

difference in score from placebo 5 days after cessation of therapy.

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## Effect of Ornithine Alpha Ketoglutarate (OAKG) on the Response of Brain Metabolism to Hypoxia in the Dog

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**SUMMARY** Hypoxia is well known to cause an increase in brain anaerobic glycolysis. Ornithine alpha ketoglutarate (OAKG) given to six dogs was shown to attenuate these metabolic disturbances caused by hypoxia. Brain oxygen utilization was higher after ornithine alpha

ketoglutarate during hypoxia than during a period of hypoxia alone.

It is suggested that the clinical usefulness of OAKG should be explored in those situations where there is cerebral hypoxia or ischemia.

BOTH AMMONIA and hypoxia can provoke cerebral anaerobic glycolysis in animals.<sup>1</sup> Ornithine alpha ketoglutarate (OAKG) given to patients with hepatic encephalopathy, who also have evidence of cerebral anaerobic glycolysis, causes a fall in cerebral glucose utilization and an increase in oxygen consumption. Similarly, ammonia intoxication in animals can be prevented by pretreatment with OAKG. In patients with hepatic encephalopathy and in animals with experimental ammonia intoxication, OAKG could act by lowering the blood ammonia levels, as suggested by Michel, Oge and Bertrand,<sup>2</sup> by bypassing the critical pyruvate decarboxylase stage affected by ammonia. Or it could accelerate the citric acid cycle by replenishing the intermediaries. The fall in cerebral glucose utilization could then be explained by a negative feed-back mechanism from the cycle. We have previously suggested that this could involve CO<sub>2</sub>. It is known that elevated CO<sub>2</sub> levels decrease,<sup>3</sup> and lowered CO<sub>2</sub> levels increase, glucose utilization by the brain.<sup>4</sup> The purpose of this study was to evaluate the effect of ornithine alpha ketoglutarate on the anaerobic glycolysis provoked by hypoxia.

### Methods

Six mongrel dogs of mean weight 15 kg (SD ± 2) were anesthetized with sodium pentobarbitone 25 mg/kg body

weight. Both femoral veins were cannulated; one for experimental drugs and the other for maintenance doses of sodium pentobarbitone.

The right femoral artery was cannulated and connected to a Bell and Howell blood pressure transducer. Arterial blood samples were also obtained via this cannula. The animals were ventilated through a tracheostomy at constant rate and volume throughout the experiment.

### Cerebral Blood Flow

The method for measuring cerebral blood flow was that of Ingvar and Lassen<sup>5</sup> using the intra-carotid injection of <sup>85</sup>Krypton. The left superior thyroid artery was identified and the common carotid artery was catheterized via this vessel. Craniotomy and cannulation of the superior sagittal sinus were carried out as previously described.<sup>6</sup>

Sufficient <sup>85</sup>Krypton gas, dissolved in 1 ml of 0.9% weight by volume NaCl solution (saline), was injected into the carotid artery to give a constant plateau of radioactivity over the left parietal region for 45 seconds. The changes in cortical radiation were measured with a small Geiger counter placed over the exposed parietal cortex. Cerebral (cortical) blood flow was measured by analysis of the first 100 seconds of the curve after the end of the injection.

Cortical oxygen and glucose consumption were calculated as the product of flow and arterio-venous difference. The superior sagittal sinus in the dog is known to drain blood only from the cortex.<sup>7</sup>

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Oxygen content was measured by the method of Linden, Ledsome and Norman<sup>8</sup> and glucose by the specific glucose oxidase method.<sup>9</sup> The pH, PO<sub>2</sub> and PCO<sub>2</sub> were measured with the appropriate electrodes.

### Experimental Design

#### a) Response to Hypoxia

In each animal two sets of control measurements were made 10 minutes apart before any experimental procedure was started. Each animal was then ventilated with air and nitrogen in the ratio 2:3, which gives 8% oxygen, for a period of 20 minutes during which flow, blood pressure and metabolic responses were recorded at 10 minute intervals.

#### b) Response to Ornithine alpha ketoglutarate

Following hypoxia each animal was ventilated with room air. After a 30 minute recovery phase, ornithine alpha ketoglutarate in a dose of 1 g/kg body weight, dissolved in 60 ml 0.9% w/v NaCl solution (saline), was infused intravenously over 10 minutes. Two sets of measurements were made over the 20 minute period following infusion.

#### c) Response to Hypoxia after Ornithine alpha ketoglutarate

As soon as the response to ornithine alpha ketoglutarate had been determined, a state of hypoxia was induced as described previously. Two sets of measurements of flow, blood pressure and metabolic responses were obtained at 10 minute intervals as before.

## Results

The arterial PCO<sub>2</sub> remained within the physiological range throughout the experiment. There was no significant difference between the values recorded (table 1).

### Control Values

The mean resting value of cortical blood flow was  $84.1 \pm 5.1$  (SE mean) ml 100 g<sup>-1</sup> cortical tissue min<sup>-1</sup>.

The mean cortical oxygen consumption was  $7.6 \pm 0.5$  (SE mean) ml 100 g<sup>-1</sup> min<sup>-1</sup> and mean cortical glucose consumption was  $8.3 \pm 5.1$  (SE mean) mg 100 g<sup>-1</sup> min<sup>-1</sup>.

Mean arterial blood pressure was  $134 \pm 4$  (SE mean) mm

Hg and the mean resting heart rate was  $159 \pm 10$  (SE mean). The mean resting arterial PO<sub>2</sub> was  $121 \pm 8$  (SE mean) and PCO<sub>2</sub> was  $39 \pm 2$  (SE mean).

### Response to Hypoxia

Ventilation with 8% oxygen caused a significant fall in arterial PO<sub>2</sub> and cortical oxygen consumption. The cortical glucose consumption and cerebral blood flow were significantly increased.

### Response to Ornithine alpha ketoglutarate

Ornithine alpha ketoglutarate had no significant effect on cerebral blood flow, but caused an increase in cortical oxygen consumption and a decrease in cortical glucose utilization. Although these changes could be due in part to the recovery from hypoxia, similar changes have previously been shown to be due to OAKG.<sup>6</sup>

### Response to Hypoxia after Ornithine alpha ketoglutarate

The same degree of hypoxia was again obtained by ventilation with 8% oxygen. The arterial PO<sub>2</sub> was not significantly different from the previous hypoxic period. However, the cortical oxygen consumption was significantly increased compared with the previous hypoxic period. The cortical glucose consumption and cerebral blood flow were significantly decreased compared to the previous hypoxic period.

Mean arterial blood pressure was significantly increased and heart rate significantly decreased.

## Discussion

The purpose of the study was to determine whether ornithine alpha ketoglutarate modified the brain's response to hypoxia. We have previously shown that anaerobic glycolysis due to hyperammonemia is attenuated by administration of the drug.<sup>6</sup> However, it remained unclear whether OAKG was having an effect on metabolism by reducing the rise in blood ammonia through by-passing the pyruvate decarboxylase stage, or by replenishing the intermediates of the citric acid cycle depleted by ammonia.

It was also unclear whether the effect was due to a specific anti-ammonia effect or was operative in other situations

TABLE 1 Effect of Hypoxia on Cortical Blood Flow, Cortical Oxygen and Glucose Consumption, Both Prior and Post Infusion of Ornithine Alpha Ketoglutarate. Total Dose 1g/kg Body Weight. Means and Standard Error of the Means are Given. (N = 6)

	Controls		Hypoxia		OAKG		Hypoxia	
CBF	84.0	84.3	109.5	121.1	85.6	85.2	89.4	96.1
ml/100g/min	± 5.6	± 8.8	± 6.0	± 5.6	± 4.9	± 4.4	± 7.5	± 11.3
CMRO <sub>2</sub>	7.5	7.7	5.0	5.3	8.8	9.4	6.2	7.0
ml/100g/min	± 0.7	± 0.8	± 0.7	± 0.7	± 0.7	± 0.8	± 0.6	± 0.9
CMRG	7.6	8.4	9.5	10.0	6.6	6.5	7.2	6.0
mg/100g/min	± 0.7	± 0.7	± 0.9	± 0.6	± 0.6	± 0.6	± 1.0	± 0.7
PO <sub>2</sub> mm Hg	120	122	40	39	112	109	42	41
	± 9	± 8	± 5	± 4	± 8	± 7	± 4	± 3
B.P. (mm Hg)	133	134	134	134.5	156	158	158	159
	± 4	± 5	± 5	± 5	± 4	± 5	± 5	± 5
Heart rate/min	158	160	161	161	148	149	142	144
	± 12	± 11	± 11	± 10	± 6	± 7	± 9	± 9

where there was anaerobic glycolysis. Accordingly, the effect on the response of the brain to hypoxia was studied.

#### Changes in Glucose Consumption

For many years glucose was considered to be the only substrate that the brain was capable of utilizing. This view is now known to be incorrect.<sup>10</sup> Since brain glucose consumption falls and oxygen utilization rises following OAKG it would appear that alpha ketoglutarate also passes the blood brain barrier and is utilized. The increase in glucose utilization due to hypoxia is virtually abolished.

#### Changes in Oxygen Utilization

Despite similar low PO<sub>2</sub> values, oxygen consumption was higher on the second occasion. The reasons for this are not clear.

Kobayashi and colleagues<sup>11</sup> have recently shown in cats that following cerebral ischemia there is a dramatic decrease in brain glutamate concentration. There is at the same time a small rise in glutamine concentration. As electrical activity increases, glutamate concentration returns toward normal values. These findings are in agreement with observations of Folbergrova who had suggested<sup>12</sup> that the decrease in glutamate was associated with the suppression of functional activity. The changes following ischemia described by Kobayashi could be secondary to ammonia detoxification, protein degradation, changes in amino acid transport or to changes in the intermediates associated with the tricarboxylic acid cycle. The fact that replenishment of ketoglutarate is associated with higher oxygen utilization would support the latter hypothesis.

The findings of the present investigation, together with the work of Kobayashi and Folbergrova, support the use of ornithine alpha ketoglutarate in situations where there is cerebral hypoxia.

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## Prevention of Cerebral Infarction in the Monkey by Omental Transposition to the Brain

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**SUMMARY** The intact omentum of 13 monkeys was lengthened, placed subcutaneously, and laid on the left cerebral hemisphere prior to occluding the left middle cerebral artery. Two of these 13 monkeys developed left cerebral infarct and a right hemiparesis. Nine other

monkeys had their left middle cerebral artery occluded without omental protection. All of these 9 developed a left cerebral infarct and 8 of them a right hemiparesis. Intact omentum may prevent a cerebral infarction when placed on the brain prior to MCA occlusion.

WE HAVE REPORTED that the intact omentum, when lengthened and transposed to the dog brain surface, results in the development of vascular connections between omentum and brain.<sup>4</sup> A subsequent study showed that cerebral in-

farction could be prevented in the dog when the intact omentum was placed on the brain prior to occlusion of the middle cerebral artery (MCA).<sup>5</sup> The purpose of the present study was to learn if cerebral infarction could be prevented in the monkey when the intact omentum was placed on the brain prior to MCA occlusion.

#### Material and Methods

Twenty-five adult stump-tailed monkeys weighing 8-10 K were used (table 1). Three of the animals (G2, G3, G7) died

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