The Effects of Clonidine and Idazoxan on Cerebral Blood Flow in Rats Studied by Arterial Spin Labeling Magnetic Resonance Perfusion Imaging

X. Du[1], H. Lei[1]

[1]State Key Laboratory of Magnetic Resonance and Atomic and Molecular Physics, Wuhan Institute of Physics & Mathematics, Chinese Academy of Sciences, Wuhan, Hubei, China, People's Republic of

Introduction Agonists of α_2-adrenoceptors are known to produce many central and peripheral effects. For example, xylazine, a selective α_2-adrenoceptors agonist, has been shown to cause region-dependent CBF decreases in rat [1]. Clonidine, an agonist for both α_2-adrenergic receptor and imidazoline receptor, is a widely used drug for treating hypertension. Its effect on CBF, however, is not well understood. In this study, continuous arterial labeling (CASL) MR perfusion imaging was used to investigate the effects of clonidine and idazoxan, an antagonist for α_2-adrenergic and imidazoline receptors, on CBF in rats.

Materials and Methods Twelve male Sprague-Dawley rats, weighting 250-320 g, were used. After intubation, the rats were anesthetized by 1.0-1.5% isoflurane in a 70:30 N_2O/O_2 gas mixture. For each rat, bilateral femoral arteries and the right femoral vein were catheterized for monitoring blood gases and blood pressure, and for delivering drugs. Rectal temperature was maintained at 37.0-37.5 ^oC using a warm water pad. After measuring baseline CBF, the rats were divided into two groups. In the first group (n=7), clonidine (10 μg/kg, i.v.) was injected first, followed by idazoxan injection (300 μg/kg, i.v.) at 30 minutes later. Perfusion maps were obtained after administration of each drug. The experimental protocols for the second group (n=5) were similar, except that the order of clonidine and idazoxan injections was reversed. Snapshot FLASH imaging combined with one-coil CASL was used to acquire quantitative perfusion images on a Bruker Biospec 4.7/30 scanner, with labeling time 1.5 s, FOV 4 cm×4 cm, matrix size 128×128, slice thickness 2 mm, TR 7.8 ms, TE 2.9 ms and 64 averages [1,2]. For perfusion calculation, apparent T_1 map was obtained for each rat using a slice-selective inversion-recovery snapshot FLASH sequence, and the degree of spin labeling (α) and brain–blood partition coefficient for water (λ) were taken as 0.75 and 0.9 ml/g, respectively [1,2]. Absolute CBF values were measured from the two hemispheres in the cortex (CT), striatum (ST), and hypothalamus/septal (HT/S) region (Fig. 1), and an average value was calculated for each region of interest.

Results Without idazoxan pretreatment, clonidine injection caused significant decreases in mean arterial pressure (MBP) and heart rate (HR) and significant changes in blood gases, which were reversed completely by the subsequent idazoxan injection (Table 1). In the second group, neither the initial idazoxan injection nor the subsequent clonidine injection resulted in any changes of MBP, HR and blood gases (Table 1). Clonidine injection in the idazoxan-naïve rats caused global CBF reductions (Figs. 1 and 2). After idazoxan antagonism, the CBF in the CT and HT/S region returned to the baseline level. In contrast, the striatal CBF recovered only partially (Fig. 2). In the second group, the initial idazoxan injection caused no significant CBF changes, and the subsequent clonidine injection resulted in CBF reduction only in the ST (Figs. 1 and 3).

Discussion Clonidine-induced global CBF reduction in the idazoxan-naïve rats may, in part, be explained by its effects on MBP, HR and blood gases, and such effects can be reversed (1st group) or blocked (2nd group) by idazoxan antagonism. No matter it is administered before or after clonidine injection, idazoxan is capable of reversing the effects of clonidine on CBF, but in a region-dependent manner. The observation that clonidine-induced reduction of striatal CBF persisted in the presence of idazoxan antagonism is intriguing, and might be related to the fact that clonidine could affect local CBF through its direct effect on central α_2-adrenoceptor subtype C and imidazoline receptor subtype I_1, both of which are located primarily in the striatum and show low affinity to idazoxan [3,4].

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Table 1 MBP, HR and blood gases data. Clo: clonidine, Ida: idazoxan

	MBP	HR	P_aO_2 (mmHg)	P_aCO_2 (mmHg)	pH
Isoflurane	99.3±6.8	363±27	119.6±14.4	36.3±3.9	7.408±0.055
Clon	72.7±10.4*	320±23*	81.9±13.2*(n=5)	53.9±15.6*(n=5)	7.298±0.118 (n=5)
Clon+Ida	101.7±7.3**	371±29**	114.2±26.9	44.8±9.4	7.355±0.074
Isoflurane	81.1±3.1	357±18	115.7±4.9	38.8±1.5	7.422±0.005
Ida	92.5±11.0	360±33	98.4 (n=1)	40.9 (n=1)	7.383 (n=1)
Ida+Clon	90±12.4	361±25	101.4±1.2	45.0±4.4	7.362±0.014

*p<0.05 compared to isoflurane, **p<0.05 compared to Clon.

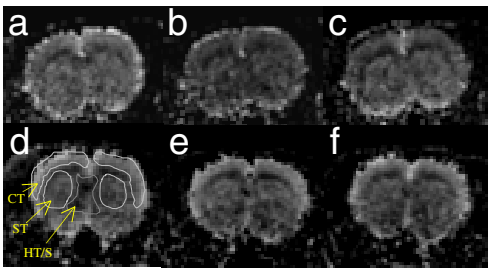

Figure 1 Perfusion images acquired from two rats (top and bottom rows) under isoflurane anesthesia (a and d), after Clon (a), Clon+Ida (c), Ida (e), and Ida+Clon (f) injections, respectively.

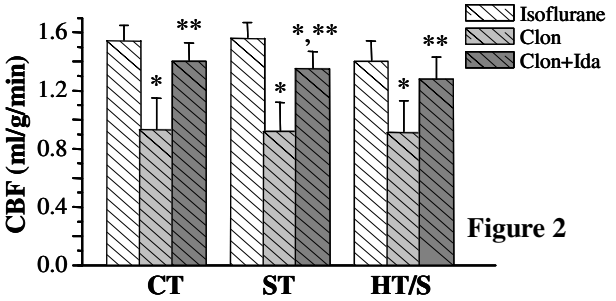

Figure 2

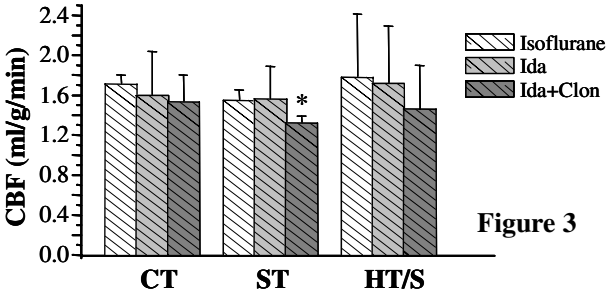

Figure 3

*p<0.05 compared to isoflurane, **p<0.05 compared to Clon.

References [1] Lei H, et al., *Brain Res* 2001; **913**:174-9. [2] Lei H, et al., *Magn Reson Med* 1999; **41**:563-8. [3] Civantos Calzada B, et al., *Pharmacol Res* 2001; **44**:195-208. [4] Eglen RM, et al., *Trends Pharmacol Sci* 1998; **19**:381-90.