Impact of Depression on Cerebral Glutamate and Cognitive Function in Abstinent Methamphetamine Users (AMU)

O. Abulseoud[1], N. Sailasuta[2], M. Hernandez[1], and B. Ross[2]

[1]U of Southern California, Los Angeles, CA, United States, [2]HMRI, Pasadena, CA, United States

Introduction: Neuropsychiatric disorders and drug abuse commonly co-exist. Abnormalities in cerebral glutamate concentration, which may reflect overall function in the dominant glutamatergic neurotransmitter system, have been reported, with reduction in glutamate + glutamine (GLX) in the anterior cingulate (Auer et al 2000, Rosenberg et al 2004, Pfleiderer et al 2003, Mirza et al 2004) and left dorsolateral prefrontal cortex (Michael et al 2003) in patients with major depressive disorder. In abstinent methamphetamine users (AMU), glutamate concentration in the prefrontal cortex was decreased in one study (Ernst and Chang 2008) but elevated in another (Sailasuta et al 2008 in press). Because major depression is common among AMU, we hypothesized that co-existent depression might explain the inconsistency in reported results. We used AMU to avoid the further confound of comorbid psychosis of concurrent methamphetamine use.

Purpose: To explore differences in brain metabolites and their associations with altered cognitive function in depressed AMU and AMU without current or past history of depression. Controls were normal healthy subjects.

Methods: Because differences in MRS methodology can contribute to inconsistency in the literature of neurochemical pathology in otherwise similar subject populations, three techniques of Proton Magnetic Resonance Spectroscopy (1H-MRS TE-Ave; PRESS TE 80ms; TE 35ms) were used to measure N-acetylaspartate (NAA), Glutamate (Glu), Glutamine (Gln), Creatine (Cr), Choline (Cho), and Myoinositol (mI) in the frontal white (FW) and posterior cingulate grey matter (PCG) of 19 AMU, 12 with major depression (DSM IV, confirmed by SCID) and 7 without current or past history of depression) and 11 healthy controls. Standard neuropsychiatry evaluations of memory, attention, response-inhibition and fine motor activity were used (see Table 3). Statistical comparison and correlation between neurochemical findings and neuropsychiatric tests were performed using SPSS 16.0; student t test, ANOVA and Pearson correlation.

Results: Demographics of Controls (not shown), AMU depressed and non-depressed were similar (Table 1).

Table 1	Non-depressed abstinent methamphetamine users (N=7)	Depressed abstinent methamphetamine users (N=12)	T-Test		
	Mean +/-SD	Mean +/-SD	t	df	P
Total years of education	13.5±1.5	12.6±2.9	0.7	16	0.4 (ns)
Age of onset of methamphetamine	23.2±10.2 years	23.6±9.1 years	0.08	17	0.9 (ns)
Total duration of methamphetamine use	12.5±6.4 years	9.9±6.9 years	0.8	17	0.4(ns)
Total amount of methamphetamine use	7002.6±7250.2 gm	4757.9±6367.2 gm	0.5	12	0.6 (ns)
Total duration of sobriety	100.4±175.4 weeks	49.4±67.5 weeks	0.8	16	0.3 (ns)

Non-depressed AMU showed significant elevation in both Glu and mI (P 0.02) in FW when compared to normal controls and to depressed AMU. Patients abusing methamphetamine, but who are depressed showed no abnormality in cerebral glutamate or in myoinositol in FW (Table 2). PCG showed no differences in Glu or mI. Different MRS techniques gave consistent results

Table 2	Healthy controls (N=11)	AMU (N=19)		T-Test		
		Non-depressed (N=7)	Depressed (N=12)	Depressed vs. non-depressed	Non-depressed vs. controls	Depressed vs. controls
Glutamate (Glu) mM	7.7±0.6	9.7±2.3	7.3±1.2	P=0.01	P<0.02	P=ns
Myo-inositol (mI) mM	6.3±1.1	9.1±3.3	6.6±1.1	P=0.04	P<0.02	P=ns

Neuropsychiatric testing showed significant differences between depressed and non-depressed AMU (Table 3).

Table 3	AMU (N=11)		T-Test		
	Non-depressed (N=5)	Depressed (N=6)	t	df	P
Rey Auditory Verbal Learning (Trial 6)	8.0±2.1	11.8±2.6	2.7	11	0.01
Rey Auditory Verbal Learning (Trial 7)	7.6±1.4	11.6±2.4	3.4	11	0.005
Grooved pegboard test (dominant hand)	86.0±7.3	71.6±7.3	3.4	11	0.005

Negative correlation was found between FW Glu and memory (AVL) for all AMU. For AMU there was also negative correlation between PCG NAA and intelligence (National Adult Reading Test) and attention (Symbol digit correln: Not shown in tables).

Discussion and Conclusions: Great care must be taken, not only in application of the correct 1H MRS techniques but in the stratification of subjects selected for investigation of psychiatric disorders in the context of drug abuse. As we show here, the impact of major depression on cerebral glutamate (a 25% reduction) entirely obscured the potent and persistent effects of methamphetamine on cerebral glutamate (21% increase).

References: 1.Auer DP, et al. Biol Psychiatry. 2000 Feb 15;47(4):305-13. 2. Rosenberg DR et al., J Am Acad Child Adolesc Psychiatry. 2004 Sep;43(9):1146-53. 3. Pfleiderer B, et al. Psychiatry Res. 2003 Apr 1;122(3):185-92. 4. Mirza Y et al. J Am Acad Child Adolesc Psychiatry. 2004 Mar;43(3):341-8. 5. Michael N et al. Psychol Med. 2003 Oct;33(7):1277-84. 6 Ernst T, Chang L. J Neuroimmune Pharmacol. 2008 Sep;3(3):165-72.

Acknowledgment: This study was supported by NIDADA21112 (NS).