Archives Italiennes de Biologie, 137: 165-179, 1999.

CEREBRAL BLOOD FLOW REGULATION IN REM SLEEP: A MODEL FOR FLOW-METABOLISM COUPLING

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INTRODUCTION

Most physiological variables are state-dependent, in the sense that the sleep state affects both the absolute value and the modalities of regulation of the variable itself. In particular, stereotyped changes in brain circulation are a constant feature of the sleep-wake cycle. Brain circulation during sleep has been the focus of many studies, with the tacit or explicit assumption that its understanding might shed light on the elusive issue of sleep function (cf. 17, 18, 58, 63, 64). The main experimental results are summarized hereafter:

a) Global cerebral blood flow (CBF) decreases during Non Rapid Eye Movement (NREM) sleep with respect to Quiet Wakefulness (QW), and rises again in Rapid Eye Movement (REM) sleep. Regional differences have also been described.

b) Spinal Cord blood flow (BF) changes parallel CBF changes (56, 77, 100). The similar trend of BF changes in brain and spinal cord during the sleep-wake cycle strongly suggests a global modulation of central nervous system (CNS) activity: whatever need sleep may fulfil, it involves the CNS as a whole, rather than specific circumscribed areas.

c) CBF fluctuations are mostly independent of systemic hemodynamic changes, particularly the blood flow redistribution in the external carotid territory (99) and other peripheral beds (57).

d) CBF fluctuations result from changes in vascular resistance whose mechanisms remain to be clarified (19).

e) Changes in neural activity, glucose and oxygen uptake accompany CBF fluctuations during the wake-sleep cycle. In particular, an increase in the above variables is observed in the transition from NREM to REM sleep.

The pattern of cerebral metabolic and circulatory changes occurring during REM sleep is also observed in different instances of functional activation, as is clear from the experimental evidence presented below. It can be assumed, therefore, that the same basic mechanisms linking blood flow to metabolism are active in the different conditions of functional activation. Hereafter, a common model of interpretation is presented, accounting for metabolic and circulatory events during functional activation of the brain.

Preliminary considerations on cerebral blood flow regulation

Control mechanisms of brain circulation aim at maintaining blood-tissue exchanges and intracellular solute concentrations adequate to metabolic needs (*flow-metabolism coupling*) and independent of changes in systemic parameters (arterial and intracranial pressure, *autoregulation*; blood gases, *chemical regulation*). The only effector generally available for controlling substrate supply and waste product removal is brain vascular resistance, which in turn controls CBF. Changes in systemic parameters such as arterial pressure and blood gases will be counteracted by locally based mechanisms apt to maintain blood flow adequate to local metabolic needs. With the exception of the myogenic vasoconstriction mainly observed in large brain arteries due to the effect of increased systemic arterial pressure [for a review see (5)], most of the changes observed in cerebral circulation at the occurrence of changes in systemic parameters can be explained on the basis of the same principles as for blood flow-metabolism coupling. A decrease in arterial pressure would determine a decrease in local blood flow and then a local condition of hypoxia and hypercapnia; a decrease in PaO_2 would produce local tissue hypoxia; an increase in $PaCO_2$ would produce a local condition of hypercapnia and acidosis. It is clear that hypoxia, hypercapnia and acidosis are the same stimuli that locally may arise during increases in metabolic activity, all inducing vasodilation. It can be concluded, therefore that the mechanisms involved in blood flow-metabolism coupling are also involved in responses to changes in systemic circulatory parameters, all aimed at maintaining adequate blood-tissue exchanges.

Experimental evidence

Brain functional activation is generally accompanied by an increase in blood flow, O_2 and glucose uptake. The increases in blood flow and glucose uptake are well correlated with each other and in most cases are substantially higher than the increase in oxygen uptake both in REM sleep (6, 9) and in other conditions of brain activation (sensory stimulation, 11, 16; mental work, 60; seizures, 4, 41, 72, 74). During activation of the alpha-chloralose-anesthetized rat sensorimotor cortex, however, parallel O_2 and glucose uptakes were observed (36, 37, 42).

The arteriovenous difference in oxygen content is reduced and the venous oxygen content is higher than at baseline (REM Sleep: 62, 66, 81; brain activation: 60, 61), while an increase is accordingly observed in the percentage of oxygenated hemoglobin (REM Sleep: 32, 70; brain activation: 33, 39, 50, 95).

As far as tissue PO_2 is concerned, an increase was found by polarographic techniques (REM Sleep: 21, brain activation: 11, 54, 55, 59, 85).

Therefore, the transition from NREM to REM sleep and from resting to activated state shares parallel changes in blood flow, glucose and oxygen uptake, arteriovenous oxygen difference and tissue PO_2.

Moreover, in the tissue, a decrease in glucose concentration (7, 59, 65, 89, cf. 96; but increments have also been described, 20), as well as an increase in lactate concentration have been observed (14, 59, 73, 75, 82, 90, cf. also 76) during brain activation. Uncoupling of oxygen and glucose utilization and extra energy supply

by non oxidative glucose metabolism during activation have been suggested (16, 59, 60, 87), whereas data obtained during anesthesia (activation of the alpha-chloralose-anesthetized rat sensorimotor cortex) supported the hypothesis that the majority of the energy required for increased cortical activation is supplied by glucose oxidation (36, 37).

The decreased arteriovenous difference in O_2 content and the increase in tissue PO_2 induced many researchers to rule out that "local hypoxia is a vasodilator signal in functional activation" (96; see also 48, 49, 58). Some researchers (51) agreed that, at low PO_2, oxygen may become the "limiting substrate for the mitochondrial enzyme systems", while others (83) discarded this hypothesis on the basis that O_2 consumption becomes limited by O_2 delivery at critical values changing with the hypoxic condition (anemia, hypoxemia, or reduction in blood flow). The present model however will show that in fact O_2 diffusion may be the limiting factor in O_2 consumption and consequently O_2 can be the mediator coupling metabolism and blood flow during brain activation.

The model

The model is based on the assumption of a substantial O_2 diffusion limitation in the brain. The limit for cell supply is usually recognized to be blood flow or blood-cell diffusion. As far as O_2 is concerned, any increase in CBF improves blood-cell exchanges not only by increasing O_2 availability to the brain (*flow limit*), but also by sustaining mean capillary oxygen concentration and then blood-cell PO_2 difference (*diffusion limit*). On the other hand, increased intracellular oxygen utilization also increases blood-cell PO_2 difference by reducing intracellular concentration.

As a consequence of oxygen diffusion limitation, brain microregions lying at mid-distance between capillaries may become hypoxic. This depends on metabolic rate and blood-cell PO_2 difference. With increasing metabolic rate, O_2 consumption in pericapillary microregions increases and the PO_2 fall becomes steeper. As a consequence, in microregions far from capillaries the increase in metabolic rate is accompanied by a decrease in PO_2. Changes in PaO_2 also affect O_2 diffusion in the brain, hypoxic microregions enlarging or shrinking in arterial hypoxia or hyperoxia, respectively. In fact, by changing PaO_2 in the range 30-400 mmHg, tissue PO_2 also changes; brain pH significantly rises with increasing tissue PO_2 and CBF decreases with increasing pH (86).

The partial recourse to non oxidative metabolism is observed in normal conditions: in quiet wakefulness the cerebral respiratory quotient is close to 1, but "the proportion of glucose that is converted to lactate has been estimated variously at between 5 and 15% of the total" (12; cf. also 10, 69).

These hypoxic microregions, which may include both whole cells and cell segments, become the site of origin of vasodilatory messages, which, through increasing blood flow, increase average capillary PO_2, thus favoring O_2 diffusion. A feedback regulation is thus established, based on the fundamental role of oxygen as flow-metabolism coupling mediator.

Regional capillary density and glucose metabolic rate are well correlated in the

brain (3, 44). This can further be shown by considering data from Table I. In gray and white matter, intercapillary distance and metabolic rate are in agreement with Einstein's equation for diffusion, holding that the amount of substance that diffuses in a given time is inversely proportional to the square of the diffusion distance. The ratio between glucose consumption in gray and white matter is ~3.2; correspondingly, the inverse ratio between the squared mean intercapillary distance in gray and white matter can be estimated as ~3.5. This suggests that capillary proliferation fulfils diffusion needs, without pointing, however, to the substance mainly involved.

However, brain capillary density increases in hypobaric hypoxia (25, 52), but it is not affected by hyperglycemia (43, 45). Microvascular anatomy is closely associated with oxidative capacity during development (93). Capillary density is also positively correlated with cytochrome oxidase activity, and reciprocal patterns exist for lactate dehydrogenase and cytochrome oxidase activity within laminated gray matter structures (3).

Summing up, all this evidence underlines the central role of O_2 in vasculogenesis and development of the cell enzyme pattern. Moreover, it also indicates that, through tissue plastic processes, O_2 diffusion and utilization are matched to regional metabolic needs; O_2 diffusion is regulated by adjusting capillary density to both regional metabolic rate and blood-cell PO_2 difference, while O_2 utilization is regulated by adjusting cell enzyme patterns. As a result, in average conditions most glucose is metabolized oxidatively, and no substantial bottleneck for O_2 exists. On the other hand, in conditions of higher-than-average metabolic rate, pericapillary microregions are characterized by high PO_2 and, if energy needs are not fulfilled by glucose oxidation, the bottleneck for O_2 consumption could be recognized in saturation of oxidative enzymes; on the contrary, in microregions far from capillaries, where PO_2 is further reduced in activation, the bottleneck might be recognized in O_2 diffusion. It should be noted, however, that local recourse to non oxidative glucose metabolism and lactate diffusion to close microregions rich in O_2 does not entail a negative connotation. Rather, local non oxidative glucose metabolism could provide signals for both long-term plastic tissue adjustments and short-term vascular resistance regulation.

To our knowledge, intracellular PO_2 has not been measured within brain cells during functional activation. As far as O_2 diffusion is concerned the analogy with active muscle may be helpful, obvious differences notwithstanding. In active muscle, different factors are involved in O_2 diffusion from blood to active mitochondria (46, 92), the site of major resistance being "the capillary and its immediate surround – i.e. the carrier free region – ... the principal bottleneck" (29; cf. also 30, 31). These factors may limit the amount of O_2 supplied. Richardson et al. (79), in human quadriceps at maximal O_2 consumption, reported the following PO_2 values (mmHg): arterial 115; femoral venous 22 [for comparison, brain venous PO_2 is indicated at 38 mm Hg in young adults at rest (10), but it would be less for the value of O_2 extraction (50%) reported by Edvinsson (12) and by Villringer (96), see below]; mean capillary 38; intracellular (myoglobin-associated) 3.1. Large

blood-cell differences in PO_2 were shown over a wide range of exercise intensities. These data indicate that capillary and venous PO_2 are not representative of cell PO_2. The blood-cell difference in PO_2 is necessary for O_2 diffusion.

The same factors as in muscle are also involved in O_2 diffusion to active mitochondria in the brain, the major difference being that myoglobin, which favours intracellular O_2 diffusion when PO_2 is very low (~3 mm Hg), is absent in brain tissue. As a consequence, the carrier-free region greatly enlarges, thus narrowing the bottleneck and increasing resistance to O_2 diffusion. In this regard, the observation by Honig (29) that "brain has no need for such an intracellular O_2 carrier, since most brain mitochondria lie just beneath the synaptic membranes that account for the bulk of the O_2 consumed" does not take into account that synaptic terminals may lie everywhere between capillaries; O_2 diffusion distance mainly depends on the distance of mitochondria from capillaries rather than from the cell membrane. Even if brain metabolic rate may be lower than in active muscle, capillary density is also lower (Table I) and myoglobin is absent. It is not unlikely therefore that O_2 diffusion limitation may exist in brain microregions lying at mid-distance between capillaries, not only during functional activation but also at rest. In fact, PO_2 may drop to increasingly low values as both distance from capillaries and metabolic rate increase, giving rise to hypoxic microregions where O_2 supply is "diffusion limited".

Table I. - *Morphofunctional parameters in the brain (data from Ref. 44) and in muscle (data from Ref. 78).*

	Brain		Muscle
	Gray matter	*White matter*	
Capillary density (n/mm^2)	400-800	160-180	240-1600
Intercapillary distance[a] (μm)	~41	~77	25-65
Glucose consumption (μmol/100g/min)	~80	~25	
Blood flow (ml/100g/min)	~100	~35	~300[b]

a, calculated from average values of capillary density; b, measured during exercise.

It is noteworthy that the quoted reports indicating an increase in tissue PO_2 during activation do not imply rejection of the model. In fact, polarographic determinations were obtained with electrodes whose size generally exceeded the average intercapillary distance in brain gray and white matter (Tab. I). As a consequence, the reported PO_2 values reflect an average between vascular PO_2 (which rises during activation), extravascular PO_2 in pericapillary microregions (where PO_2 may also rise during activation), and extravascular microregions far from capillaries (where PO_2 is normally lower than in pericapillary microregions and, according to the model, is further reduced during activation). A further confusing factor may arise from inequalities in blood oxygenation in activated

regions. Turner (94) suggested that during cortical activation venous blood oxygenation decreases in activated columns and increases in the non activated ones. This enhances the heterogeneity of tissue PO_2 and the variability of measurements.

In conclusion, the above considerations indicate that the hypothesis of a decreased intracellular PO_2 during activation in brain microregions characterized by high metabolic rate and relatively high distance from capillaries is not negated by the reviewed data on tissue PO_2.

The hypothesis may hold even if reduction in intracellular pH has not been consistently observed during brain activation. By magnetic resonance spectrography, during seizures a decrease in intracellular pH and phosphocreatine, associated with an increase in inorganic phosphate, has been reported (74); during photic stimulation a decrease in phosphocreatine/total phosphorus ratio in the human cortex, not associated with intracellular acidosis was found (40). However, intracellular pH is well controlled, so that it is reduced by only 0.15-0.20 units under sustained seizures (15, 88), and an increase in intracellular pH occurs in astrocytes during activation (8), which further contributes to increasing average intracellular pH during activation.

The hypothesis that a "substantial diffusion limitation of oxygen transfer" could also occur in brain tissue was initially considered by Gjedde et al. (22) and Kuwabara et al. (49). On the basis of this hypothesis, they implied that only an increase in perfused capillary density might improve oxygen transfer, through reducing intercapillary distances and increasing the diffusion surface of capillaries. During functional activation, however, contrary to the prediction, they found an increase in capillary density in proportion to the change in blood flow, but no increase in O_2 consumption. These results did not evidence a diffusion limit for O_2 consumption.

It is now accepted that about 95% capillaries are open for plasma perfusion in baseline conditions (101). No substantial capillary recruitment occurs even in the case of CBF increments up to 70-100%, which have been measured in the transition from NREM to REM sleep in rats (99). Moreover, data on erythrocyte flow indicate that as much as 91% of capillaries are erythrocyte perfused at rest in the brain (97). Therefore the increase in O_2 uptake observed in functional activation occurs in the absence of capillary recruitment. It is noteworthy, however, that while the BF increase in the absence of capillary recruitment specifically favours the transfer of flow-limited substances, it also helps supply diffusion limited substances, like O_2, by sustaining average capillary concentration.

In conclusion, the present model holds that in REM sleep, as well as in other conditions of brain activation, hypoxic microregions may form in the brain due to the limitation of O_2 diffusion. In fact, O_2 is consumed at a higher rate by pericapillary zones, so that in microregions at mid-distance from capillaries the increase in metabolic rate is accompanied by a decrease in oxygen availability; as a consequence, these microregions become hypoxic.

The model underlines the role of oxygen as a mediator of flow-metabolism coupling and is compatible with the experimental data.

Model-based interpretations of experimental results

Based on the assumptions of O_2 diffusion limitation in the brain and resulting hypoxic microregions, the quoted data on the transition from NREM to REM sleep, as well as data on different conditions of brain functional activation, may be consistently interpreted, in spite of their apparent heterogeneity.

1) In quiet wakefulness the cerebral respiratory quotient is close to 1, and "the proportion of glucose that is converted to lactate has been estimated variously at between 5 and 15% of the total" (12; cf. also 10, 69). It can be assumed that in this condition, due to O_2 diffusion limitation, brain O_2 consumption may be large enough to determine very low PO_2 in microregions distant from capillaries. Partial recourse to non oxidative glucose utilization results, in order to fulfil energy needs. The possibility of a metabolic bottleneck also accounting for these data is discussed below.

2) In the transition from NREM to REM sleep, the increase in glucose uptake is higher than the increase in O_2 uptake, as indicated by the reduction of the arteriovenous difference in O_2 content, but not in glucose content (6, 9). It can be assumed that in this condition increased oxygen consumption in the presence of oxygen diffusion limitation enlarges the microregions characterized by very low PO_2 and resorting to non oxidative glucose metabolism. Indeed, the arteriovenous difference for lactate also increases (6).

3) A similar condition develops in the activated brain regions in other instances of functional activation (16, 59, 60, 87). Thus, it is true that "oxygen is available in excess during neuronal activation most of the time" (96), but microregions distant from capillaries cannot take advantage of it, due to oxygen diffusion limitation.

Our model contrasts with the conclusions of Fox et al (16) that "the disproportionate increase in CBF that accompany physiological activation causes PO_2... to rise... arguing strongly against glucose oxidation as a regulator of CBF under physiological conditions." On the contrary, to the extent that O_2 needs develop in hypoxic microregions, glucose oxidation can be a regulator. This is further supported by the fact that, with increasing PaO_2 in the range 30-400 mmHg, pH also increases and CBF is reduced (86).

4) Under alpha-chloralose anesthesia, most of the energy required for brain activation in going from a resting to an activated state is supplied by glucose oxidation (36, 37) and no lactate accumulation occurs (42). It can be assumed that in this condition the baseline energy needs are lower than in wakefulness and, even during activation, PO_2 does not reach such low values as to activate non oxidative glucose metabolism.

5) It is well known that ambient hypoxia affects sleep architecture reducing Total Sleep Time and in particular the percentage of REM sleep both in humans (1, 67), cats (35) and rats (53, 71). According to Huertas (35) "a mechanism closely related to the metabolism of oxygen in the brain must play an important role in the production of paradoxical sleep". The sleep disturbances may be reduced by enrichment of room air with O_2 (98). Interestingly, ambient hypoxia affects blood-

cell O_2 diffusion more than O_2 transport to the brain. In fact, halving arterial PO_2 reduces O_2 content by ~15%, but blood-cell PO_2 difference by 50%.

6) Lactate is a substrate for oxidative metabolism both in brain slices (38, 84) and in vivo (47). According to the present model, lactate is produced in microregions far from capillaries, and by diffusion reaches high PO_2 pericapillary microregions where it is aerobically metabolized. This may help explain why lactate concentration increases little from arterial to venous blood during brain activation (60). This also entails reduced glucose utilization in pericapillary microregions (cf. Pasteur effect, 10), increased glucose availability for diffusion to hypoxic microregions, and removal of excess lactate from hypoxic microregions, thus preventing toxic effects. This backflow of lactate towards pericapillary regions also partially relieves O_2 diffusion limitation. In fact in regions where O_2 could not reach substrates, the substrate (lactate) diffuses towards O_2. This is conceivable, since the product (Diffusion Coefficient) X (Concentration) is 5.5 times higher for lactate than for O_2 [1], whereas 3 molecules of O_2 must diffuse in order to oxidize 1 molecule of lactate. As a consequence, substrate requirements should be 16.5 times easier to satisfy for lactate than for oxygen. Thus, the hypothesis of lactate backflow is justified.

7) As far as the identification of the mediator between metabolism and blood flow is concerned, it is noteworthy that the brain normally extracts 10% of glucose and up to 50% of oxygen from arterial blood (12, 96). Moreover, the rate-limiting reaction for glucose catabolism is the rate of phosphorylation (12). Likewise, "glucose transport is not the rate-limiting step in glycolysis" in isolated rat brain (27). Moreover, the product (Diffusion Coefficient) X (Concentration) is 8 times larger for glucose than for O_2 (see footnote), whereas 6 molecules of O_2 must diffuse in order to oxidize one molecule of glucose. As a consequence, substrate requirements should be 48 times easier to satisfy for glucose than for oxygen. On the basis of these figures, as far as diffusion limitation is concerned, in spite of the low efficiency of ATP production by anaerobic compared with aerobic glucose utilization (2 ATP molecules vs 33), it should be easier to obtain ATP from glucose diffusion and anaerobic glycolysis than from O_2 diffusion and glucose oxidation. Thus diffusion limitation is more likely to occur for O_2 than for glucose. Finally, "during hypoglycemia, cerebral blood flow does not increase significantly until peripheral glucose levels are very low (2.0 mmol/l), that is well below the blood glucose threshold for impairment of cognitive functions (3.0 mmol/l)" (91). Thus, in normal conditions, glucose does not appear to be a good candidate as a mediator of blood flow-metabolism coupling, due to its low extraction fraction, high diffusion capacity and metabolic limitations. Oxygen seems to be a better candidate to couple metabolism and blood flow.

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[1] In brain tissue, the concentration of O_2 may be evaluated as ~0.15 ml/100ml, i.e. ~0.07 mM at PO_2 in the range of 50 mmHg and O_2 diffusion coefficient (D_{O2}) is about 85% as in water (28), i.e. 1.7 X 10^{-5} cm^2/s; the concentration of lactate is ~1mM (24, 80) and $D_{lactate}$ is ~0.660 X 10^{-5} cm^2/s (2, 34); the concentration of glucose is ~2 mM (13, 68) and $D_{glucose}$ is ~0.5 X 10^{-5} cm^2/s (23, 26).

CONCLUSIONS

It is worth considering that different "dominant" needs may occur in different conditions. In the case of tissue acidosis, for example, needs for waste product removal may act as dominant factor regulating brain blood flow. Thus, the assumption that O_2 requirement is normally involved in sustaining arteriolar vasodilatation when metabolic rate is high does not exclude that in special cases different needs may generate parallel vasodilatory messages, the resulting effect on local circulatory resistance depending on a summation of all of them. However, the model-based analysis of experimental results in REM sleep as well as in other conditions of brain activation points to the central role of oxygen as a mediator of cerebral flow-metabolism coupling.

SUMMARY

The pattern of metabolic and circulatory changes occurring during REM sleep in the whole brain is also observed at a regional level in different instances of functional activation. This pattern is characterized by an increase in metabolic rate, blood flow, glucose and oxygen uptake, the increase in glucose uptake generally exceeding oxygen uptake. A model of interpretation is presented, based on the assumption that substantial limitation to oxygen diffusion exists in the brain. According to the model, microregions lying at mid-distance between capillaries may become hypoxic, depending on metabolic rate and blood-cell PO_2 difference. At increasing metabolic rates, O_2 consumption in pericapillary microregions increases and the PO_2 drop becomes steeper. As a consequence, in microregions far from capillaries a decrease in O_2 availability occurs, in concomitance with the increase in metabolic rate, so that non-oxidative glucose metabolism develops locally. A similar spatial PO_2 pattern forms in the case of arterial hypoxia, when capillary PO_2, and then blood-cell PO_2 difference, is reduced. The hypoxic microregions are the source of vasodilatatory messages, the consequent vasodilatation increasing average capillary PO_2 and then favoring O_2 diffusion to the tissue. Oxygen thus appears to be a better candidate than glucose as a mediator of blood flow-metabolism coupling. This is supported by its higher extraction fraction and by the fact that, in physiologic conditions, arterial hypoxia (and not hypoglycemia) acts on cerebral blood flow. Moreover, the diffusion capacity of glucose in the brain is higher than that of oxygen, so that diffusion limitation is more likely to occur for oxygen. The present model allows consistent organization of the stereotyped changes in cerebral blood flow and glucose and oxygen uptake occurring both in REM sleep and in other instances of brain activation.

Acknowledgements. - The authors thank Professors E. Perez and G. Zamboni for their comments on the manuscript. This work was supported by grants from Ministero dell'Università e della Ricerca Scientifica and Consiglio Nazionale delle Ricerche.

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