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CEREBRAL OXYGENATION IN ARTERIAL HYPOXIA

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Pronounced increases in CBF occur in arterial hypoxia (see, for example Kety and Schmidt 1948, Cohen et al. 1967). The mechanisms of this hyperemia have never been clarified but it has been postulated that a decreased extracellular pH is responsible. The following evidence has been quoted in favour of this hypothesis. First, pronounced increases in CBF are observed in hypercapnia and hypoxia, conditions that are associated with cerebral acidosis. Second, in hypoxic hypoxia CBF increases when arterial P_{O_2} is reduced below about 50 mm Hg (Courtice 1941, McDowall 1966, Kogure et al. 1970) and, at this degree of hypoxia, there is also accumulation of lactic acid in the tissue (Gurdjian et al. 1944, Siesjö and Nilsson 1971). Third, it has been reported that induced hypoglycemia, by limiting the supply of glucose for cerebral glycolysis, prevents the increase in CBF which otherwise occurs in hypoxia (Kogure et al. 1970).

The evidence cited is far from conclusive and recent results, which will be briefly summarized, indicate that other factors than the cerebral extracellular pH is responsible for the CBF increase in hypoxia. Most of these results have been reported from our laboratory, and for original data and further discussion, the reader is referred to the articles quoted.

General methodology.

The experiments were carried out in rats that were exposed to hypoxic hypoxia (reduction of Pa_{O_2} to minimal values of 20 mm Hg) or to isovolemic, anemic hypoxia (reduction of

hemoglobin content to minimally 3 g per 100 ml). Hypoglycemia was induced by administration of insulin (2-4 I.U. per kg of body weight) 2-3 hrs prior to induction of hypoxia. Animals anaesthetized with 70% N_2O were used for studies of anemic hypoxia and of hypoxic hypoxia of 45 sec duration, or longer. Hypoxic hypoxia of short duration (10 or 20 sec) was studied in unanaesthetized animals. Cerebral energy metabolism was evaluated from the cortical tissue contents of glycolytic and citric acid cycle intermediates, and of organic phosphates, after freezing the tissue in situ. Both the freezing technique (Pontén et al. 1973) and the analytical techniques (Folbergrová et al. 1974, Norberg and Siesjö 1975 a and b) have been described previously. For freezing the tissue in unanaesthetized animals the tissue was "freeze-clampled" according to Quistorff (see Norberg et al. 1975). Cerebral (cortical) blood flow (CBF) was measured according to Kety and Schmidt (1948), using the ^{133}Xenon desaturation technique previously described from the laboratory (Norberg and Siesjö 1974). Cerebral metabolic rate for oxygen (CMR_{O_2}) was calculated from the CBF and the arteriovenous difference in oxygen content (AVD_{O_2}). For non-steady state situations, changes in CBF were derived from AVD_{O_2}, or from continuous measurements of venous outflow from the cannulated retroglenoid veins (see Nilsson 1974). In some experiments the regional CBF was estimated using the technique of Landau et al. (1955, see also Reivich et al. 1969) as adopted to ^{14}C-ethanol and a 30 sec infusion period (Eklöf et al. 1974).

Results and discussion.

1. Anemic hypoxia. Results obtained with anemic hypoxia can be summarized as follows (see Jóhannsson and Siesjö 1974, 1975, Borgström et al. 1975). When the hemoglobin content was reduced from 15 to 12 and 9 g · (100 ml)$^{-1}$, CBF increased significantly. At 6 and 3 g · (100 ml)$^{-1}$, CBF increased to about 250 and 500 per cent of normal, respectively. CMR_{O_2}, cerebral venous P_{O_2} and cerebral venous saturation remained unchanged. At a hemoglobin content of 3 g · (100 ml)$^{-1}$, there was a small increase in the lactate content of the tissue but no other metabolic changes, suggestive of tissue hypoxia.

There has been some discussion whether or not the reduced viscosity in anemic hypoxia contributes to the increase in CBF (Häggendal and Norbäck 1966, Paulson et al. 1973). The results quoted here demonstrate that the increase in CBF occurring in moderate anemia must, at least partly, be due to reduced viscosity. However, when the hemoglobin content is reduced to 6 g · (100 ml)$^{-1}$, or lower, the increase in CBF is far in excess of what could be due to viscosity changes. By itself, this finding suggests that tissue hypoxia contribute. However, since venous

P_{O_2} and oxygen saturation are upheld, and since metabolic changes in the tissue are discrete, it is questionable if true tissue hypoxia is present. Thus, the mechanisms eliciting an increased CBF in anemic hypoxia remain undefined.

2. Hypoxic hypoxia. Results on hypoxic hypoxia have been described (Johannsson and Siesjö 1974, 1975, Borgström et al. 1975, Norberg and Siesjö 1975 a and b, Nilsson et al. 1975) and can be summarized as follows.

When the Pa_{O_2} was reduced in steps from 140 to 50 mm Hg there was a small, gradual increase in CBF. With further reduction in Pa_{O_2}, i.e. to values below 50 mm Hg, there was a steep increase in CBF which, at Pa_{O_2} values of 20-25 mm Hg, reached values of about 500 per cent of normal. At all Pa_{O_2} values studied, CMR_{O_2} remained constant. It has previously been shown that the energy state of the brain, as this can be evaluated from the tissue concentrations of ATP, ADP and AMP, remains essentially unaltered at even very low arterial P_{O_2} values (see e.g. Bachelard et al. 1974). It has recently been postulated that hypoxia is accompanied by a reduction in cerebral energy requirements, and that this may contribute to prevent energy failure (Duffy et al. 1972). However, since CMR_{O_2} remains constant the increase in CBF seems to provide the sole mechanism preventing a disruption of cerebral energy state.

In steady state hypoxia there is a rough correlation between the increase in CBF, and the severity of lactic acidosis in the tissue (see above). However, such a correlation does not exist in non-steady state hypoxia. Thus, when the Pa_{O_2} is abruptly reduced to about 25 mm Hg the maximal CBF response is obtained within 2 min (Borgströme et al. 1975) although very little lactic acid accumulates during this period (Norberg and Siesjö 1975 a). In fact, since the Pa_{CO_2} rapidly falls following induction of hypoxia, it can be calculated that no net acidosis develops in the first 2 min. Thus, there is a precipitous increase in CBF in spite of the fact that a transient alkalosis seems to develop (see Siesjö et al. 1975). Additional results were obtained in unanaesthetized animals exposed to about 6% O_2 (Norberg et al. 1975). There was no increase in the lactate concentration at 10 sec, a small accumulation at 20 sec and an increase by about 1.5 $\mu mol \cdot g^{-1}$ at 60 sec. However, since Pa_{CO_2} fell by almost 10 mm Hg, no net acidosis could have developed. In order to study the increase in CBF under similar conditions, rapid hypoxia was induced by switching between two respirators and CBF was estimated by measuring the venous outflow from the brain (Nilsson et al. 1975). The results showed that CBF increased at 10 sec and reached a maximal value at 30-40 sec.

The results quoted make it doubtful if the increase in CBF during hypoxia is at all related to extracellular acidosis. A similar conclusion has been reached by Ponte and Purves (1974) who conclude that the hyperemia is elicited reflexly from carotid body chemoreceptors.

3. Hypoxic hypoxia in hypoglycemic animals. Since the results reported by Kogure et al. (1970) seemed to provide a compelling argument for a coupling between lactic acidosis and increase in flow, these experiments were repeated. Six animals were made hypoglycemic by means of insulin. At the time of induction of hypoxia the blood glucose concentrations varied between 2.03 and 2.47 $\mu mol \cdot g^{-1}$, and all had a slow wave pattern in the EEG. The arterial P_{O_2} was then decreased to about 25 mm Hg at constant ventilation and arteriovenous differences in oxygen content were determined at 2 and 5 min. Since AVD_{O_2} was determined also before hypoxia was induced, the change in CBF could be derived from the AVD_{O_2}, assuming constant CMR_{O_2}.

The results are shown in the table. At 2 and 5 min, the blood pressure was similar to that recorded in the prehypoxic period and, since the mean Pa_{CO_2} had decreased by 3 and 5 mm Hg, respectively, neither increase in blood pressure nor hypercapnia could have contributed to the increase in CBF (to 490 and 333 per cent of normal, respectively).

In the experiments quoted, the induction of hypoxia caused a further, rapid fall in blood glucose concentration and several animals developed an isoelectric EEG during prolongation of the hypoxia. Thus, there can be no doubt that the animals were profoundly hypoglycemic (see Lewis et al. 1974). In order to verify that CBF increased, i.e. that the assumption of a constant CMR_{O_2} was valid, hypoxia was induced in three additional, hypoglycemic animals, and regional CBF was estimated from the uptake of ^{14}C-ethanol. At 2 min of hypoxia these showed increases in CBF to about 300 per cent of normal. Since the ^{14}C-ethanol method tends to underestimate CBF at high flow values (see Eklöf et al. 1974) the results are in close agreement with those obtained with the AVD_{O_2} method.

In conclusion, the results obtained do not support the hypothesis of a coupling of lactic acidosis and increase in CBF during hypoxia. It must be concluded that other mechanisms than acidosis are responsible for the homeostatic increase in CBF. These mechanisms may well involve a neurogenic control of the cerebral resistance vessels.

TABLE. Influence of insulin-induced hypoglycemia upon CBF response to hypoxia.

Exp. group	MABP	Pa_{O_2}	$[T_{O_2}]_a$	$[AVD]_{O_2}$	CBF
	mm Hg	mm Hg	ml · (100 ml)$^{-1}$		%
Control (normoxia)	150 ±5	104 ±6	23.70 ±0.21	9.44 ±0.72	100
Hypoxia 2 min	150 ±2	25.6 ±0.9	7.49 ±0.33	2.14 ±0.27	487 ±83
Hypoxia 5 min	150 ±3	25.0 ±1.1	7.80 ±0.50	3.25 ±0.56	329 ±52

Prior to induction of hypoxia the blood glucose contents were 2.03-2.49 μmol · g^{-1}. The table includes data for mean arterial blood pressure (MABP), arterial oxygen content ($[T_{O_2}]_a$), arteriovenous difference in oxygen content (AVD_{O_2}), and changes in CBF calculated on the assumption of constant CMR_{O_2}. Means ± S.E.M. n = 6 in all groups.

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