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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 PO_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 PaO_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% N₂O 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-clamped" according to Quistorff (see Norberg *et al.* 1975). Cerebral (cortical) blood flow (CBF) was measured according to Kety and Schmidt (1948), using the ¹³³Xenon desaturation technique previously described from the laboratory (Norberg and Siesjö 1974). Cerebral metabolic rate for oxygen (CMRO₂) was calculated from the CBF and the arteriovenous difference in oxygen content (AVDO₂). For non-steady state situations, changes in CBF were derived from AVDO₂, or from continuous measurements of venous outflow from the cannulated retroglennoid 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 ¹⁴C-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. CMRO₂, cerebral venous PO₂ 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

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PO_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 (Jóhannsson 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 PaO_2 was reduced in steps from 140 to 50 mm Hg there was a small, gradual increase in CBF. With further reduction in PaO_2 , *i.e.* to values below 50 mm Hg, there was a steep increase in CBF which, at PaO_2 values of 20-25 mm Hg, reached values of about 500 per cent of normal. At all PaO_2 values studied, $CMRO_2$ 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 PO_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 $CMRO_2$ 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 PaO_2 is abruptly reduced to about 25 mm Hg the maximal CBF response is obtained within 2 min (Borgström *et al.* 1975) although very little lactic acid accumulates during this period (Norberg and Siesjö 1975 a). In fact, since the $PaCO_2$ 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 $1.5 \mu\text{mol} \cdot \text{g}^{-1}$ at 60 sec. However, since $PaCO_2$ 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 $\mu\text{mol} \cdot \text{g}^{-1}$, 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.

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

Exp. group	MABP	Pa _{O₂}	[T _{O₂}] _a	[AVD] _{O₂}	CBF
	mm Hg	mm Hg	ml · (100 ml) ⁻¹		%
Control	150	104	23.70	9.44	100
(normoxia)	±5	±6	±0.21	±0.72	
Hypoxia	150	25.6	7.49	2.14	487
2 min	±2	±0.9	±0.33	±0.27	±83
Hypoxia	150	25.0	7.80	3.25	329
5 min	±3	±1.1	±0.50	±0.56	±52

Prior to induction of hypoxia the blood glucose contents were 2.03-2.49 $\mu\text{mol} \cdot \text{g}^{-1}$. The table includes data for mean arterial blood pressure (MABP), arterial oxygen content ($[\text{T}_{\text{O}_2}]_a$), arteriovenous difference in oxygen content ($[\text{AVD}]_{\text{O}_2}$), and changes in CBF calculated on the assumption of constant CMRO_2 . Means $\pm$ S. E. M. $n = 6$ in all groups.

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References.

1. Bachelard, H. S., L. D. Lewis, U. Pontén and B. K. Siesjö, Mechanisms activating glycolysis in the brain in arterial hypoxia. *J. Neurochem.* 1974. **22**, 395-401.

2. Borgström, L., H. Jóhannsson and B.K. Siesjö, The influence of acute normovolemic anemia on cerebral blood flow and oxygen consumption of anaesthetized rats. Acta physiol. scand. 1975. In press. 14.
3. Borgström, L., H. Jóhannsson and B.K. Siesjö, The relationship between arterial P_{O_2} and cerebral blood flow in hypoxic hypoxia. Acta physiol. scand. 1975. In press. 15.
4. Cohen, P.J., S.C. Alexander, T.C. Smith, M. Reivich and H. Wollman, Effects of hypoxia and normocarbica on cerebral blood flow and metabolism in conscious man. J. appl. Physiol. 1967. 23. 183-189. 16.
5. Courtice, F.C., The effect of oxygen lack on the cerebral circulation. J. Physiol. 1941. 100. 198-211. 17.
6. Duffy, T.E., S.R. Nelson and O.H. Lowry, Cerebral carbohydrate metabolism during acute hypoxia and recovery. J. Neurochem. 1972. 19. 959-977. 18.
7. Eklöf, B., N.A. Lassen, L. Nilsson, K. Norberg, B.K. Siesjö and P. Torlöf, Regional cerebral blood flow in the rat measured by the tissue sampling technique; a critical evaluation using four indicators C^{14} -antipyrine, C^{14} -ethanol, H^3 -water and Xenon 133 . Acta physiol. scand. 1974. 91. 1-10. 19.
8. Folbergrová, J., B. Ljunggren, K. Norberg and B.K. Siesjö, Influence of complete ischemia on glycolytic metabolites, citric acid cycle intermediates, and associated amino acids in the rat cerebral cortex. Brain Res. 1974. 80. 265-279. 20.
9. Gurdjian, E.S., W.E. Stone and J. E. Webster, Cerebral metabolism in hypoxia. Arch. Neurol. Psychiat. 1944. 51. 472-477. 21.
10. Häggendal, E. and B. Norbäck, Effect of blood viscosity on cerebral blood flow. Acta chir. scand. 1966. Suppl. 364. 13-22. 22.
11. Jóhannsson, H. and B.K. Siesjö, Blood flow and oxygen consumption in the rat brain in dilutional anemia. Acta physiol. scand. 1974. 91. 136-138. 23.
12. Jóhannsson, H. and B.K. Siesjö, Cerebral blood flow and oxygen consumption in the rat in hypoxic hypoxia. Acta physiol. scand. 1975. In press. 24.
13. Kety, S.S. and C.F. Schmidt, The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral oxygen consumption of normal young men. J. clin. Invest. 1948. 27. 484-492. 25.

14. Kogure, K., P. Scheinberg, O.M. Reinmuth, M. Fujishima and R. Busto, Mechanisms of cerebral vasodilatation in hypoxia. J. appl. Physiol. 1970. 29. 223-229.
15. Landau, W.M., W.H. Freygang, Jr., L.P. Rowland, L. Sokoloff and S.S. Kety, The local circulation of the living brain; values in unanesthetized and anesthetized cat. Trans. Amer. neurol. Ass. 1955. 80. 125-129.
16. Lewis, L.D., B. Ljunggren, R.A. Ratcheson and B.K. Siesjö, Cerebral energy state in insulin-induced hypoglycemia, related to blood glucose and to EEG. J. Neurochem. 1974. 23. 673-679.
17. McDowall, D.G., Interrelationships between blood oxygen tension and cerebral blood flow. In: Oxygen Measurements in Blood and Tissues, ed. J.P. Payne and D.W. Hill. pp. 205-214. Churchill, London 1966.
18. Nilsson, B., Measurement of overall blood flow and oxygen consumption in the rat brain. Acta physiol. scand. 1974. 92. 142-144.
19. Nilsson, B., K. Norberg, C.-H. Nordström and B.K. Siesjö, Influence of hypercapnia and hypoxia on CBF in rats. 7th Intern. Symp. on Cerebral Circulation and Metabolism, Aviemore, Scotland. Submitted for publication.
20. Norberg, K. and B.K. Siesjö, Quantitative measurement of blood flow and oxygen consumption in the rat brain. Acta physiol. scand. 1974. 91. 154-164.
21. Norberg, K. and B.K. Siesjö, Cerebral metabolism in hypoxic hypoxia. I. Pattern of activation of glycolysis; a re-evaluation. Brain Res. 1975. In press.
22. Norberg, K. and B.K. Siesjö, Cerebral metabolism in hypoxic hypoxia. II. Citric acid cycle intermediates and associated amino acids. Brain Res. 1975. In press.
23. Norberg, K., B. Quistorff and B.K. Siesjö, Effects of short-term hypoxia on energy metabolism in the cerebral cortex of unanaesthetized and anaesthetized rats. Brain Res. Submitted for publication.
24. Paulson, O.B., H.H. Parving, J. Olesen and E. Skinhøj, Influence of carbon monoxide and of hemodilution on cerebral blood flow and blood gases in man. J. appl. Physiol. 1973. 35. No. 1. 111-116.
25. Ponte, J. and M.J. Purves, The role of the carotid body chemoreceptors and carotid sinus baroreceptors in the control of cerebral blood vessels. J. Physiol. (Lond.) 1974. 237. 315-340.

26. Pontén, U., R.A. Ratcheson, L.G. Salford and B.K. Siesjö, Optimal freezing conditions for cerebral metabolism in rats. J. Neurochem. 1973. 21. 1127-1138.
27. Reivich, M., J. Jehle, L. Sokoloff and S.S. Kety, Measurements of regional cerebral blood flow with antipyrine ^{14}C in awake cats. J. appl. Physiol. 1969. 27. 296-300.
28. Siesjö, B.K. and L. Nilsson, The influence of arterial hypoxemia upon labile phosphates and upon extracellular and intracellular lactate and pyruvate concentration in the rat brain. Scand. J. Clin. Lab. Invest. 1971. 27. 83-96.

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