EFFECTS OF ANAESTHESIA, HYPERCARBIA AND HYPOCARBIA ON REGIONAL CEREBRAL BLOOD FLOW IN THE GOAT

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NUMEROUS REPORTS concerning the effects of various agents on cerebral blood flow and metabolism in both man and animals have appeared in the literature. In most instances, results from these studies have been interpreted with the tacit assumption that measurements of total cerebral blood flow and oxygen extraction across the cerebral vascular bed were more or less representative for all regions of the brain. More recent studies, however, have shown that the brain contains discreet regions of high vascularity and is not homogenously perfused.¹⁻⁴ If this is true, then during situations of altered cerebral flow, such as those occurring with anaesthesia, all regions of the brain may not be affected to the same extent. The purpose of this study was, therefore, to define regional cerebral blood flow (rCBF) in unanaesthetized goats and to determine what effects anaesthesia with halothane, ketamine and pentobarbitone might have on regional flow.

METHODS

Regional cerebral blood flow and changes in rCBF were determined in awake and unanaesthetized goats by comparing the intracerebral distributions of strontium⁸⁵ (Sr^{85} ; 2.7 mCi/gm) and cerium¹⁴¹ (Ce^{141} ; 2.6 mCi/gm) labelled microspheres ($15 \pm 5 \mu\text{m}$, 3 M Co.) following injection into the cerebral circulation.

The goat was selected as the experimental animal because the arterial blood supply to the brain is uncomplicated.⁵ Briefly, the external carotid arteries carry the sole supply of blood to the brain. The vertebral arteries do not contribute to the cerebral circulation. The external carotid artery bifurcates extracerebrally to form the lingual and internal maxillary arteries. Arising from the internal maxillary artery are the ramus anastomotica and the arteria anastomotica which empty into the rete mirabile. The rete mirabile is a complex maze of intersecting, anastomosing arteries just distal to the circle of Willis.

Forty mature female goats weighing 28 kg were used. The animals were divided into six groups of six goats each, except group I which consisted of ten animals. In group I Sr^{85} and Ce^{141} labelled microspheres were injected into awake goats in separate doses one hour apart. The use of two differently labelled microspheres permitted the measuring of rCBF at two different times. In all cases 3×10^5 micro-

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spheres were suspended in 10 ml of saline after being exposed for 5 minutes to ultra-sound to insure the elimination of microsphere "clumping". Microspheres were injected in pulse fashion over a ten-minute period, i.e. 1 ml per minute over the ten-minute period. The injection was done while the animals were standing unrestrained in a yoke and staff. The animals appeared to tolerate the injections well and showed no signs of pain or discomfort. The rationale for injecting awake animals twice was to determine if the act of injecting microspheres in itself would cause changes in cerebral haemodynamics.

In group II anaesthesia was induced with ketamine 10 mg/kg intramuscularly and maintained with 2 mg/kg intravenously as needed. Before induction of anaesthesia, Sr^{85} microspheres had been injected into the animals while awake. One hour from the first injection and after induction of anaesthesia the second dose of Ce^{141} microspheres was injected. Group III animals were anaesthetized with pentobarbitone 35 mg/kg intramuscular and injected with microspheres as described for group II. Group IV consisted of animals anaesthetized by halothane (1.5 per cent in 100 per cent oxygen) in which normocarbica was maintained. Groups V and VI animals were also anaesthetized with 1.5 per cent halothane, but in group V hypocarbica was produced through mechanical hyperventilation with 100 per cent oxygen. Hypercarbica was produced in group VI by ventilation with 5 per cent carbon dioxide and 95 per cent oxygen. Animals in groups IV through VI were injected with microspheres as described for group II.

Except for the hypercarbica group, the lungs of all anaesthetized animals were ventilated mechanically with 100 per cent oxygen to maintain normal blood gas levels. A sample for blood gas determinations was drawn before each microsphere injection. Arterial blood pressures were monitored through a femoral artery catheter which was inserted after the induction of anaesthesia.

Microspheres were injected into the cerebral circulation via the temporal artery rather than the left ventricle as is customary for this technique. Deviation from the usual method was possible due to the presence of the rete mirabile which provided thorough mixture of the microspheres with the blood before reaching the brain. This change greatly simplified the measuring of rCBF in awake animals by eliminating the need for chronic catheterization of the left ventricle. On the day before microsphere injection a catheter was implanted in the temporal artery under light halothane anaesthesia. This procedure generally took less than 45 minutes and the animals had fully recovered by the next day.

After each experiment the animals were immediately sacrificed by injecting concentrated potassium chloride, the skull was opened, and the brain removed and weighed. In experiments involving awake animals the animal was anaesthetized with pentobarbitone just before the injection of potassium chloride. The brain was then bisected along its longitudinal axis. The experimental half, i.e. the side which had received the microspheres, was weighed and homogenized in 100 ml of saline after removal of regional tissue samples as indicated in Figure 1. The regions of the brain selected for study were the thalamus, gray and white matter of the cerebral hemisphere, cerebellum and hypophysis. Each sample was weighed and the Ce^{141} and Sr^{85} activities determined and differentiated by gamma scintillation as described by Hales.⁶ Results were obtained by dividing the radioactivity per

FIGURE 1. Sampling sites for rCBF determinations. Shaded area indicates the portion of the brain which received microspheres.

gram for each region by the radioactivity per gram of total brain tissue of the experimental side and expressed as a percentage. The formula used was:

$$\left(\frac{\text{CPM rBT}}{\text{CPM tBT}} \times 100 \right)$$

where: CPM = counts per minute

rBT = regional brain tissue

tBT = total brain tissue from experimental side.

Significance of differences between Sr^{85} and Ce^{141} distribution was determined by t-test or analysis of variance.

RESULTS

Analysis of the intracerebral distribution of Ce^{141} labelled microspheres from normal unanaesthetized goats reveals significant differences in rCBF (Figure 2). Of the regions studied the thalamus was the most highly perfused and cortical white matter was the least perfused. Regions ranked as follows: thalamus (151 ± 11 per cent, > gray matter (111 ± 14 per cent) > cerebellum (92 ± 17 per cent) > hypophysis (75 ± 4 per cent) > cerebral white matter (47 ± 4 per cent).

In the awake goat the distribution of Sr^{85} microspheres, injected one hour later, was not significantly different from the distribution of Ce^{141} microspheres, indicating that the act of injecting microspheres or the presence of microspheres in the brain did not produce subsequent changes in rCBF (Figure 3).

The effects on rCBF of ketamine (10 mg/kg), pentobarbitone (35 mg/kg) and

Brain Ce¹⁴¹ Distribution in Awake Goats

FIGURE 2. Regional distribution of Ce¹⁴¹ microspheres in the brain of the awake goat. Each bar represents the mean value $\pm$ SD, $n = 10$. Flow to the thalamus was significantly higher than to grey matter and cerebellum $p < 0.05$. Flow to grey matter and cerebellum was significantly higher than flow to hypophysis and white matter $p < 0.05$. Flow to the hypophysis was significantly higher than flow to white matter, $p < 0.05$. Significance was determined through one way analysis of variance.

halothane (1.5 per cent) anaesthesia at varying P_{aCO_2} can be seen in Table I. The ranking of regional flows was unaltered following anaesthesia when compared to the ranking observed in awake goats (Figure 2). However, significant quantitative changes in relative rCBF were produced by each anaesthetic and by change in carbon dioxide tension.

Blood gases, haematocrit, and mean arterial blood pressure prior to Ce¹⁴¹ and Sr⁸⁵ microsphere injections for controls and for anaesthetized animals are listed in Tables II and III. No significant differences in blood gases or haematocrit were observed in any of the experimental groups except in those groups where deliberate hypocarbia or hypercarbia were produced. Thus none of the changes observed in rCBF following the test procedures could be accounted for by changes in these parameters. Ketamine produced a significant increase in mean arterial blood pressure when compared to values seen in other experimental groups.

DISCUSSION

The intracerebral distribution of microspheres in awake, normocarbic goats clearly demonstrates significant differences in rCBF (Figure 2). Of the regions studied the thalamus is the most highly perfused while the white matter of the cerebral cortex is the least perfused. These observations are in general agreement

FIGURE 3. The distribution patterns of Ce¹⁴¹ microspheres and Sr⁸⁵ microspheres injected one hour apart in awake goats were not significantly different, indicating that the act of injecting microspheres in itself does not produce changes in rCBF. Each bar represents mean value $\pm$ S.D. Significance was tested by one-way analysis of variance.

with those from other studies in which anaesthetized subjects were used.¹⁻⁴ It has been reported in man,⁷ in the cat,⁸ and in the monkey⁹ that the ratio of cerebral gray matter blood flow to white matter flow is approximately 4:1. In this study, however, the ratio was found to be about 2:1. This ratio was also observed in the goat by Miletich, *et al.*¹⁰ These authors noted that the ratio of gray-white flow was dependent on the site from which the cortical white matter was selected for study. If the white matter was taken from the central portion of the cortex then the resultant ratio was 4:1 as reported for other species. If, however, the white matter was selected from a site away from the center of the cortex and adjacent to the gray matter, as it was in our study, the resultant ratio was reduced to about 2:1. It would appear that in the goat flow through the cortical white matter becomes progressively greater from the center of the cortex to the periphery. Based on these data, the gray-white 4:1 ratio observed in previous studies for other species may not necessarily be typical for all mammalian brains.

The demonstration that regions of the brain differ significantly in terms of blood flow logically leads to speculation as to the physiological implications of these differences. Ordinarily extensive vascularity is an indication of high metabolic activity, or tissue so perfused is one which must be particularly exposed to substances borne in the blood.¹¹ Sites of high vascularity usually also have extensive autoregulatory capability. It is possible that in the normal animal the phenomenon known as cerebral autoregulation of blood flow is in fact a composite of the autoregulatory responses of several highly perfused regions.

TABLE I
PERCENTAGE RELATIVE CHANGE IN rCBF DURING KETAMINE, PENTOBARBITONE AND HALOTHANE ANAESTHESIA
WITH NORMOCARBIA, HYPOCARBIA, AND HYPERCARBIA

	Pentobarbitone	Ketamine	Halothane and normocarb	Hypercarb	Hypocarb
Thalamus	-38±19†	-75±31†	-65±28	+68±28	-63±15
Gray matter	-27±18†	+25±10	*	+55±34	+42±27
Cerebellum	*	*	*	*	*
Hypophysis	-24±15	*	*	*	*
White matter	+61±23	*	*	*	*

*No significant change in region.

†All values are mean percent ± S.D., $p < 0.05$, $n = 6$.

‡ $n = 5$ for that region.

TABLE II
MEAN ARTERIAL BLOOD PRESSURE AND HEMATOCRIT OF EXPERIMENTAL GROUPS

	Control (awake)	Ketamine	Pentobarbitone
MABP (mm Hg)	94±5*	121±12†	106±11
Haematocrit	29±6	32±6	27±5
	Halothane and normocarb	Halothane and hypercarb	Halothane and hypercarb
MABP (mm Hg)	92±10	96±15	91±13
Haematocrit	32±3	29±5	30±9

*Mean values ± S.D.

†Statistically significant, $p < 0.05$, $n = 6$; by t-test.

TABLE III
MEAN ARTERIAL BLOOD GASES OF EXPERIMENTAL GROUPS

	Control (awake)		Ketamine		Pentobarbitone	
	Ce ⁴¹	Sp ⁸⁸	Awake	Anaesth.	Awake	Anaesth.
Paco ₂ (mm Hg)	30 ± 2.8	29 ± 1.5	30 ± 2.5	30 ± 3.4	30 ± 1.7	33 ± 3.3
PaO ₂ (mm Hg)	93 ± 6	92 ± 7	90 ± 4	440 ± 31	91 ± 8	412 ± 67
pH	7.44 ± 0.04	7.45 ± 0.09	7.47 ± 0.02	7.48 ± 0.04	7.48 ± 0.02	7.41 ± 0.03
	Halothane and normocarbua		Halothane and hypocarbua		Halothane and hypercarbua	
	Awake	Anaesth.	Awake	Anaesth.	Awake	Anaesth.
Paco ₂ (mm Hg)	28.8 ± 2.5	33 ± 5	30 ± 2	19 ± 2†	29 ± 4	65 ± 7†
PaO ₂ (mm Hg)	92 ± 7	418 ± 34	90 ± 7	261 ± 153	86 ± 4	330 ± 82
pH	7.49 ± 0.05	7.43 ± 0.06	7.48 ± 0.03	7.6 ± 0.06	7.41 ± 0.02	7.2 ± 0.04

*Mean values ± S.D.

†Statistically significant, $p < 0.05$, $n = 6$; by t-test.

While the physiological significance of heterogenous cerebral flow must await further study, the results in this report concerning the effects of ketamine, pentobarbitone and halothane anaesthesia on relative changes in regional flow are of interest. All the anaesthetics tested, including halothane anaesthesia in combination with either hypocarbia or hypercarbia, produced striking changes in relative regional blood flow. These changes distinctly demonstrate that not all regions of the brain are affected to the same degree by anaesthetics and blood carbon dioxide tension. One consistent finding was that all the anaesthetics reduced flow to the thalamus relative to other regions of the brain except halothane anaesthesia with hypercarbia. It may be that the potent cerebral vasodilating effects of an elevated blood carbon dioxide tension masked the "normal" effects of halothane anaesthesia that were seen during normocarbia.

Because reduction in thalamic flow was consistently observed irrespective of the chemical nature of the anaesthetic employed it is tempting to speculate that this region is in some way uniquely sensitive to chemical intervention. Possibly a direct vascular effect could account for these decreases. However, this seems unlikely since halothane and ketamine have been demonstrated to be cerebral vasodilators.^{12,13}

A second possibility is that reduced thalamic flow might be secondary to a decrease in thalamic metabolism. Ordinarily blood flow through an organ is closely governed by its metabolic rate; that is, increased flow is associated with increased metabolism and decreased metabolism results in decreased flow. However, anaesthetics appear to uncouple this normal physiological relationship. For example, halothane decreases cerebral metabolism but increases cerebral flow^{12,14} while barbiturates decrease both metabolism and flow.¹⁵ Despite the ambiguity concerning the effects of anaesthetics on flow and metabolism, it is plausible that the relative decreases in thalamic flow seen in this study may have been brought about by a decrease in thalamic metabolism. These thalamic manifestations could have important implications on the mechanisms of anaesthesia since it is believed that the thalamo-cortical projections are critical to the maintenance of consciousness.¹⁶

Finally, in the evaluation of these results it is important to keep in mind the distinction between relative and absolute changes in blood flow. For example, in animals anaesthetized with pentobarbitone, relative blood flow to white matter was seen to increase as compared to other areas, but the actual net flow to this part of the brain may have been lower or unchanged compared to normal awake values. However, relative flow changes, while lacking in dimension, are indicative of the susceptibility of the various regions of the brain to intervention. It is clear from the data presented here that in situations of reduced cerebral flow not all areas of the brain share the burden equally.

SUMMARY

Regional cerebral blood flow (rCBF) was evaluated by radioactive microsphere indicator technique in unanaesthetized goats and in goats anaesthetized with ketamine, pentobarbitone and halothane. In addition, rCBF was studied in goats anaesthetized with halothane associated with hypercarbia and hypocarbia. Micro-

sphere distribution in unanaesthetized goats demonstrated significant differences in rCBF of the following order and magnitude: thalamus, 151 ± 11 per cent; cerebral gray matter, 111 ± 14 per cent; cerebellum, 92 ± 17 per cent; hypophysis, 75 ± 4 per cent; cerebral white matter, 47 ± 4 per cent (100 per cent = average flow per gm brain). Microsphere distribution following anaesthesia indicated significant changes in relative rCBF to various regions. Ketamine (10 mg/kg) produced a relative decrease in thalamic flow (75 ± 31 per cent) while increasing gray matter flow (21 ± 10 per cent). Pentobarbitone (35 mg/kg) produced a relative decrease in thalamic (38 ± 19 per cent), gray matter (27 ± 18 per cent), and hypophysis (24 ± 15 per cent) flow, with substantially higher relative flow to white matter (61 ± 23 per cent). Halothane (1.5 per cent) at normocarbica decreased relative thalamic flow (65 ± 28 per cent) but had no effect on other regions. Halothane (1.5 per cent) with hypocarbica decreased relative thalamic flow (65 ± 15 per cent) while increasing relative gray matter flow (42 ± 27 per cent). Halothane (1.5 per cent) with hypercarbica caused a relative increase in thalamic (68 ± 28 per cent) and gray matter (55 ± 34 per cent) flow.

Based on these observations, it was concluded that the goat brain is a heterogeneously perfused organ, and that anaesthesia causes significant shifts in regional cerebral blood flow.

RÉSUMÉ

Le débit sanguin régional cérébral a été évalué au moyen de microsphères radioactives chez la chèvre à l'état d'éveil et chez cet animal soumis à une anesthésie à la kétamine, au pentobarbitone et à l'halothane. On a de plus fait l'étude de l'influence de l'hyper et de l'hypocarbica sur le débit cérébral régional de l'animal anesthésié à l'halothane.

La distribution de microsphères a permis de mettre en évidence des différences significatives dans le débit cérébral régional des animaux à l'état d'éveil, soit, en ordre décroissant: thalamus, 151 ± 11 pour cent; matière grise, 111 ± 14 pour cent; cervelet, 92 ± 17 pour cent; hypophyse, 75 ± 4 pour cent; matière blanche, 47 ± 4 pour cent. Ces pourcentages sont exprimés par rapport au débit sanguin cérébral moyen que l'on dit correspondre à 100 pour cent fin de comparaison.

Sous anesthésie, on a observé des modifications profondes des débits régionaux.

Par exemple, la kétamine (10 mg/kilo) a causé une diminution relative du débit thalamique (75 ± 31 pour cent), associée à une augmentation de débit dans la substance grise (21 ± 10 pour cent).

Le pentobarbitone (35 mg/kilo) amenait une diminution relative du débit thalamique (38 ± 19 pour cent), de celui de la substance grise (27 ± 18 pour cent) et du débit hypophysaire (24 ± 15 pour cent) avec une augmentation importante du débit dans la substance blanche (61 ± 21 pour cent).

L'halothane à 1.5 pour cent en normocarbica causait une diminution relative du débit thalamique (65 ± 15 pour cent) sans affecter le débit aux autres régions. La même concentration d'halothane, en hypocarbica, diminuait le débit thalamique de 65 ± 15 pour cent tout en augmentant le débit à la substance grise de 42 ± 27 pour cent. En hypercarbica, l'halothane à 1.5 pour cent augmentait cette fois le débit thalamique de 68 ± 28 pour cent et le débit à la substance grise de 55 ± 34 pour cent.

Nous concluons que le cerveau de la chèvre est un organe perfusé de façon hétérogène et que l'anesthésie amène des modifications significatives des débits cérébraux régionaux.

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