Acute Effect of Methadone Maintenance Dose on Cerebral Blood Flow in Heroin Users under Methadone Maintenance Treatment

Chien-Yuan Eddy Lin[1,2], I-Hsiao Yang[3,4], Hsiu-Ling Chen[3,4], Meng-Chang Tsai[5], Pei-Chin Chen[3,4], Meng-Hsiang Chen[3,4], and Wei-Che Lin[3,4]

[1]GE Healthcare, Taipei, Taiwan, [2]GE Healthcare China, Beijing, China, [3]Department of Diagnostic Radiology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, [4]Chang Gung University College of Medicine, Kaohsiung, Taiwan, [5]Department of psychiatry, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

Purpose: Alteration of cerebral blood flow (CBF) in heroin users under methadone maintenance treatment (MMT) had been reported[1] but the acute effect before and after methadone administration is still less known. The purpose of this study is to investigate the acute changes of CBF in MMT subjects one hour before and after methadone administration by using arterial spin labeling[2] (ASL) perfusion MRI, and their relationships with history of heroin usage and methadone treatment.

Material & Methods: Twenty-five MMT patients were enrolled in this study. The anatomical T1-weighted image and ASL image were performed on 3.0T Signa HDx and 1.5T MR450 scanners (GE Healthcare, Milwaukee, WI, USA), respectively, using a body coil as transmission and an 8-channel head coil as signal reception. A pseudo-continuous arterial spin labeling (pCASL)[2] with a 3D background suppressed fast spin-echo stack-of-spiral readout module was employed for ASL perfusion MRI and its scanning parameters is as follows: TR= 4548 ms, post label delay= 1525 ms, TE= 10.5 ms, matrix size= 128 × 128, number of excitation= 3, 38 slices with a 4.0 mm thickness with whole brain coverage, total 4 minutes acquisition time. CBF maps were calculated from scanner console with FuncTool 3D-pCASL (GE Healthcare). All data were preprocessed using FSL v4.1.7 (Functional Magnetic Resonance Imaging of the Brain Software Library; http://www.fmrib.ox.au.uk/fsl) and SPM8 (Statistical Parametric Mapping. Wellcome Department of Imaging Neuroscience, London, UK; available online at http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 7.3 (MathWorks, Natick, MA, USA). A DARTEL-based T1 VBM approach was used for pre-processing of whole brain T1-weighted images[3,4]. The CBF maps were normalized to the study-specific gray matter template previously generated, and mapped into MNI space using an affine transformation, re-sliced to an isotropic voxel size of 1.5 mm and spatially smoothed using an 6 mm full-width at half-maximum Gaussian kernel. By using voxel-based statistics, differences of the CBF maps before and after methadone administration were determined in MMT subjects. Correlations between the difference of CBF and other clinical variables, including duration or dose of heroin usage and MMT, were assessed by multiple regression analysis.

Table 1. Regions showing decreased CBF in patient one hour before and after methadone maintenance treatment

MNI atlas coordinates			Corresponding cortical area	Voxel size	T value	Brodmann area
x	y	z				
-36	23	-35	Left Superior Temporal Gyrus	2658	5.57	38
-12	-87	39	Left Cuneus	4134	4.97	19
-2	-72	7	Left Lingual Gyrus		4.43	18
9	-31	12	Right Thalamus	4794	4.87	-
39	9	-8	Right Claustrum		4.7	-
-54	-21	-36	Left Inferior Temporal Gyrus	1429	4.52	20
10	-33	49	Right Precuneus	1412	4.39	7
-42	-15	1	Left Insula	840	4.12	13
63	-24	18	Right Postcentral Gyrus	772	3.89	40
-40	-85	-5	Middle Occipital Gyrus	632	3.78	18

Table 2. Correlation among decreased CBF in corresponding cortical area, interval from last heroin usage, period and daily dosage of methadone maintenance treatment after adjustments for age, gender, history of smoking and alcohol use.

Clinical variables	Decreased CBF in corresponding cortical area	β-value	P-value
Interval from last heroin usage (months)	Right precuneus	-0.174	0.001
	Left cuneus	-0.278	0.001
	Left insula	-0.189	0.006
	Left inferior temporal gyrus	-0.175	0.033
	Left middle occipital gyrus	-0.235	0.004
Daily dosage of methadone maintenance treatment (mg)	Right postcentral gyrus	-0.109	0.003
Period of methadone maintenance treatment (months)	Left superior temporal gyrus	-0.087	0.031

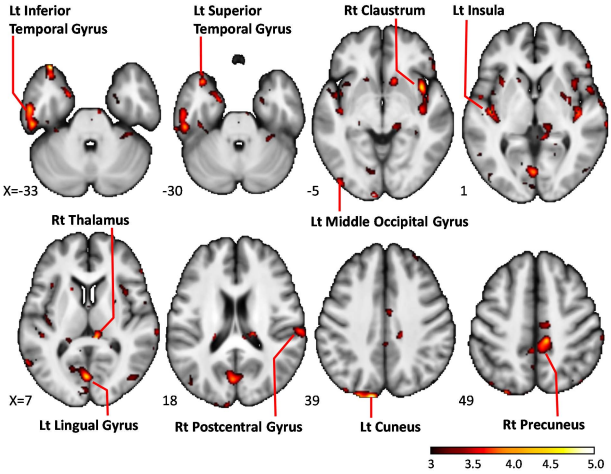

Figure 1. Regional CBF differences in patient one hour before and after methadone maintenance treatment. The hot color map showed decreased CBF after methadone maintenance treatment (Corrected P < .05). Lt, left; Rt, right.

Results & Discussions: Exploratory comparison in MMT subjects revealed decreased CBF after administration of the daily methadone dose in several brain locations, including right precuneus, left cuneus, left insula, left superior and inferior temporal gyrus, left middle occipital gyrus and left postcentral gyrus (Figure 1 and Table 1). Our results suggested that methadone might alter blood flow in emotion and different cognitions associated circuits with consequent comorbidities in MMT. Furthermore, the time interval since last heroin administration correlated negatively with differences of CBF in right thalamus, precuneus, left cuneus, insula, inferior temporal gyrus and middle occipital gyrus. The higher daily dosage of MMT was associated with the less differences of CBF in right postcentral gyrus. The longer duration of MMT was also correlated with the less differences of CBF in left superior temporal gyrus (Table 2). In present study, we noted that MMT who were currently using heroin had more dramatically decrease of CBF in reward associated network. Thus, recent reuse of heroin appears to directly affect effect of methadone to cerebral blood flow measures in the MMT. Our results also suggested that degree of CBF response in methadone task might reflect the short and long-term plasticity modulated by heroin and methadone.

Conclusion: The CBF was dramatically lessened by methadone, and can be predicted by the history of heroin usage and methadone treatment. The ASL might help to monitor the therapeutic effects and medical complaints in MMT non-invasively.

References: 1.Herning et al., Neuropsychopharmacology, 28(3):562-8, 2003. 2. W. Dai et al., Magn Reson Med, 60(6):1488-97, 2008. 3. J. Ashburner et al., Neuroimage, 15;38(1):95-113, 2007. 4. J. Ashburner et al., Hum Brain Mapp., 9(4):212-25, 2000.