Neurogenic control of pharmacologically induced hemodynamic changes.

Y.I. Chen, A.J-W. Chen, T.V. Nguyen, A.E. Talele, B.G. Jenkins
Dept. of Radiology Massachusetts General Hospital, Charlestown, MA, USA

Introduction The problem of coupling neuronal activity to a given hemodynamic change is one whose solution is paramount for proper interpretation of either task-related or pharmacologically-induced brain mapping experiments. A large number of vasoactive molecules are present in the brain, and many are also neurotransmitters. Such molecules include, among others, dopamine, adenosine and acetylcholine. Dopaminergic ligands such as cocaine and amphetamine produce strong hemodynamic responses in dopamine rich regions of the brain. In order to better understand the factors that may couple a change in dopamine concentration to a hemodynamic change we studied the effects of dopaminergic and adenosinergic antagonists upon MRI signal changes induced by amphetamine (AMPH).

Methods ***Drugs*** - 1) Amphetamine enhances the release of dopamine; 2) SCH-23390 is a selective D1 antagonist; 3) Eticlopride is a selective D2 anatagonist. It can disrupt autoregulation of dopamine release via the D2 autoreceptor; 4) DMPX is an A2 antagonist with some selectivity for A2a over A2b. (1). ***MRI*** - Sprague-Dawley rats were used in this study. All studies were perfomred on a 4.7T GE Omega CSI. A conventional GE sequence was used to acquire images (TR/TE 600ms/20ms) as described earlier (2). A superparamagnetic contrast agent, mion, was used to sensitize the phMRI signal to rCBV changes. Baseline images were collected before and after mion injection, then AMPH was injected (2 or 3mg/kg) and 20 min afterwards, the selective antagonist ligand (SCH23390 (0.5-0.75mg/kg ip; n=5), or DMPX (5mg/kg iv; n=6) was injected. rCBV maps were created by converting signal intensity changes to ΔR2* changes. The degree of the blockade ($Block_{index}$) was determined by the percent changes in the integration of ΔrCBV (ΣΔrCBV) over the pure-AMPH period ($\Sigma\Delta rCBV_{AMPH}$) and 20 min after the post-treatment of the antagonist ligand ($\Sigma\Delta rCBV_{antagonist}$):

$$Block_{index} = (\Sigma\Delta rCBV_{AMPH} - \Sigma\Delta rCBV_{post})/ \Sigma\Delta rCBV_{AMPH}$$

Eticlopride (0.2mg/kg; n=6) was injected before AMPH (3mg/kg), these data were collected using BOLD imaging as described in (2).

Results and Discussion We first investigated the effects of dopaminergic antagonists upon the regional hemodynamic changes induced by AMPH. We found that SCH-23390 caused a partial decrease in the AMPH-induced signal changes immediately upon injection of SCH-2390 as shown in Fig. 1A. Our prior data indicated that SCH-23390 completely blocked the effects of the cocaine analog β-CFT (3). We also investigated the effects of D2 antagonism upon AMPH-induced signal changes. In contrast to the D1 effects, D2 antagonism potentiated the effects of AMPH, causing a prolonged timecourse for the signal changes with no change in the overall magnitude (Fig. 1B). These effects are consistent with antagonism of pre-synaptic D2 autoreceptor induced regulation of dopamine release.

Both pharmacological and behavioral studies indicate that dopamine D2 receptors and adenosine A2 receptors act in an antagonistic fashion (4). A1 and the A2b receptors are widely distributed over the brain while the A2a receptors are primarily, and most densely, localized in the basal ganglia (4). Administration of the A2 antagonist DMPX results in antagonism of the hemodynamic changes induced by AMPH that is quite strong in the striatum, and weaker in the frontal cortex. This is shown by maps of both the CBV changes induced by AMPH alone (Fig. 2A) and then by the decrease in CBV induced by DMPX (displayed as a $Block_{index}$ map in Fig. 2B). Plots of CBV changes in striatum and frontal cortex after DMPX administration are shown in Fig. 3. Administration of DMPX alone resulted in very small global decreases in CBV that could not explain the large effects on AMPH-induced changes (not shown). The results are summarized in Table I.

Conclusions These results are consistent with prior data suggesting that dopamine is a coupling agent between neuronal activity and a CBV change (2). The D1 antagonism further suggests that the dopamine effects may be modulated by D1 receptors on the vasculature. Second, they point out that dopaminergic control through A2 receptors has an important modulatory influence upon hemodynamic effects. These experiments point the way towards methods to develop a more complete understanding of the neuronal-vascular coupling problem that is common to both fMRI and phMRI.

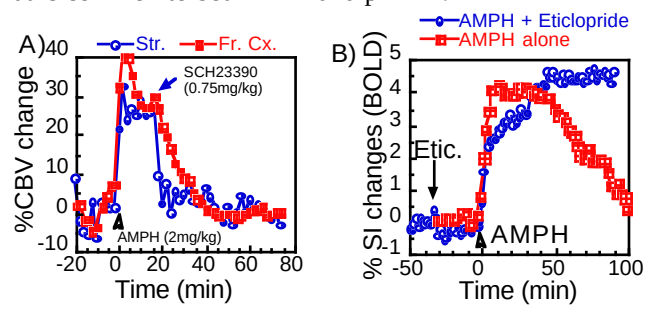

Figure 1. rCBV increases due to AMPH stimulus as modulated by (A) SCH-23390 (B) eticlopride. Arrows indicate injection points.

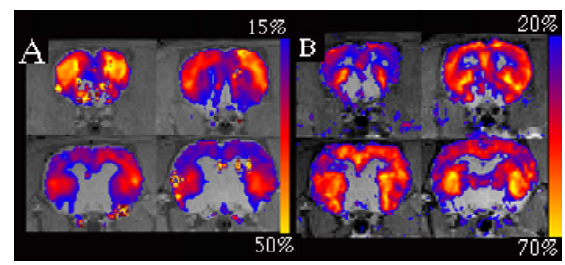

Figure 2 (A) Percent of rCBV increase due to AMPH stimulus (average of the 1st 20 min.). (B) Degree of AMPH activation blocked by DMPX (map of **$Block_{index}$**).

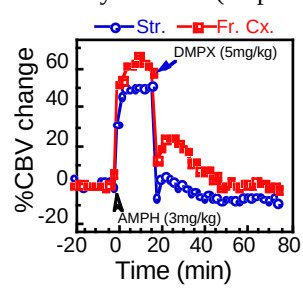

Figure 3. rCBV increases due to AMPH stimulus were attenuated in a regionally specific manner by DMPX injection at the time shown (arrow).

Table I. Blockade Indices ($Block_{index}$) -- Degree of rCBV drop from pure amphetamine stimulus.

Brain area	*DMPX*	*SCH-23390*
Frontal Cortex	35.03%	61.17%
Striatum	56.29%	63.72%
N. Accumbens.	34.34%	23.93%

References

1.Svenningsson P et. al. Prog. Neurobiol. 59:355-396 (1999).
2.Chen YI et. al., NeuroReport 10:2881-2886 (1999).
3. Chen AJW et al. NeuroImage Human brain mapping P0243 (1998)
4. Sebastiao AM, Ribeiro JA. Prog Neurobiol 48:167-89 (1996).