Live Brain MRI Detection of Glia Activation by Psychostimulant Exposure

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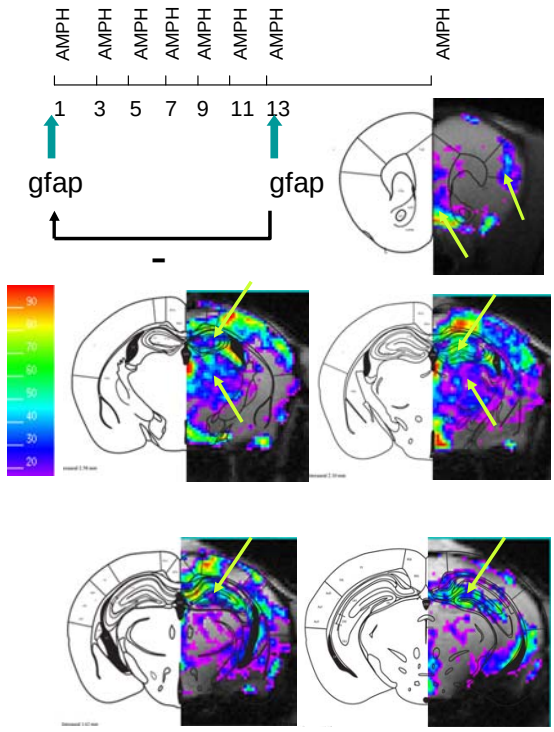
Introduction Neuroscience research on drug addiction has focused on morphological and molecular adaptations of neuronal activities in response to chronic drug exposure. However, our understanding of the role of glial (non-neuronal) cells in drug addiction is limited [1]. There is increasing interest in understanding how gene modulation affects the development of glia-related neuroplasticity in drug addiction; however, the techniques typically used to detect gene activities in the brain are restricted to in vitro examination of brain slices or postmortem brain tissue samples [2-4]. In this study, we utilized a novel MR contrast probe targeting mRNA of the Glia Fibrillary Acidic Protein (SPION-gfap) in conjunction with in vivo MRI to detect altered gene transcripts in astroglia of mouse brains as the indicator of glia activation after an acute or chronic exposure to amphetamine. Target specificity, signal sensitivity and image resolution of our SPION-gfap probe have enabled the localization of gliosis after global ischemia in live brains [5].



Methods For chronic treatment, male C57black6 mice were injected intraperitoneally (IP) with amphetamine (4mg/kg, denoted as chronic group) or saline (denoted as acute group) every other day for two weeks (see schematic plot on top of the figure). On the day of the experiment, mice were first ICV infused with the contrast probe (SPION-gfap =190 pmol Fe/kg) similar to what was described before [6] under gas anesthesia (with pure O_2 plus 2% halothane [800 ml/min flow rate]). Three hours later, both groups received a challenge dose of amphetamine (4mg/kg). We acquired MR images in live animals using a 9.4Tesla magnet three hours following the amphetamine challenge. We acquired R_2* maps using serial GEFI sequences (TR/TE=500/3, 4, 6, 8ms, FOV=1.5cm, 128×128, α=30). Hotspots of elevated probe retention was determined based on the subtraction R2* maps between the two animal groups [ΔR2* in % inc = (R2* $_{chronic}$ – R2* $_{acute}$)/ R2* $_{acute}$ * 100%)]. We determined the potential regions of interest to have the majority of pixels with percent R2* signal elevation greater than 10% from those of the acute group in the same locations.

Results ΔR2* maps identified hotspots with elevated GFAP mRNA levels in chronically exposed compared to acutely exposed brain to include the cortices (insular, fronto-orbital, medial-prefrontal, somatosensory), the hippocampus and thalamus (arrows). These regions are involved in mood state, memory and learning as well as decision making in human and may be heavily involved in the development of addictive behaviors

Conclusions Brain regions exhibiting elevated R2* by the challenge amphetamine dose to the chronic group are similar to what were reports by other investigators using positron emission tomography (PET) in human subjects [7] and in vitro studies using rodent brain samples [2-4]. Our data imply that the SPION-gfap can be used to assess glia activation by psychostimulant exposure in live brains.

1. Haydon et al (2008) NeuroPharm (online). 2. Armstrong, V et al (2004) Eur J Parmacol 488 (1-3), pp111-5. 3. Bowers, MS et al (2003) Eur J Neurosci 17(6), pp 1273-8, 4. Frey, BN et al (2006) Prog Neuropsy Biol Psych 30(7), pp 1231-4. 5. Liu, CH et al (2008) FASEB J 22(4), pp 1193-203. Liu, CH et al (2007) J Neurosci 27(3), pp 713-22. 7. Sekin, Y et al (2008) J Neurosci 28(22), pp5756-61.