increased PCr levels in females with relatively large amounts of lifetime tobacco smoking (67, 68). Thus, the gender differences in tobacco smoking effects may be due to higher levels of estrogen in females. Second, chronic nicotine treatment has been reported to reverse memory and learning impairment in hypothyroidism (i.e., rats with a surgically removed thyroid gland) (69). Of note, amphetamine administration is associated with thyroid hormonal changes (70) and several of its actions are thought to be similar to those of thyrotropin-releasing hormone (71). Third, the high prevalence of depression in female methamphetamine users may have affected our findings. Since it is reported that severe depression is associated with lower PCr levels compared to mild depression (72), PCr

levels might be changed if tobacco smoking improves depressive symptoms as a self-treatment in subgroups with a genetic predisposition such as a dopamine D4 receptor gene polymorphism (73-75).

PCr is the substrate reservoir for the PCr $\leftrightarrow$ ATP energy exchange in the creatine kinase reaction, serving as a buffer to maintain constant ATP levels in highly active neuronal cells (76). Decreased PCr levels suggest that methamphetamine use may be associated with a disruption in brain energy metabolism (11). When methamphetamine rapidly decreases ATP levels (77), the PCr-creatine kinase system provides an intracellular buffer against ATP depletion. PCr and creatine levels are also known to affect mitochondrial respiration in brain (78, 79). Thus, increased PCr levels may help buffer high energy phosphate metabolism as well as protect from neuronal damage. For example, significant neuroprotection from cerebral ischemia has been noted following phosphocreatine pre-injection in rodents (80). Also, increases in PCr levels have been reported after coenzyme Q10 treatment in patients with mitochondrial cytopathies (81). Of special interest, PCr modifying agents such as creatine monohydrate increased brain PCr levels in humans (82, 83) as well as in animals (84). While the mechanism for potential gender differences in nicotine modulation of pregenual anterior cingulate PCr levels cannot be fully characterized by ^{31}P -MRS alone, our data provide a rationale for future investigations examining the impact of gender on the relationship between tobacco smoking and PCr concentrations. To start with, gender differences have been found in diverse stages of drug abuse and dependence (30, 85, 86). For example, the accelerated progression to treatment entry among women dependent on opioids, cannabis or alcohol, suggests gender-based differences in vulnerability to the adverse effects of addiction (87). In terms of drug initiation, binge use and relapse, women appear to be more susceptible than men, a phenomenon thought to involve estrogen interactions with neuronal reward and stress systems (29). Further, women, in comparison with men, experience a greater mood-altering effect of psychostimulants (88). The psychoactive effects of methylenedioxy-methamphetamine (MDMA) are reported to be more intense in women than in men, including greater perceptual changes and thought disturbances, in addition to acute adverse effects (89). Taken together, the exact mechanism of the gender differences reported here has yet to be determined, but estrogen changes have been implicated in stimulant drug response and behavioral sensitization (88, 90). For instance, estrogen in female mice may increase methamphetamine-induced neurotoxicity under certain conditions, such as when nigrostriatal dopaminergic systems have been impaired by methamphetamine administration (91).

The results of this study suggest that the significant correlation between lifetime tobacco smoking and PCr level may be confined to prefrontal region of the cortex, since we found no significant correlation in either the occipital or temporoparietal lobes. This finding suggests that methamphetamine and tobacco smoking-related interactions for brain changes are not uniform, which is consistent with prior reports of significant regional differences in methamphetamine-induced brain changes. For example, a regional study of rats found that the hypothalamus is relatively resistant to the long-term dopaminergic deficits of methamphetamine (92). Also, the nucleus accumbens is less susceptible than the striatum to dopaminergic insults caused by methamphetamine (93-95).

There are several limitations to the present study. First, the lack of a tobacco smoking-only group prevented the exploration of isolated tobacco smoking effects on PCr levels. Thus, our findings of the alterations of brain PCr levels by tobacco smoking should be interpreted only in the context of methamphetamine dependence. The individual effects of tobacco smoking may be distinct from the interactive effects of tobacco smoking and methamphetamine in female subjects that we report here. Future studies using larger samples should consider including a tobacco smoking-only group to measure the independent effects of nicotine on ^{31}P metabolites. Second, we did not control for menstrual cycle stage in this study's female subjects, which may have introduced some variability to our data. Future studies will need to collect menstrual phase data from participants, in order to test for a significant effect. The lack of control for depressive symptoms is another limitation, but our follow-up methamphetamine study has been designed to overcome this limitation. Third, although we have segmented and co-registered anatomical images to account for gray matter tissue fraction in our voxels, "pure" tissue-specific estimation of metabolite levels would not be possible, partly because of the large voxel size and low signal to noise ratios of the ^{31}P -MRS data. Moreover, potential nonlinear associations between brain tissue component and PCr levels could not be fully addressed in our linear statistical models. Fourth, corrections for multiple comparisons were not performed for exploratory statistical analyses. Caution is required when reviewing these analyses, except for the *a priori* hypothesis.

Our findings should be interpreted with caution, since the neurochemical benefits from tobacco smoking in female methamphetamine users are outweighed by the toxicity and potential harms of tobacco usage. If nicotine is to be used therapeutically, the properties that confer benefit would need to be separated from the harmful properties. For instance, the differential effects of nicotinic receptor subtypes are deserving of investigation. Also, psychiatric symptom assessment and longitudinal studies would be required to identify the mechanism of the interaction between tobacco smoking and methamphetamine usage.

5. Conclusion

To the best of our knowledge, the present study provides the first evidence that tobacco smoking may have a positive correlation with *in vivo* prefrontal PCr levels in methamphetamine dependent females. This is compatible with tobacco smoking's association with a reduced incidence of Parkinson's disease, especially in light of the fact that methamphetamine toxicity on nigrostriatal dopamine neurons mimics the neurodegenerative process in Parkinson's disease (96). Interestingly, heavy female methamphetamine dependent subjects demonstrated increased benefits from tobacco smoking in PCr levels. Further study is warranted, to explore the potential for interactive effects between tobacco smoking and other PCr modifying agents such as creatine monohydrate, in order to develop novel therapeutic agents acting outside of dopaminergic reward circuits, as targeted treatments for methamphetamine users and methamphetamine-induced neurotoxicity.

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Figure 1.

(A) Axial view of grid placement in two dimensional chemical shift imaging and region of interest (ROI). (B) Coronal and sagittal view of the ROI. Each blue box indicates the same ROI. (C) An illustration of phosphorus-31 magnetic resonance spectra with 10 Hz of apodization. PME, phosphomonoester; Pi, inorganic phosphate; PDE, phosphodiester; PCr, phosphocreatine; NTP, nucleoside triphosphate; ppm, parts per million

Figure 2.

A significant regression slope difference between female and male methamphetamine-dependent subjects with regard to the relationship between phosphocreatine levels and lifetime tobacco consumption (i.e. a significant interaction of gender $\times$ lifetime tobacco smoking, $F(1, 53) = 5.31$, $p = 0.03$, in the methamphetamine-dependent subjects). Please note that the graphics display simple correlations without covariates. (A) A significant positive relationship between brain phosphocreatine levels and total lifetime tobacco use in methamphetamine-dependent females ($r = 0.58$, $p < 0.01$), (B) but not in males ($r = 0.09$, $p = 0.67$). Lifetime Tobacco (n) represents cumulative numbers of lifetime cigarettes. The dotted line represents linear model. The area of the gray zone represents 95% confidence intervals of the regression line.

Figure 3.

A significant interaction between two continuous variables of lifetime amount of methamphetamine and lifetime amount of tobacco smoking $F(1, 26) = 7.0, p = 0.01$, with regard to brain PCr levels in female methamphetamine-dependent subjects, which suggests that lifetime tobacco use may have a more significant impact on brain PCr levels in heavy as opposed to light to moderate methamphetamine-dependent females. The illustration displays marginal predictions at two representative amounts of lifetime methamphetamine at (A) 100 mg, representing “light to moderate” and (B) 800 mg, representing “heavy” use patterns. Lifetime Tobacco (n) represents cumulative total numbers of lifetime cigarettes. Error bars represent the 95% confidence interval (CI).

Table 1

Demographics, clinical characteristics, and drug use history

Subject demographics	Total (n = 57)	Female methamphetamine users (n = 30)	Male methamphetamine users (n = 27)	Significance (p-value)
Age (years)	34.0 (1.0)	32.8 (1.5)	35.2 (1.1)	0.21
Education (years)	12.7 (0.3)	12.5 (0.4)	12.9 (0.3)	0.54
Handedness (right/left)	50/7	26/4	24/3	0.56
Race (white/others)	51/6	27/3	24/3	0.61
Methamphetamine onset (yrs)	21.9 (1.0)	20.9 (1.4)	23.1 (1.3)	0.26
Methamphetamine duration (yrs)	12.0 (1.0)	11.9 (1.4)	12.1 (1.4)	0.90
Methamphetamine abstinence (days)	35.8 (5.6)	41.3 (9.3)	29.6 (5.4)	0.30
Lifetime drug use ^a				
Methamphetamine (hits)	1486 (241)	1125 (221)	1887 (437)	0.11
Nicotine (packs ^b)	967 (119)	895 (150)	1047 (190)	0.53
Amphetamine	Varies	—	—	—
Alcohol (drink-years ^c)	22 (7)	9 (3)	33 (13)	0.08
Cocaine (grams)	1406 (377)	971 (391)	1889 (662)	0.23
Opiates (grams)	290 (177)	50 (27)	558 (368)	0.15
Hallucinogens	Varies	—	—	—
Cannabis (joint)	2774 (558)	1761 (663)	3837 (887)	0.06

^aData are expressed with mean (SEM). Total lifetime drug amount was estimated using “average daily dosage × frequency × duration.”

^bA pack is defined as twenty cigarettes.

^cAlcohol intake calculated in drink-years (1 drink/day in 1 year).

Table 2

Comparisons of brain PCr levels and other phosphorus metabolites between female and male methamphetamine dependent subjects.

Metabolites [†]	Female methamphetamine users (n = 30)	Male methamphetamine users (n = 27)	p-value
	mean (SD)	mean (SD)	
PCr	0.212 (0.021)	0.220 (0.020)	0.20
PME	0.211 (0.040)	0.208 (0.033)	0.75
Pi	0.078 (0.011)	0.074 (0.013)	0.19
PDE	0.276 (0.042)	0.280 (0.037)	0.70
α-NTP	0.244 (0.017)	0.242 (0.017)	0.65
β-NTP	0.183 (0.029)	0.189 (0.020)	0.39
γ-NTP	0.283 (0.022)	0.278 (0.016)	0.40

Abbreviations: PCr, phosphocreatine; PME, phosphomonoester; Pi, inorganic phosphate; PDE, phosphodiester; NTP, nucleoside triphosphate

[†] metabolite ratios over total phosphate pool.