GABA Re-uptake Inhibitor Trigged Neuronal Cascading Effect Detected by fMRI

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Introduction: BOLD fMRI methods were used to study the temporal and spatial signal changes in rat brain induced by NO-711 hydrochloride, a potent Gama-aminobutyric acid (GABA) reuptake inhibitor. Upon administration of NO-711, BOLD signal changes were detected in nucleus accumbens (NAc), thalamus subsequently, and in the frontal cortex regions. These BOLD signal changes demonstrated an inter-correlated temporal and spatial nature among regions in NAc, Thalamus, and cortices. It is suggested that BOLD fMRI could be used to detect drug induced neuronal cascading effects, which could help to elucidate the neuronal circuits at a systemic level.

Material and Methods: ***Animal Preparation:*** 4 Sprague-Dawley rats weighted 300-350g were used for fMRI study. The surgical procedures were the same as in our previous study and during the experiment, rat physiology conditions were kept stable [1]. Femoral vein was catheterized for drug deliver while artery for blood pressure and gas monitor. ***fMRI experiments:*** A gradient echo EPI sequence with TR of 2s, TE 27.2ms, FOV 3.5mm, matrix 64 X 64, in-plane resolution of 550 X 550 um were used. Study was conducted on a Bruker Biospec 3T/60cm scanner. ***Scan protocol:*** Every rat underwent two separate 30 minutes scan. First scan is for control purpose that saline (0.3ml, IV) was injected at 5 min. Then is a short gap of 10 minutes between the first and second scan. During the second scan NO-711 hydrochloride (Sigma) 1mg/kg, was administered into the rat at 5 min. ***Data analysis:*** A typical voxel timecouse was picked from NAc region by using AFNI software [2]. A cross-correlation map was generated and signal percentage changes were calculated with the voxels of significance (P<0.01 with Bonferroni correction) in region of NAc, thalamus and frontal cortex. Paired t-test was used to compare the regional signal change with the baseline before NO-711 treatment.

Results: Fig.1 shows the timing and BOLD Signal changes in specific brain regions upon NO-711 administration. Administration of NO-711(1mg/kg) at 5 min immediately induced BOLD signal decreases in the NAc and thalamus regions during a period of Time 1 (5-9 min). The decreased BOLD signals subsequently return to the baseline level or above while signal in the frontal cortex begin to rise during Time 2 (9.5-13 min). The signal in NAc and thalamus stayed in the same levels after the signal in the cortex increased 4.5% at time 3. During time 4, signals in both NAc and thalamus regions decreased while signal in the cortex backed to baseline level.

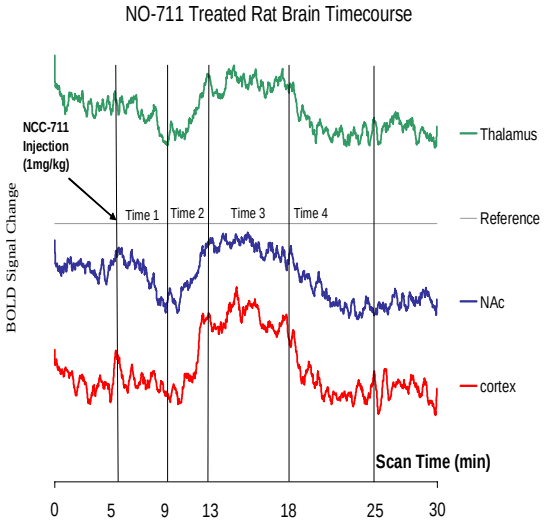

Fig 1. Time courses and regional responses upon NO-711 administration.

Table 1: Timing and BOLD Signal changes in specific brain regions upon NO-711 administration. Region with significant changes (P<0.05, t-test) were marked with asterisk.

Signal change (%) of Time	NAc	Frontal Cortex	Thalamus
Time1	- 5.2 ± 2.1 *	0.7 ± 1.0	-3.1 ± 2.2 *
Time2	1.6 ± 2.5	2.1 ± 1.4 *	5.4 ± 3.2 *
Time 3	3.4 ± 2	4.5 ± 2.5 *	8.9 ± 4.9
Time 4	- 8.4 ± 5.8 *	2.6 ± 2.7	-1.6 ± 2.2

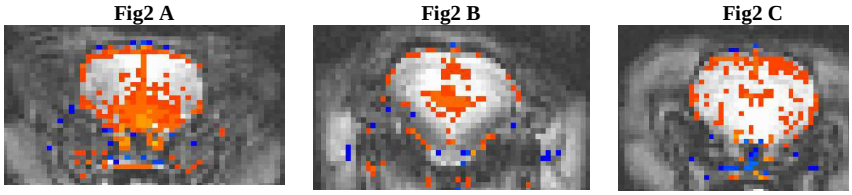

Fig 2. Cross-Correlation map upon NO-711 administration (P<0.01 with Bonferroni correction). Acivated voxels showed in NAc (A), thalamus (B), and frontal cortex region (C).

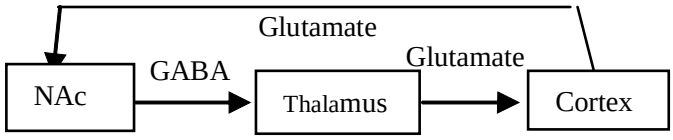

Fig3. A diagram of neuronal cascade event

Discussion and conclusion: Administration of NO-711 significantly decreased the signal in the NAC, suggesting that NO-711 blocked GABA re-uptake and caused local GABA concentration increase. The increased GABA subsequently inhibited neural activity in the NAc where approximately 90% of neurons are GABAergic neurons. The accumulation of GABA in NAc trigged disinhibition mechanisms and caused cortex activation as seen during the time 2 period. Since the concentration of NO-711 was low and only had an effect for a few minutes, the signal in NAc returned to the baseline in the time 3 period [3]. Because prefrontal cortex has a direct connection to NAc, the activated cortex may excite the GABAergic neurons. This suggests that the continuous excitation in the NAc results in GABAergic neuron activation and therefore releases more GABA in the region. The increase in GABA concentration trigged a signal decrease in NAc again during the time 4 period. As described above, NO-711 increased GABA concentration that trigged activation in frontal cortex, which in turn trigged cortex GABAergic neurons in NAc and subsequently resulted in the signal decrease. The observed signal changes and the timing of the activated brain areas indicate the existence of a cascade event and demonstrate their potential to study neuronal circuit connectivity.

Reference:

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2. Cox RW. Comput Biomed Res 29 (3),162-73,1996
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