Agonists of alpha2-Adrenoceptors and Imidazoline Receptors Show Selectivity-Related Differential Effects on Cerebral Blood Flow in Rat: An MR Perfusion Imaging Study

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Introduction Agonists/antagnoists of α_2-adrenoceptor and imidazoline receptor are known to affect cerebral blood flow (CBF) (1-3). However, it is still unclear whether the CBF changes induced by these drugs are simply secondary to cardiovascular responses or mediated through direct interactions of the drugs with the α_2-adrenoceptor/imidazoline receptors located in the central nervous system (CNS). In this study, we investigated, with continuous arterial labeling (CASL) perfusion imaging, the CBF changes induced by intravenous injection of xylazine (Xyla), clonidine (Clon) and moxonidine (Mox) in isoflurane-anesthetized rats. Xyla is an agonist for α_2-adrenoceptors, while Clon and Mox are agonists with receptor affinities for both α_2-adrenoceptors and imidazoline receptors, but each has different selectivity for the two types of receptors (4). The results showed that the three drugs have similar peripheral cardiovascular effects, but exhibit remarkably different effects on CBF, suggesting that the CBF-modulating effects of these drugs are mediated through central mechanisms.

Materials and Methods Twenty nine male Sprague-Dawley rats, weighing 230-300 g, were intubated and maintained under 1.0-1.5% isoflurane (in a 70:30 N_2O/O_2 gas mixture) anesthesia. 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 throughout the experiments at 37.0-37.5 ^oC using a warm water pad. After measuring baseline blood gases and CBF, the rats were injected intravenously with Xyla (0.2 mg/kg body weight, n=8), Clon (10 μg/kg body weight, n=10) and Mox (0.3 mg/kg body weight, n=11), respectively. Perfusion imaging on a brain slice at the level of striatum was performed repeatedly after injections. Snapshot FLASH imaging combined with one-coil continuous arterial spin labeling was used to acquire perfusion images on a Bruker Biospec 4.7/30 scanner (5), 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. Images of relative CBF were calculated as $(M_{con}-M_{tag})/M_{con}*100\%$. All relative CBF images were coregistrated to the same template, spatially smoothed using a 0.47-mm full-width at half-maximum isotropic Gaussian kernel and analyzed pixel-by-pixel within the framework of general linear model. Significance was determined with an FDR-corrected $p<0.05$.

Results All three drug induced significant reductions in mean arterial blood pressure (MABP) and heart rate (HR) (Fig. 1). Clon had a faster effect on MABP relative to the other two drugs. Blood gases data are listed in Table 1. Xyla resulted in significantly decreased pH and pO_2 and significantly increased pCO_2; Clon induced significantly decreased pO_2; Mox caused no significant changes in the blood gases. Xyla caused persisted global reduction of CBF up to 33 min after injection (Fig. 2, left column). Compared to Xyla, Clon induced milder CBF reductions in the cortex and striatum at 6 min, but had no effect on the CBF in the hypothalamus/septum (Fig. 2, middle column). Clon-induced CBF reductions recovered almost completely at 33 min after injection. No significant reductions of CBF were found after injection of Mox.

Discussion Our results show that agonists of α_2-adrenoceptors and imidazoline receptors can have differential effects on CBF in spite that they may have produced similar peripheral cardiovascular responses. Among the three drugs, Xyla is affinitive to α_2-adrenoceptors only, and induced the largest and longest global CBF reductions. Clon shows similar receptor affinities for α_2-adrenoceptors and imidazoline receptors (I_1/α_2 selectivity ratio:3.8) (4), and resulted in milder and short-lived CBF reductions in the cortex and striatum. Mox is more selective to imidazoline receptors than to α_2-adrenoceptors (I_1/α_2 selectivity ratio: ˜33) (4), and seemed to have no effects on CBF. Our results suggest that the differential effects of Xyla, Clon and Mox on CBF are mediated through central mechanisms and may be related to the spatial distributions of α_2-adrenoceptors and imidazoline receptors in the brain and the differential selectivity of these drugs to the receptors.

Table 1. Blood gases data measured before and 60 min after drug administration. *p<0.01 vs. baseline.

	pH	pCO_2(mmHg)	pO_2(mmHg)		pH	pCO_2(mmHg)	pO_2(mmHg)
Baseline	7.402±0.030	36.8±5.6	111.0±10.3	Xyla	7.362±0.031*	46.7±8.4*	94.2±7.3*
Baseline	7.392±0.019	35.6±4.1	122.1±5.5	Clon	7.372±0.040	38.9±6.5	113.6±10.7*
Baseline	7.398±0.024	34.2±4.6	113.8±15.7	Mox	7.382±0.033	37.9±4.6	105.3±9.0

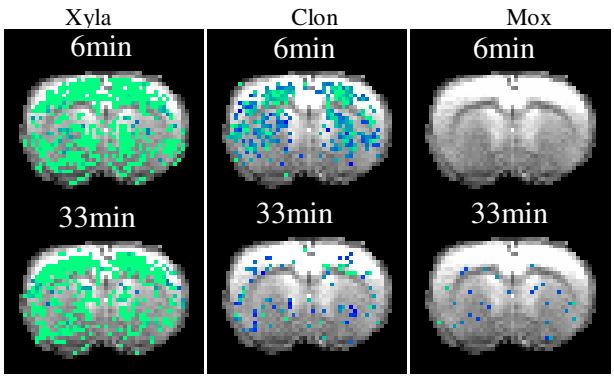

Figure 2 Changes of CBF after administration of Xyla, Clon and Mox. Coregistered raw perfusion-weighted proton density images are shown in the background. The color voxels represent the regions showing significant CBF reductions, relative to the baseline values, detected with a pixel-by-pixel statistical analysis. The amplitude of CBF reduction is color-coded and the green color denotes larger CBF reduction than the blue color.

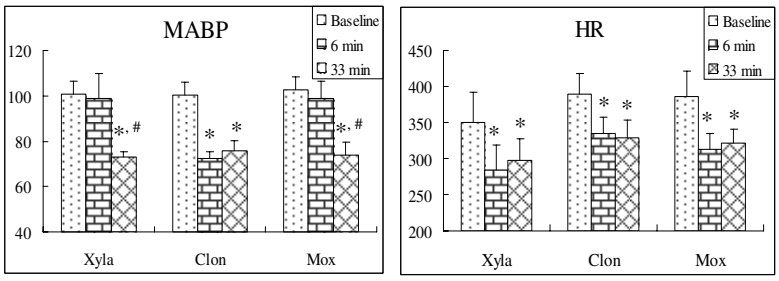

Figure 1 Changes of MABP and HR after intravenous administration of xylazine (Xyla), clonidine (Clon) and moxonidine (Mox) in isoflurane-anesthetized rats. *p<0.05 compared to baseline and # p<0.05 compared to data obtained at 6 min.

References 1. Lei H, et.al. Brain Res 2001; 913:174-179. 2. Kanawati IS, et.al. J Cereb Blood Flow Metab 1986; 6:358-365. 3. Csete K, et.al. J Cardiovasc Pharmacol 2000; 35:417-421. 4. Ziegler D, et al. J Cardiovasc Pharmacol 1996; 27 Suppl 3:S26-37. 5. Lei H, et.al. Magn Reson Med 1999; 41:563-568.