Excitatory Neurotransmitter Dysfunction is Induced in Frontal Brain After Excitatory Drug Abuse

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Purpose: Define cerebral neurotransmitter response to human methamphetamine abuse.
Background: Of all the human drugs of abuse, methamphetamine appears to be the one with the simplest mode of action and
therefore amenable to MRS investigation of neurochemical dysfunction at each stage of the drug abuse cycle: use, dependency, craving, abstinence, relapse and recovery (1-2). Amphetamine, the parent compound is demonstrably an excitatory agent with a mode of action involving the dominant excitatory neurotransmitter glutamate. Attempts to demonstrate the expected increase in brain glutamate in human methamphetamine abusers have hitherto been unsuccessful.
Human subjects, definition and selection of methamphetamine abuse patient and MRS Methods: DSMIV and SCID are the applicable criteria for defining drug, including methamphetamine abuse and exclusion of co-morbid psychiatric conditions. Multi-drug use and depression which could confound the study were specifically excluded. Because methamphetamine use causes mania, itself a significant confound, the present study was confined to abstinent methamphetamine dependent (AMD) subjects. Twenty two AMD, 35 ±9 ages-yrs, period of abstinence weeks-weeks were recruited from dedicated Centers where urine screen, drug history were available. Controls were normal healthy individuals age and gender matched, but with no drug abuse history. Proton MRS for specific quantification of cerebral glutamate was performed on GE 3 Tesla clinical MR with 8-channel head coil, TE Average sequence in voxels localized to frontal white matter (FWM) and posterior cingulate gyrus grey matter (PCG). Statistically significant quantitative results were compared in student t-test after Bonferroni correction ($P<0.05$).
Results: i) 19% increase in [glutamate] in FWM ($P=0.001$), with 16% reduction in neuronal marker NAA ($P= 0.01$) (Fig1)
ii) No significant abnormalities in either [glutamate] or [NAA] ($P=0.2$) in PCG.
iii) FWM changes in [glutamate] and [NAA] correlate with duration of abstinence ($P=0.01$)
iv) [glutamate] correlated with [NAA] in both FWM and PCG. (Fig 2) In AMD, it is clear that for any given [glutamate], NAA is significantly reduced compared to control, suggestive of neurotoxicity.

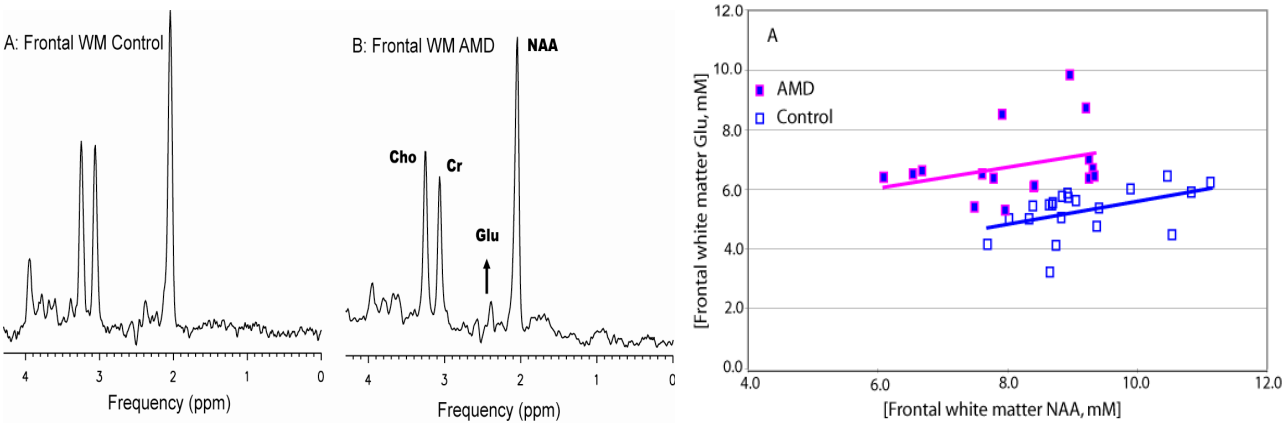

Figure 1 (left) Representative MRS spectra from an AMD subject and a control. Figure 2 (right) Correlation between concentration of Glu and NAA are expected as each metabolite represents a similar cell population with the voxel location selected in MRS experiment. In frontal white matter linear relationship between Glu and NAA is defined and reflected the persistent neurochemical abnormalities in AMD subjects. NAA and Glu is concentrations are lower in AMD than in control.

Discussion and Conclusions: Although this is the first conclusive demonstration that the concentration of the primary excitatory neurotransmitter, glutamate, is increased in the frontal lobe of the human brain, the observation is entirely consistent with prior animal studies and with the theory of action of amphetamine, an excitatory drug operative through the glutamate system (3). Previous attempts to document such changes may relate to patient selection criteria (co-morbid depression for example) or to non-specific MRS methodology (low field assay of combined glutamate plus glutamine, commonly referred to as Glx). Cross sectional study design precludes any discussion on the temporal relationship between the two neurochemical changes documented in AMD. Persistence of neurochemical dysfunction into the abstinent period and their presence in FWM rather than PCG is in accord with the known long term deleterious effects of methamphetamine on cognitive function.
References: (1) Boireau A, et al Neurosci Lett 1995;195(1): 9-12. (2) Davidson C, et al. Brain Res Rev 2001; 36(1): 1-22. (3) Nash JF, et al Brain Res (1992) 581(2): 237-243.
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