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Research report

Changes in rat cerebral blood volume due to modulation of the 5-HT_{1A} receptor measured with susceptibility enhanced contrast MRI

B. Ellen Scanley[a,*], Richard P. Kennan[b], John C. Gore[b]

[a]*Department of Psychiatry, Yale University School of Medicine, Fitkin B27, P.O. Box 208042, New Haven, CT 06520-8042, USA*
[b]*Department of Diagnostic Radiology, Yale University School of Medicine, P.O. Box 208042, New Haven, CT 06520-8042, USA*

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Abstract

Brain blood volume changes in the rat in response to 5-HT_{1A} agonist and antagonist administration were measured using susceptibility contrast enhanced magnetic resonance imaging (MRI). Administration of the 5-HT_{1A} agonist 8-OH-DPAT resulted in decreases in fractional brain blood volumes. Administration of the 5-HT_{1A} antagonist WAY-100635 following a dose of 8-OH-DPAT resulted in increases in fractional blood volumes greatest in hippocampus and cortex and smallest in thalamus and caudate-putamen. The magnitude of the regional increases in blood volumes paralleled the distribution of 5-HT_{1A} receptors in the rat brain. Administration of WAY-100635 alone resulted in decreases in cortical blood volume and increases in cerebellar blood volume.

Theme: Neurotransmitters, modulators, transporters, and receptors

Topic: Serotonin receptors

Keywords: 5-HT_{1A} receptor; 8-OH-DPAT; WAY-100635; Cerebral blood volume; MRI

1. Introduction

The neurotransmitter/neuromodulator serotonin (5-hydroxytryptamine, 5-HT) is involved in a wide variety of phenomena from the regulation of cerebral blood flow (CBF) to sleep, learning, mood, appetite and aggression. Serotonergic neuron cell bodies are located in the raphe nuclei in the brainstem and project throughout the brain. At this time, 15 different 5-HT receptors have been identified within seven main 5-HT receptor types [21]. Of the many 5-HT receptors, the 5-HT_{1A} receptor is thought to be particularly involved in the pathophysiology of stress and depression [8]. 5-HT_{1A} receptors are located both presynaptically (on the dendrites and cell bodies of the serotonergic neurons in the raphe nuclei) and postsynaptically, with particularly high postsynaptic receptor densities in the hippocampus, amygdala, septum and cortex [20]. Presynaptically, 5-HT_{1A} receptors act as autoreceptors, so that agonist binding to presynaptic 5-HT_{1A} receptors inhibits the firing of raphe neurons. Postsynaptically, stimulation of 5-HT_{1A} receptors primarily inhibits neuronal firing with exceptions including motor cortex [3,11]. Studies indicate that there are significant changes in 5-HT_{1A} receptors following treatment with several classes of antidepressants [3,4,22]. It has been proposed that some antidepressants work by desensitizing 5-HT_{1A} autoreceptors in the raphe nuclei resulting in increased serotonergic neuron output. Alternatively, other antidepressants may function by increasing the sensitivity of post-synaptic 5-HT_{1A} receptors. Either way, a desensitization of presynaptic- or sensitization of postsynaptic 5-HT_{1A} receptors results in an increase in serotonergic neurotransmission.

An in vivo measurement of 5-HT_{1A} receptor function would be useful in the evaluation of the serotonin system and the response to medication treatment. In this study cerebral blood volume (CBV) changes were measured as

*Corresponding author. Tel.: +1-203-785-6410; fax: +1-203-785-6534.

E-mail address: ellen.scanley@yale.edu (B.E. Scanley).

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an indirect indicator of 5-HT_{1A} receptor activation using magnetic resonance imaging (MRI) and an intravascular susceptibility contrast agent. 5-HT_{1A} receptor activation was modulated with the 5-HT_{1A} agonist (±)-8-hydroxy-dipropylamino-tetralin HBr (8-OH-DPAT) and the selective 5-HT_{1A} antagonist WAY-100635 [5]. It was hypothesized that 8-OH-DPAT would cause decreases in CBV correlated with its inhibitory actions on neurons and that WAY-100635 would reverse the effects of 8-OH-DPAT.

2. Materials and methods

2.1. Theory

Blood volume measurements were made using intravenous injections of an iron oxide intravascular contrast agent (AMI-227, Advanced Magnetics, Inc., Cambridge, MA). This agent is comprised of iron oxide particles of submicron diameter that cannot cross the intact blood brain barrier. AMI-227 is a superparamagnetic agent that alters the magnetic susceptibility within blood vessels, creating local magnetic field inhomogeneities and decreasing magnetic resonance relaxation times as the concentration of AMI-227 increases in the vascular volume of each voxel. MR image intensity decreases as the concentration of AMI-227 increases in the vascular volume of each voxel. At a constant concentration of AMI-227, images become brighter as blood volume decreases and darker as blood volume increases.

Fractional blood volume changes that occur relative to a basal state can be quantified in terms of changes in the transverse relaxation rates (R_2^*) before and after administering the contrast agent as described by Kennan et al. [13]

$$\frac{\Delta V_{bl}}{V_{bl}} = \left[\log \left[\frac{S_{postDrug}}{S_{preDrug}} \right]_{postAMI} - \log \left[\frac{S_{postDrug}}{S_{preDrug}} \right]_{preAMI} \right] \Big/ \log \left[\frac{S_{postAMI}}{S_{preAMI}} \right]_{preDrug}$$

where $\Delta V_{bl}/V_{bl}$ is the fractional change in blood volume occurring due to administration of drug or other intervention (e.g. sensory or other stimulation, etc.) and R_2^* is the transverse relaxation rate ($=1/T_2^*$). The numerator of this calculation is obtained by measuring MRI signal intensity differences before administration of 8-OH-DPAT (pre-drug) and after administration of 8-OH-DPAT (post-drug), both prior to injection of AMI-227 (pre-AMI) and after injection of AMI-227 (post-AMI). The denominator is from MRI signal intensity differences measured before and after administration of AMI-227 prior to injection of 8-OH-DPAT.

During sensory stimulation studies, the percent blood volume changes can be directly measured within each animal because the stimulation (corresponding here to 'post-drug') can be performed 'on' and 'off' both before and after contrast agent administration. With pharmacological studies, the vast majority of pharmacologic agents do not clear rapidly enough to allow a pre-AMI drug bolus to clear before administration of AMI-227. However, a good approximation can be made to give the percent volume changes with a single animal. The R_2^* change comparing the pre-drug to the post-drug images prior to administration of contrast agent (the second term of the numerator) can be made much smaller than the signal change after administration of contrast agent (the first term of the numerator). For a sensory stimulation experiment the signal change upon stimulation in the presence of a similar dose of AMI is in the range of 20% while in the absence of AMI the fMRI signal change is in the range of 1–3% [14]. Since the pre-AMI image intensity changes will be in the opposite direction to the post-AMI signal changes, omitting the pre-AMI term results in only a small underestimate of the percent blood volume change [16].

2.2. Animals

Female Sprague–Dawley rats (180–260 g) were anesthetized with urethane 1.2–1.4 g/kg i.p. ($n=8$) or isofluorane 0.75–1.2% ($n=8$). The femoral artery and vein were cannulated to monitor blood pressure and blood gases and to administer drugs, respectively. The animals were tracheotomized and ventilated with an FIO_2 of 38–42% and an i.p. catheter was placed for subsequent administration of a paralytic agent (tubocurarine 0.5 mg/kg administered shortly before beginning data acquisition). The animal was placed supine in a perspex holder and was kept at body temperature by hot air blown into the bore of the magnet. 8-OH-DPAT and WAY-100635 were purchased from RBI Inc. (Natick, MA). 8-OH-DPAT was dissolved in degassed saline the morning of each study. All drugs were administered intravenously. Four rats received 8-OH-DPAT (0.1 mg/kg) followed by WAY-100635 (0.25 mg/kg) and four rats received a single dose of WAY-100635 (0.25 mg/kg). These eight rats were anesthetized with isofluorane. For dose–response experiments, eight rats were anesthetized with urethane and each received two doses of 8-OH-DPAT. The blood volume change at the cumulative dose is reported in the dose–response curve. For comparison of anesthetic effects we also include in the dose–response curve, the data at the 0.1 mg/kg dose for rats under isofluorane. The dose–response studies were completed first and then the anesthesia was switched from urethane to isofluorane because of persistent problems of hypotension with urethane.

2.3. Imaging

All imaging was performed at 2.0 T using a 2.25-inch diameter, birdcage coil. After approximate localization with a low-resolution sagittal image, axial localizer images were obtained with TR 1.5 s, TE 40 ms, slice thickness 1.5

mm, FOV 60 mm, 128×64 matrix, 1 NEX. High resolution, multislice anatomic images were then acquired with a gradient echo sequence TR 1.5 s, TE 40 ms, FOV 60 mm, 256×256 matrix, slice thickness 1.5 mm, eight slices, 0.5 mm interslice gap, 2 NEX. The slices were positioned so that the fifth slice back was through the dorsal hippocampus. Blood volume data were acquired with multislice gradient echo images: TR 500 ms, TE 15 ms, slice thickness 1.5 mm, FOV 60 mm, 128×64 matrix, eight slices, 0.5 mm interslice gap, 2 NEX. One multislice image was acquired every 64 s. AMI-227 was injected intravenously (5–7 mg/kg) after ~15 baseline images were acquired and 10–15 post-AMI images were then acquired prior to injection of drug. A map of the percent change in CBV was then created for each dose of drug as described by Kennan et al. [13]. Average voxel intensities were calculated for the first 10–15 baseline images, from the five post-AMI images just prior to injection of drug, and from five images at each dose of drug (skipping the two images acquired during and just after injection of drug). Regions of interest (ROIs) were drawn for every animal using a cursor on the anatomic images. Fractional blood volume changes for hippocampus were averaged for dorsal and ventral hippocampal regions in adjacent slices, and for cortical and cingulate regions were the average of ROIs on adjacent slices. Data are presented as the mean±standard deviation. Studies were excluded if the BP fell below 60 mmHg for more than 1 min following injection of 8-OH-DPAT.

3. Results

3.1. Physiological monitoring

8-OH-DPAT had significant hypotensive effects. Average blood pressure prior to all 8-OH-DPAT injections was 80±11.6 mmHg and during injection fell to 60±14.8 mmHg. By 1 min and 4 min post-injection BPs averaged 77±9.8 and 97±9.3, respectively. The magnitude of the fall in BP did not correlate directly with the dose. WAY-100635 alone did not significantly change the blood pressure (89±9.0 mmHg before and 91±5.0 mmHg 4 min after dosing). However, injection of WAY-100635 after injection of 8-OH-DPAT did increase BP significantly from 89±8.0 to 101±11.5 mmHg (Student's two-tailed, paired *t*-test, $P=0.036$). Blood gases obtained before and after each study demonstrated a trend for an increase in P_{CO_2} during the studies. The pre-study blood gases were pH 7.4±0.05, P_{CO_2} 31±7.0 and P_{O_2} 165±31.9. The post-study blood gases were pH 7.3±0.08, P_{CO_2} 40±11.0, and P_{O_2} 150±31.1.

3.2. Percent blood volume changes

In all regions examined and at all doses, 8-OH-DPAT caused decreases in CBV. The time course of cortical signal intensity for one study is shown in Fig. 1. Following several baseline images the image intensity drops significantly upon injection of AMI-227. The magnitude of the signal decrease is proportional to the regional blood volume. Upon injection of 8-OH-DPAT, the ROI intensity increases indicating a decrease in blood volume. Upon injection of WAY-100635 the image intensity drops again indicating an increase in blood volume approximately back to baseline. Fig. 2 shows maps of the percent blood volume changes for this study in one slice through the dorsal hippocampus. Following 8-OH-DPAT injection (Fig. 2C) there is a general decrease in blood volume that, in this slice, is greatest in the cortex. When averaged over all experiments, the percent CBV increase following subsequent WAY-100635 injection shows largest changes in hippocampus (Figs. 2D and 5). A single dose of 8-OH-DPAT (0.1 mg/kg, i.v.) caused the largest fractional CBV decrease in hippocampus and septum and the smallest decrease in cerebellum and caudate-putamen (Fig. 3).

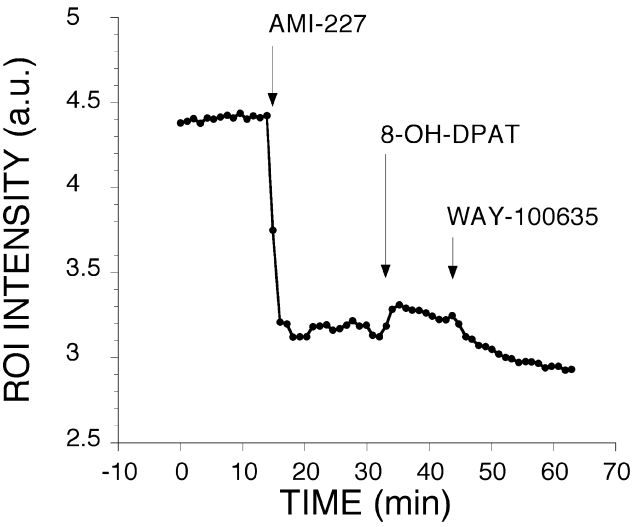

Fig. 1. Time course of image intensity from a cortical region of interest through the duration of one study. Doses: AMI-227 6 mg/kg, i.v., 8-OH-DPAT 0.1 mg/kg, i.v., WAY-100635 0.25 mg/kg, i.v.

Global percent CBV decreases following 8-OH-DPAT injection ranged from −0.25% at 0.01 mg/kg to 7% at 0.5 mg/kg (Fig. 4). Single factor ANOVA did not show a statistically significant effect of dose due to the large variability of dose response at 0.15 mg/kg. When WAY-100635 was given following a dose of 8-OH-DPAT, blood volumes increased. Global blood volume decreased by 4±1.6% following a 0.1 mg/kg dose of 8-OH-DPAT but then increased by 11% (to 7±3.7% above baseline) upon administration of WAY-100635 (0.25 mg/kg, $n=4$). The increase in percent CBV which occurred upon administration of WAY-100635 following the administration of 8-OH-DPAT was greatest in hippocampus and smallest in caudate-putamen (Fig. 5).

Administration of WAY-100635 (0.25 mg/kg) alone

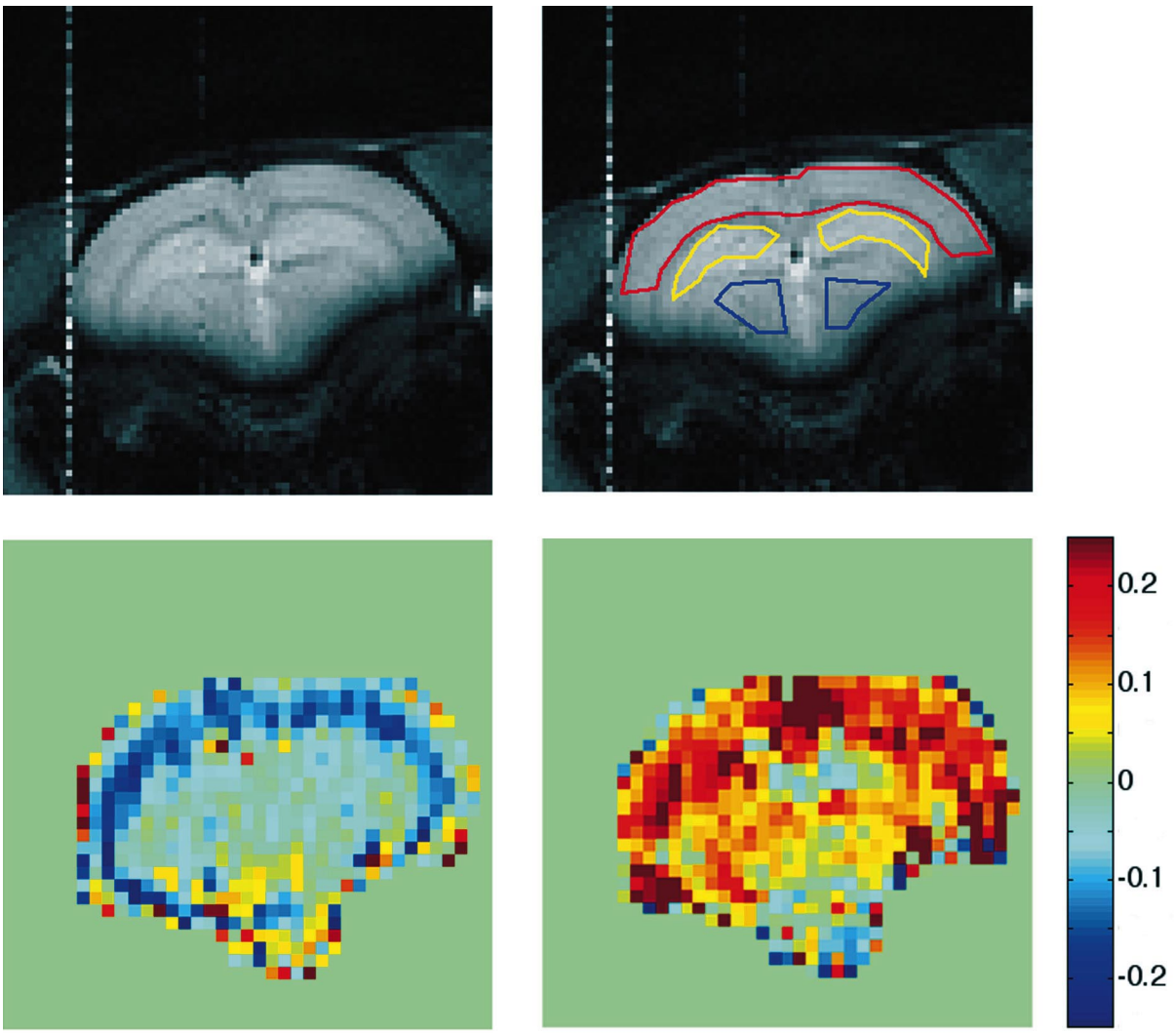

Fig. 2. Maps of percent blood volume changes. (A) Anatomical image, (B) anatomical image with superimposed regions of interest, (C) percent blood volume changes after administration of 8-OH-DPAT (0.1 mg/kg, i.v.) and (D) percent blood volume changes after administration of WAY-100635 (0.25 mg/kg, i.v.). A susceptibility inhomogeneity artifact causes loss of signal around the ventral aspect of the brain in this slice.

caused a small non-significant decrease in global CBV of −3±3.1%. Regionally (Fig. 6), WAY-100635 caused a decrease in cortical CBV of 6±0.8% and an increase in cerebellar CBV of 9±8.4%.

4. Discussion

These studies demonstrate a dose- and region-dependent decrease in blood volume in several brain regions following administration of the 5-HT_{1A} agonist 8-OH-DPAT. This decrease in CBV was reversed by administration of the 5-HT_{1A} antagonist WAY100635. Administration of WAY-100635 alone resulted in decreased cortical and increased cerebellar percent CBV. The percent CBV changes following 8-OH-DPAT decreased in parallel with the regional distribution of 5-HT_{1A} receptors [20] although there were large variations in the magnitude of the blood volume changes between studies.

The reversal of the 8-OH-DPAT-induced decrease in CBV by WAY-100635 indicates that this CBV decrease is a pharmacologically specific effect due to $5HT_{1A}$ receptor binding, ruling out non-selective effects of 8-OH-DPAT at other receptors such as the 5-HT_7 receptor [5]. A decrease in percent CBV might occur due to the inhibitory action of 8-OH-DPAT at 5-HT_{1A} receptors both pre- and post-synaptically. Consistent with this hypothesis, Kelly et al. [12] and Freo et al. [7] reported decreases in hippocampal glucose utilization (GU) following 8-OH-DPAT administration. Wree et al. [24] demonstrated decreases in GU in all regions of the hippocampus in conscious rats using the 5-HT_{1A} agonist ipsapirone.

However, a decrease in blood volume following 8-OH-DPAT administration is not consistent with the findings of McBean et al. [19]. McBean et al. using combined

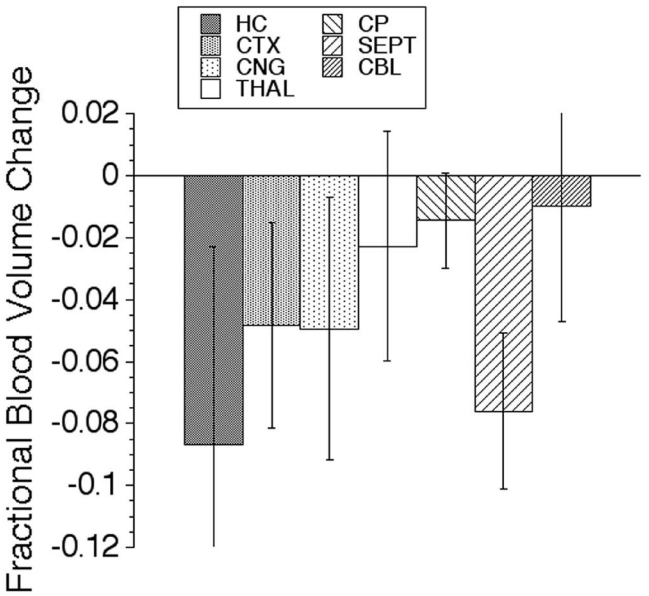

Fig. 3. Regional blood volume decreases upon administration of 8-OH-DPAT (0.1 mg/kg, i.v.), $n=4$.

[^{14}C]FDG and [^{14}C]iodaantipyrine autoradiography reported an increase in the CBF to GU ratio in conscious rats upon administration of 8-OH-DPAT. They reported increases in absolute CBF in almost all regions examined. They argued that 8-OH-DPAT, via its agonist effect on the 5-HT$_{1A}$ autoreceptor, caused a decrease in cerebral extracellular serotonin thereby reducing serotonergically-mediated vasoconstriction. The difference in the results reported by McBean et al. and those reported here may be due to the use of anesthesia in this study. In the awake animal a serotonin behavioral syndrome occurs at the dose of 8-OH-DPAT used which would alter the patterns of

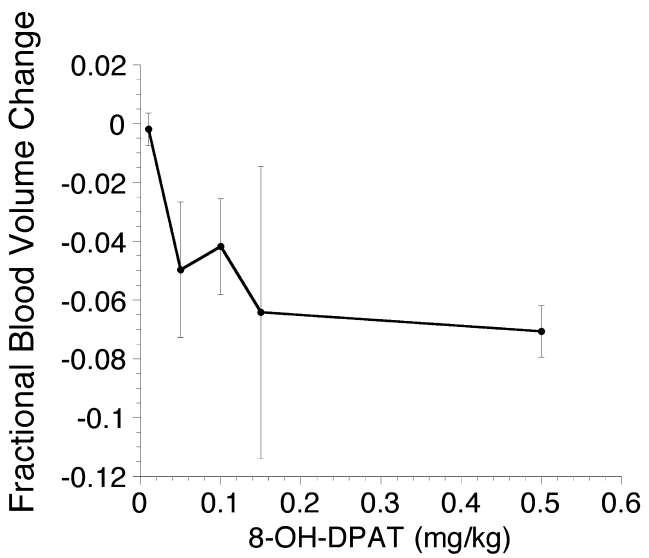

Fig. 4. Fractional global blood volume decreases as a function of cumulative 8-OH-DPAT dose: 0.01 mg/kg ($n=2$), 0.05 mg/kg ($n=3$), 0.1 mg/kg ($n=4$), 0.15 mg/kg ($n=3$), 0.5 mg/kg ($n=4$).

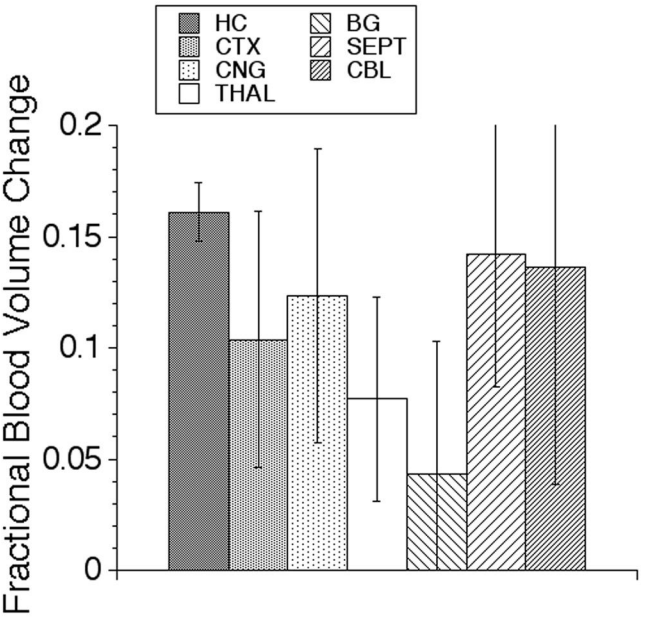

Fig. 5. Regional blood volume increases upon administration of WAY-100635 (0.25 mg/kg) following a dose of 8-OH-DPAT (0.1 mg/kg), $n=4$.

neuronal activity compared to the anesthetized animal. Additionally, the basal activity of serotonergic neurons is significantly reduced during sleep compared to wakefulness [10]. Serotonin may induce vasodilation or vasoconstriction depending on the state of contraction of blood vessels [17] thus the baseline state of the animal may be important. In the data reported here there was no qualitative difference between the response to 8-OH-DPAT whether the anesthetic used was urethane or isofluorane.

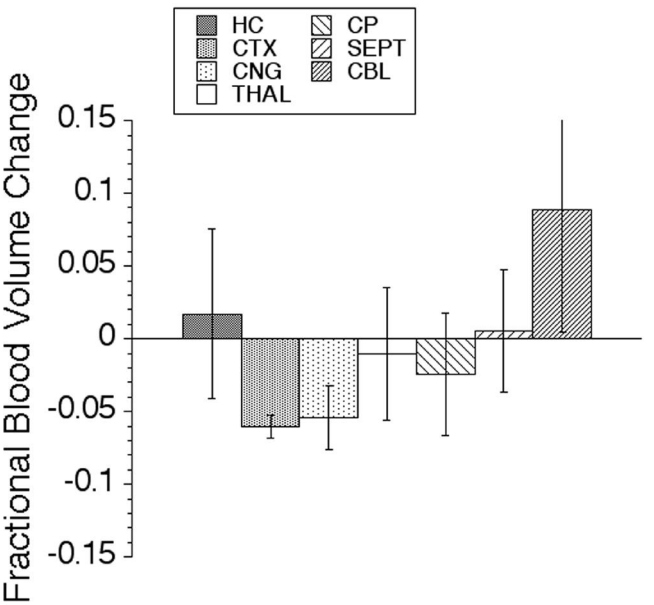

Fig. 6. Regional fractional blood volume changes upon administration of a single dose of WAY-100635 (0.25 mg/kg, $n=4$).

This suggests that the differences we found compared to those of McBean et al. are due to the difference in the serotonergic system between the awake and anesthetized state and are not due to one specific anesthetic agent.

Another possibility for the decreases in CBV with 8-OH-DPAT is that it is causing a direct vascular constriction. Although, in the rat, the serotonin receptors most predominantly involved in serotonergically mediated vasoconstriction are the 5-HT_{2A} and the 5-HT_{1B} receptors [9,17,23], high concentrations of 8-OH-DPAT administered in vitro have been shown to cause significant vasoconstriction. Nishimura [23] reported an EC_{50} of 6 μM for vasoconstriction for 8-OH-DPAT in rat basilar arteries and Hamel et al. [9] reported large maximal contraction of the feline middle cerebral artery caused by 8-OH-DPAT although this was at quite high concentrations. The plasma levels of 8-OH-DPAT in this study may have been transiently in a range sufficient to cause direct vasoconstriction. Mason et al. [18] found plasma levels of 8-OH-DPAT in rats to exceed 10 μM very briefly after a 1 mg/kg i.v. dose. However, it is not known if the direct vasoconstriction would be regionally specific as found here.

The changes in CBV that occurred following WAY-100635 administration alone were unexpected. Studies in anesthetized animals have demonstrated that WAY-100635 did not increase extracellular 5-HT levels [1] nor did it significantly increase dorsal raphe serotonergic nerve firing [6]. The decrease in cortical CBV could be explained if WAY-100635 could have stimulated the raphe nuclei. These results would then be comparable to Bonvento et al. [2] who showed decreases in cortical blood flow upon electrical stimulation of the dorsal raphe in anesthetised rats. The increase in cerebellar CBV is unexpected because of the very low density of 5-HT_{1A} receptors in cerebellar tissue [20], however, 5-HT_{1A} receptors have been shown to modulate excitatory neurotransmission in cerebellum [15]. The increase in CBV in the cerebellum following WAY-100635 administration was the same whether WAY-100635 was given alone or was preceded by 8-OH-DPAT.

Several additional factors may have contributed to the results reported. These factors are addressed briefly here: (1) in the majority of these studies the blood pressure dropped significantly for a period of 1–2 min following administration of 8-OH-DPAT. In two studies however, there was no drop in blood pressure and the overall pattern of CBV changes were the same, suggesting that this is not an artifact of reduced blood pressure. Additionally the degree of hypotension did not correlate with the dose and as shown in Fig. 3 the decrease in blood volumes was dose dependent. (2) There was an overall increase in arterial P_{CO_2} from the beginning to the end of each study. The increased P_{CO_2} would have acted to increase CBV which is the opposite of what was seen with 8-OH-DPAT administration. (3) Washout of the AMI-227 during the study will correspond to an increasing image intensity and therefore, artificially to a decreasing CBV. Although the clearance of AMI-227 is very slow this may have contributed to the percent decreases in CBV that were measured, though this would not be a regionally specific effect. (4) Two different anesthetics were used. Isofluorane was preferred compared to urethane because of persistent problems of hypotension with urethane. The two anesthetics were not directly compared at the same dose of drug, however, the dose–response curve indicates that the magnitude of CBV decrease found with urethane was consistent with that seen with isofluorane. (5) This study used female rats with unmonitored estrous cycles. Due to the high variability of the serotonin system in rats through the estrous cycle this may have contributed to the high degree of variability found between animals.

This study lends support to the value of quantitative MRI measures of brain blood volumes for the study of neuropharmacologic effects. The coincidence of the largest 8-OH-DPAT-induced blood volume decreases with regions with highest densities of 5-HT_{1A} receptors suggests that the most likely cause of the blood volume decreases is the inhibitory effect of post-synaptic 5-HT_{1A} receptor binding. More regionally nonspecific changes might be expected from direct vascular or pre-synaptic effects. However, a comparison of these results with studies of 8-OH-DPAT used in awake animals suggests that the results obtained may vary widely between awake and anesthetized animals.

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