

Methylphenidate's Effects on the Metabolomic Profile of the Rat Brain measured by ^1H -MRS

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Introduction: Methylphenidate is a stimulant used in the treatment of Attention Deficit Hyperactivity Disorder. The effects of methylphenidate (MP) have been characterized in the adult human brain using positron emission tomography (PET) to demonstrate MP's blocking effects of dopamine transporters and increases in synaptic dopamine and norepinephrine. However, there is lack of information as to the short- and long-term effects of MP on brain function and neurotransmission in children and juveniles treated with MP. Such studies are lacking because PET requires radioactive ligands which cannot be routinely used in young children. However, proton magnetic resonance spectroscopy (^1H MRS) can be safely used in all age groups and can provide valuable information about metabolic and neurochemical status changes in response to pharmacological challenges. Here we applied ^1H MRS to characterize neurochemical status in the rodent brain anesthetized with isoflurane before and after an intravenous challenge with MP (5mg/kg).

Methods: Female Sprague Dawley rats were used and divided into two groups: Group 1 was exposed to MP (5mg/Kg MP, N=9) and Group 2 was exposed to Placebo (0.9%NaCl, N=9). All animals were anesthetized with 2~2.2% isoflurane in a 50:50% Air: O_2 mixture and mechanically ventilated. Non-invasive monitoring of body temperature, oxygen saturation, respiratory rate, mean arterial blood pressure (MABP) and heart rate was performed using optical sensors and recorded continuously during the study. ^1H MRS experiments were designed as a time-course study where ^1H MRS spectra were acquired in the rat striatum in parallel with hemodynamic monitoring 30-min before and 30-min after the intravenous (IV) challenge with either MP or Placebo. All imaging and ^1H MRS acquisitions were performed on a 9.4T/20 MRI instrument equipped with a volume coil as a RF excitation and a custom-made surface coil as a RF reception. Following anatomical scans and first and second order shimming procedure, a PRESS sequence in striatum was performed using following parameters: TR=4000ms, TE=12ms; Number of acquisition=512; spectral width=8012 Hz and number of acquired complex points=4096. A water unsuppressed scan was acquired as an internal concentration reference. Metabolite concentrations were quantified by LC model with a macro-molecular baseline acquired *in vivo*.[1]

Result: Physiological data: Blood gases were within normal range and did not vary between groups. The MABP decreased slightly and transiently following the MP challenge; however, it was still within normal range for preservation of cerebral blood flow via autoregulation.

^1H MRS data: SNR and FWHM of spectra were in the ranges of 10-20 and 0.015-0.020ppm, respectively. Figure 1a shows a representative spectrum from rat striatum. A one-way repeated measure ANOVA performed on single metabolites over time before and after placebo or MP demonstrated a significant reduction in the concentration of glutamate (Glu) (8%), guanidoacetate (Gua) (12%), lactate (Lac) (11%), and total creatine (tCr) (5%) which lasted until the end of an experiment (34min post administration). Figure 1b shows a representative spectral profile of Glu before (red) and after (black) MP administration and demonstrates the slight Glu reduction following MP. There were no significant differences in metabolite concentrations over time in the placebo group.

Conclusion: Here we report that MP administered at an IV dose of 5mg/kg significantly decreased [Glu] in the rat striatum an effect which lasted for 34-min. Further, MP also decreased [Gua], [Lac] and N-Acetyl-Aspartate independent of the parallel transient decrease in MABP. Glu is an excitatory neurotransmitter in the central nervous system; and [Glu] correlates with neuronal mitochondrial metabolism (V_{TCAn}). From the point of view of [Glu] representing 'energy metabolism' and/or V_{TCAn} the decrease observed in the striatum would be in agreement with human studies demonstrating that MP can decrease CMRglu in some individuals; an effect that is accentuated under conditions of higher glucose demand.[2] The reduction in CMRglu is thought to be a consequence of synaptic dopamine increase; as application of DA in the striatum decreases the activity of spontaneously active neurons depressing basal neuronal activity.[3]

References: 1. Provencher MRM (1993) 2. Volkow ND et al. PLoS One. (2008) 3. Kiyatkin EA et al. J Neurophysiol. (1996)

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