THE BRAIN AT HIGH ALTITUDE: CLINICAL RESEARCH AND MOLECULAR PHYSIOLOGY

ALTITUDE HYPOXIA EFFECTS ON BRAIN

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RESUMEN: Efectos de la Hipoxia de Altura en el Cerebro

La vasodilatación cerebral hipóxica es mediada por una vía compleja a través de células gliales ubicadas entre neuronas y arteriolas cerebrales. Esta vía supone la liberación de K^+ y adenosina en el líquido extracelular (ECF). La acidosis láctica es menos importante de lo que se había asumido previamente. Durante las primeras horas en altura, el flujo sanguíneo cerebral (CBF) incrementa 30-60% y luego de algunos días cae a valores casi normales. La magnitud de este incremento transitorio depende de la altitud, de la sensibilidad vascular cerebral y de la sensibilidad ventilatoria individual tanto al O_2 como al CO_2. La reducción posterior del flujo es un problema no bien comprendido, pero es explicado al menos en parte por incrementos de la P_aO_2, del pH del liquido cefalorraquideo (CSF pH) y por una caida de P_aCO_2, pero no por la policitemia ni por la sensibilidad reducida de los vasos cerebrales a la hipoxia. Los efectos tardios de la hipoxia incluyen reducción de base tampón en sangre y CSF, sensibilidad creciente de quimiorreceptores periféricos, hematocrito creciente y tal vez expresión de VEGF en macrófagos. Ninguno de los factores conocidos como reguladores del CBF (incluyendo la policitemia) pueden explicar por completo la evidencia de que el CBF sea normal o subnormal en nativos de altura y en sujetos completamente aclimatados, en comparación con sujetos normales de nivel del mar. Se ha reportado un $CMRO_2$ cerebral reducido en humanos nativos de altura, lo que podria ayudar a explicar el bajo CBF. El mal de montaña agudo (AMS) y el edema cerebral de altura (HACE) pueden acompañarse por un alto CBF, pues el P_aO_2 es menor, pero AMS y HACE no pueden ser causados por un CBF alto, ya que la hipercapnia no puede producir enfermedad sintomática, a pesar de un flujo mayor. La injuria cerebral sutil observada en montañistas puede estar relacionada con vasoconstricción hipocápnica y con una marcada caída en el PO_2. La injuria capilar de altura puede deberse a la citoquina VEGF liberada en el cerebro hipóxico por los macrófagos que inician la angiogénesis.

Palabras claves: Altitud; Hipoxia; Cerebro; Flujo sanguíneo

RÉSUMÉ: Effets de l'hypoxie d'altitude sur le cerveau.

La vasodilatation cérébrale hypoxique s'effectue par une voie complexe, par l'intermédiaire de cellules gliales situées entre les neurones et les artérioles cérébrales. Cette voie suppose la libération de K^+ et d'adénosine dans le liquide extracellulaire (ECF). L'acidose lactique est moins importante que ce que l'on supposait auparavant. Au cours des premières heures en altitude le flux sanguin cérébral (CBF) augmente de 30 à 60 % et retombe à des valeurs presque normales au bout de quelques heures. L'ampleur de cette élévation passagère dépend de l'altitude, de la sensibilité vasculaire cérébrale et de la sensibilité respiratoiore individuelle à l'O_2 et au CO_2. La réduction ultérieure du flux est un phénomène imparfaitement compris, mais qui s'explique au moins en partie par des augmentations de la P_aO_2, du pH du liquide céphalorachidien (CSF pH) et par une chute de la P_aCO_2, mais pas par une polyglobulie ni par une sensibilité réduite des vaisseaux cérébraux à l'hypoxie. Les effets tardifs de l'hypoxie incluent la réduction de la base tampon dans le sang et le CSF, la sensibilité croissante des chimiorécepteurs périphériques, l'hématocrite en augmentation et éventuellement l'expression de VEGF en macrophages. Aucun des facteurs connus comme étant des régulateurs du CBF (y compris la polyglobulie) ne peuvent expliquer intégralement l'évidence d'un CBF normal ou subnormal chez les natifs des régions de grande altitude et chez les sujets complètement acclimatés, en comparaison avec des sujets normaux du niveau de la mer. Un $CMRO_2$ cérébral réduit a été signalé chez des natifs de hautes régions, ce qui pourrait aider à expliquer le CBF déprimé. Le mal des montagnes aigu (AMS) et l'oedème cérébral de grande altitude (HACE) peuvent être accompagnés d'un CBF élevé car la P_aO_2 est moindre, mais la cause de l'AMS ou du HACE ne peut être un CBF élevé, l'hypercapnie ne pouvant produire une maladie symptomatique, malgré un flux plus élevé. La légère atteinte cérébrale observée chez les alpinistes peut être liée à la vasoconstriction hypocapnique et à une chute marquée de PO_2. L'atteinte capillaire d'altitude pourrait être due à la cytokine VEGF libérée dans le cerveau hypoxique par les macrophages commençant l'angiogenèse.

Mots-clés : Altitude, Hypoxie, Cerveau, Flux sanguin.

SUMMARY: Hypoxic cerebral vasodilation is mediated by a complex pathway through glial cells positioned between neurones and cerebral artenoles, and involving both K^+ and adenosine release into ECF. Lactic acidosis is of less importance than had been assumed. During the first hours at altitude, CBF rises 30-60% and then after some days, falls to nearly normal values. The magnitude ofthis transient rise

depends on the altitude and the individual cerebral vascular and ventilatorz sensitivities to both 0_2 and CO_2 The subsequent reduction of flow remains poorly understood, but is at least partly explained by rises of PaO_2, CSF pH, and fall of $PaCO_2$, but neither by polycythemia, nor reduced sensitivity of cerebral vessels to hypoxia Later effects of hypoxia include reduced blood and CSF buff'er base increasing peripheral chemo receptor sensitivity, rising Hct and perhaps macrophage expression of VEGF None of'the known factorsregulating C'BF (including polycythemia) can fully acount for the evidence that in several studies, natives of high altitude, and those fully acclimatized, have been found to have normal or subnormal CBF (compared with sea level normals) Reduced brain $CMRO_2$ has been reported in humans native to high altitude, which could help explain the low CBF AMS and HACE may be accompanied by high CBF, because PaO_2 is lower. but AMS and HACE cannot be caused by high CBF since hypercapnia fails to cause symptomatic illness, despite higher flow Subtle brain injury seen in mountaineers may be related to hypocapnic vasoconstriction and a marked alkaline Bohr downshift in capillary PO_2. Capillary inJury at high altitude may result from the cytokine VEGF released in hypoxic brain by macrophages initiating angiogenesis.

HYPOXIA AND CBF

Cerebral blood (CBF) rises 30-50% inmediately at altitudes such as 4000-6000M. but falls to near normal; after a few days at altitude 'I'he reduction is not fully explained by improved SaO_2, Hct or CSF pifl CBF is affected by ventilatory responses to hypoxia and CO_2. With neuronal activation, O_2 consumption and local CBF rises within 1-2 CBF: is regulated by local metabolism at the level of capillaries and precapillary sphincters (1). but pressure u pstream from alterioles is regulated by the larger conducting arteries with autonomic innervation which reduce lumen diameter when arterial pressure rises (2, 3). Flow is independent of mean systemic arterial pressure between approximately 60 and 150 mm Hg, (4). Both during and following severe hypoxia autoregulation may be disrupted (5, 6).

Blood flow in individual capillaries in brain is intermittent, resulting in 6-12 per min ±30% oscillations in tissue Po2 (7-9). Vasodilators increase the number of capillanes perfused at any moment (10). Average cortex PO_2 is about 9 mm Hg as determined with recessed. calibrated gold-plated microoelectrodes (11). Neuronal mitochondrial cytochrome is normally not fully saturated with O_2, such that the redox state is not fully oxygenated, and some 'anaerobic metabolism defined as lactate excretion is normal.

CBF rises in proportion to the severity of hypoxia, but with extreme variability between individuals and species, primarily due to the effects of hypoxic hypervelitilation on $PaCO_2$. While studies in humans at altitude have found rises of the order of 30-60% during the initial hours or days, flow was shown to be increased by as much as 250% in awake sheep at PaO_2 = 40 mm Hg (12) and more than 4 fold in rats at PaO_2 = 24 mm Hg (13)

CO_2 is usually kept constant when testing CBF sensitivity to hypoxia. In 9 healthy male volunteers, (14) a step reduction of PaO_2 to 34.6±1.6 mm Hg (SE) (66% SaO_2) increased CBF about 70% (from 0.45 to 0.77 ml-gm $^{-1}$-min^{-1}) accompanied by a 27% rise in glucose consumption (CMR_{glu}) and a 4 fold rise in cerebral lactate production (CMR_{lac})$CMRO_2$ was maintained constant by the Pasteur effect(ADP controlled glycolysis) In fetal lambs made hypoxic by acute maternal isocapnic hypoxemia, CBF was an approximately linear function of fetal SaO_2 down to nearly zero at which point flow was increased to about 250% of control (15) Isocapnic hypoxia CBF in normal men at 3810m altitude (16)(Figure 1) rose 45% at 66% SaO_2. Hemodilution increases cerebral blood flow in polycythemic patients and in subjects with high normal Hct (17).

MEDIATORS OF HYPOXIC CEREBRAL VASODILATION

Cerebral arterioles are dilated by low PO_2 (14) and low O_2 content (anemia) (17). Increased local neuronal activity (18), hypercapnia (19), increasing vascular smooth muscle ECF [H] (20), [K] (21), adenosine (22) intravascular NO (nitric oxide) generated in endothelia (23) and a variety of autocoids and cytokines (4). Hypoxia may have other still unknown direct vasodilating mechanisms. Cerebral vasodilation in both hypoxia and with neuronal activity is mediated by glial cells which "connect" neurones to the nearest arteriolar smooth muscle cells. Neuronal K^+ is their putative input signal while adenosine generated by glia, K^+ (and possibly NO) may serve as the vasodilators at the sphincter surface.

CBF CHANGES DURING ACCLIMATIZATION

During acclimatization of normals at 3810m altitude, Severinghaus et al (24) reported a rise of 24% after 6-12 hrs with mean PaO_2=43 5 mm Hg, $PaCO_2$=35.0, pH_a=7 45, and pH_{CSF}=7 32 (n=4) CBF fell to 13% above sea level control values at 3-5 days as PaO_2 rose to 51.2 mm Hg, $PaCO_2$ falling to 29 7 mm Hg After 10 mill of 30% O_2 (acute normoxia), CBF fell to sea level control values on both occasions, while $PaCO_2$ remained low at 35.1 mm Hg at 6-12 hrs, and 30.9 mm Hg at 3-5 days.

After3-5 days at altitude, during acute,normoxia, when CO_2 was increased to 35 mm Hg tor 10 min, CBF rose to 33.8% above sea level control. This greatly increased response to a $PaCO_2$ of 35 is a result of the fall of ECF HCO_3-during acclimatization and its eff'ect on arteriolar ECF pH. At sea level, a reduction of $PaCO_2$ to 35 mm Hg would have reduced CBF by about 10%.

Jensen et al (25) in 19 subjects, ascending from 150 to 3,475 m, found CBF was 24% increased at 24 h and 4% increased at 6 days. In nine subjects, ascending from 3,200 to 4,785-5,430 m, CBF increased 53% above estimated sea-level values In 13 young male soldiers transported to 3700m altitude, Roy et al (26) found that CB F was 40% above control at 12-36 hrs of hypoxia, and diminished to 4% above control after 4 days. Gradual fall of CBF with time in CillOlliC hypoxia has also been reported by others (27-29)

However, not all subiects show initial vasodila.ion. Those with vigorous carotid chemoreceptor responses may hyperventilate enough to block the hypoxic vasodilation (27,30). In view of the evidence that flow falls with time at altitude, one might expect the sensitivity of CBF to an acute hypoxic challenge to decrease in the course ot' altitude acclimatization. However, it apparently does not. During 5 days at 3810m in 6 normal adults, Jensen et al (16, 31) found a 34% rise of the hypoxic CBF sensitivity (Figure 1). They concluded that the observed fall of CBF with time at altitude cannot be attributed to adaptation ofthe vascular sensitivity to hypoxia.

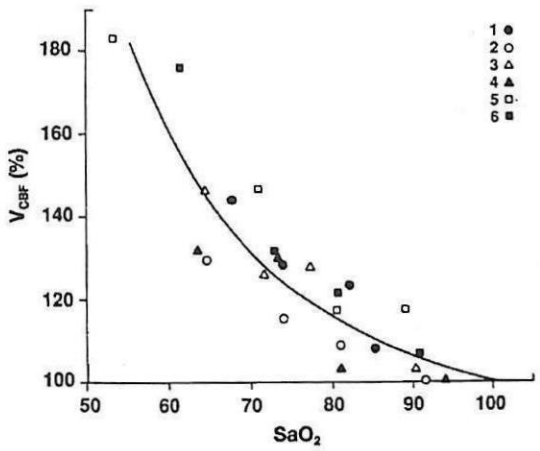

Fig. 1. CBFv% (% of control CBF velocity by TCD) in response to 5 min steps to 4 levels of isocapnic step hypoxia in 5-6_ normal subjects after 3-4 days at 3810m altitude (16). The hyperbolic empiric relationship was:

$$CBFv\% = 100(1 + X[(60/(Sa0_2-40))- 1]).$$

Factor X was found to average 0.35±0.11 at sea level and 0.46±0.08 after 5 days at altitude X may be interpreted as the fractional increase in CBFv induced by 5 min of hypoxia at 70% SaO_2.

Factors which might contribute to the slow reduction of CBF at altitude include: 1) gradual improvement of arterial PO_2; 2) gradual rise of CSF pH, as the carotid chemosensitivity increases, driving ventilation up and PCo_2 down; 3) an upward shift of P_{50} facilitating unloading of O_2 in tissue; 4) increased Hct; 5) postulated increased sympathetic cerebral arterial tone (32); 6) some remodeling of the microcirculation or the length of the critical diffusion paths between capillaries and cytochrome; and 7) a decrease in $CMRO_2$. Krasney et al (29, 33) demonstratėd in 1985 that the gradual fall of CBF with time at altitude did not occur over the course of 4 days isocapnic hypoxia in sheep if $PaCO_2$ and PaO_2 were kept constant, thus ruling out any short term adaptation of the hypoxic vasodilation of cerebral arteriolar smooth muscle. Manohar et al (34) were unable to identify any factor responsible for the gradual loss at high altitude of hypoxic cerebral vasodilation. Acute hypoxia at 3500m (simulated) altitude (PaO_2=49 mm Hg) increased CBF in control calves from 75 to 101 ml $l00g^{-1}$ min^{-1}. After 7-8 weeks of hypoxia, while still in the hypobaric chamber, CBF averaged 69 ml $100g^{-1}$ min^{-1}. With acute normoxia CBF was 79 ml $100g^{-1}$ min^{-1} (n s). $PaCO_2$ was 40 mm Hg in control calves, 35.5 in chronic hypoxia and 38 in acute normoxia. Hct did not rise and there was no right shift of P_{50}.

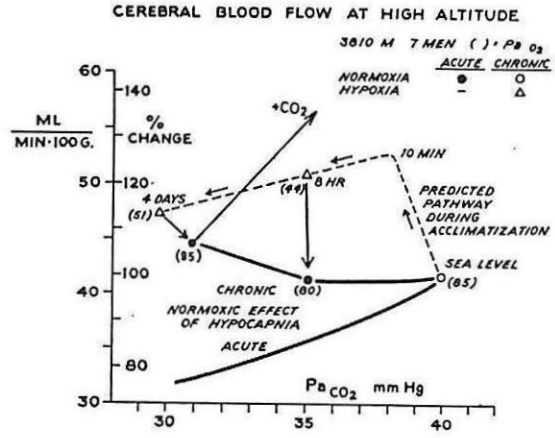

Fig. 2 Time course of CBF in newcomers at 381 Om altitude, showing the acute responses to normoxia and hypercapnia, demonstrating the gradual fall of CBF with time, and the resetting of hypercapnic response to a lower Pco_2 (24).

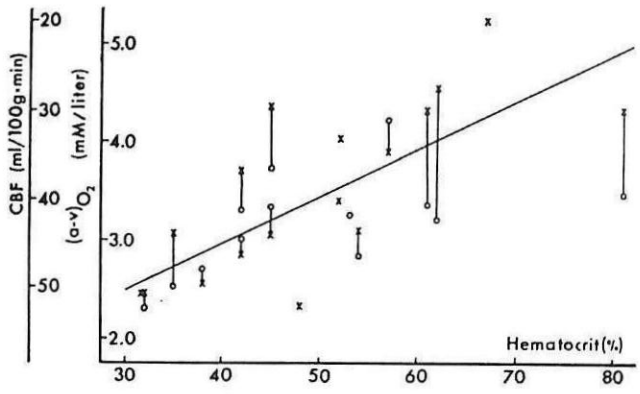

Fig. 3. CBF of natives ofthe Bolivian altiplano was found to be an inverse linear function of Hct, with normal flow corresponding to the sea level normal relationship to Hct. The relationship may be approximated by: CBF = [65-0.5Hct](ml-1Oog^{-1}min^{-1}). Circles: Acute hyperoxia at altitude. P_I0_2>l50 mm Hg; x: Ambient hypoxia at 3700m (La Paz), P_I0_2= 90 mm Hg (64).

CHRONIC HYPOXIA AT ALTITUDE

Natives of high altitude may have low cerebral metabolic rates (by as much as 20%), which could be responsible for lower CBF (35) In 8 normal adult natives of 4300M altitude (Cerro de Pasco, Peru), with a mean Hct=57.8±6.3% and mean PaO_2=43.6±2.4 mm Hg, Milledre and Sorensen (36) found that breathing 100% 0_2 increased the arterial-internal jugular 0_2 content difference from 7.89±1.01 to 9.58±1.17 ml dl^{-1}. representing an 18% decrease of CBF with hyperoxia. The study demonstrated the presence of a lifelong vasodilation due to ambient hypoxia Yet their mean (a-v) O_2 content difference while breathing ambient air was greater than that of sea level normals, suggesting a sub-normal CBF.

In the relationship of CBF to Hct, no significant difference has been detected between sea level natives studied at sea level and altitude natives studied at altitude (Figure 3) Marc-Vergnes (37) repo. ted sub-normal CB F in 16 natives ofthe Bolivian altiplano (40 compared with his normal of 50 ml 100g^{-1} min^{-1} in sea level natives). Putting these observations together suggests that, while natives at altitude always retain evidence of hypoxic vasodilation, flow is anomalously low considering their chronic hypoxia, and cannot be fully explained by the known controls, hypoxia, ECF pH, Hct etc. Several animal studies have not supported the finding of a return to normal of CBF in chronic hypoxia (34, 38-40)

AMS AND HACE: ROLE OF CBF?

Subjects with AMS are suspected to have a poor ventilatory response to hypoxia and thus to be more hypoxic and have a higher Pco_2, both of which should result in higher CBF (41) Three related questions have been addressed: 1) Are subjects with AMS more hypoxic and/or hypercapnic than their healthier associates? 2) If so i s their CBF higher? and 3) Does the high flow cause or exacerbate the AMS (31, 42, 43)?

At 4559M, overall CBFv increased 48% in subjects who developed AMS and 27% in subjects without symptoms (44). In 12 normal subjects, increases in CBF at 3475m were similar in subjects with or without AMS In six, CBF was measured before and after therapeutic intervention (25). At 2h, CBF increased 22% above pretreatment values in three subjects given 1.5 g acetazolamide, while three subjects given placebo showed no change. Overall, the results indicated that increases in CBF were similar in subjects with or without AMS while acetazolamide-provoked increases of CBF in AMS subjects caused no acute change in symptoms. The authors concluded that high CBF cannot be directly implicated in the pathogenesis of AMS.

ROLE OF LOW Pco_2

Maher et al (45) tested whether prevention of hypocapnia and alkalosis would ameliorate the symptoms of acute mountain sickness (AMS). Five subjects were exposed to simulated high altitude for 4d with 3 8% CO_2 added to the chamber to

maintain normocapnia. Four other subjects were exposed for 4 d to hypobaric hypoxia without $C0_2$ supplementation. and became hypocapnic. Barometric pressure was lower in the group with added CO_2 so that alveolar oxygen tensions (55-60 mm Hg) would not be different. The severity of symptoms was clearly greater in normocapnic than in hypocapnic subjects. The control hypocapnic subjects presumably had more alkaline pHa, thus a left shifted ODC resulting in better lung O_2 uptake, higher SaO_2 and a lower CBF (assumed) compared with the experimental CO_2-supplemented normocapnic group. Bartsch et al (46) randomly allocated twenty mountaineers with AMS at 4559 m to 3 treatment group 1) with 33% 0_2 . 2) with 3% CO_2. in air and 3) an air control. 33_% O_2 significantly relieved symptorms of AMS, and reduced CBF but $C0_2$ addition did not significantly ameliorate AMS, despite the rise of Pco_2, ventilation and alveolar Po_2.

In order to determine the role of CO_2, Yang et al (47) exposed chronically instrumented ewes to 96 h of hypoxia (PaO_2=40 mm Hg) in an environmental chamber One group of 12 was permitted to become hypocapnic ($PaCO_2$= 27 mm Hg) while the other group of 9 was kept eucapnic ($PaCO_2$ = 37 mm Hg). AMS, estimated from food and water intakes and behavior, occurred in 9 of 12 with hypocapnia and 9 of 9 with normocapnia. Intracranial pressure and the pressure gradient betwenit and sagittal sinus increased only in AMS sheep. CBF was high in all, but greater in the normocapnic animals. Brain edema occurred only in AMS sheep.

To test whether high CBF alone could cause cerebral edema, S.P.Yang and Krasney (48) kept sheep for 4 days in elevated CO, (52-55 mm Hg) CBF remained about twice normal, and $CMRO_2$ was increased both during exposure and in the post hypercapnic period. They observed no symptoms like those of AMS or HACE although brain water rose slightly fionl 79.8±0.24 to 80.3±0.2% ($p<0.05$) High CBF is unlikely to be the root cause of HACE.

ROLE OF ANGIOGENESIS IN HACE?

Retinal petechial hemorrhages found in many climbers at extreme altitude suggest a pathologic process involving cerebral circulation which may be assumed to exist throughout the brain This may be a result of the first step in the process called angiogenesis (49). Tissue hypoxia is the initiating stimulus of angiogenesis, a multistep process which (e. g. in tumors) ultimately leads to growth of new capillaries into the hypoxic tissue. A variety of protein cytokines are expressed both by the hypoxic cells and by macrophages attracted to those cells. The principal initial cytokine is VEGF (vascular endothelial growth factor, formerly termed VPF, vascular permeability factor). VEGF attacks and dissolves capillary basement membranes, permitting plasma and red cell leakage, as a precursor to growth of endothelia toward the hypoxic region. In preliminary experiments (unreported), F. P.Xu at UCSF has demonstrated transient rises in mRNA for VEGF and in VEGF protein during the first 1-3 days of steady severe hypoxemia in rats and rabbits. Dexamethasone has been found to be a highly potent inhibitor of angiogenesis, suggesting that perhaps its well established ability to prevent and treat AMS and HACE might be related to inhibiting capillary leakage initiated by VEGF in the earliest stage of angiogenesis.

Acetazolamide

Acetazolamide (AZ) has been used by mountaineers for many years, facilitating sleep at altitude and increasing cerebral 0_2 delivery Oral administration of I g of AZ to 8 normoxic subjects studied at sea level caused an acute 38% increase in CBF (50, 51). During the subsequent prolonged oral treatment with I g of AZ daily, CBF returned to normal within 2 days, The alveolar CO_2 tension decreased gradually to 70% of the control value. Based on this, the authors speculated that little of the benefit of AZ at altitude is due to increased CBF, that the beneficial effects are more due to increased ventilation raising PaO_2 affording a significant increase of the arterial oxygen content. However, in these normoxic studies, some of the flow reduction with time can be attributed to the 30% fall of $PaCO_2$. In the absence of hypoxia these studies may not be applicable to altitude effects.

Understanding the various effects of AZ on CBF during acclimatization at altitude is complicated by the slow rise of $PaCO_2$ during blood transit from lung to brain arterioles. The uncatalyzed time constant of rbc HCO_3 dehydration to dissolved CO_2 in blood is about 7 s. Due to its stimulation of ventilation, $PaCO_2$ and end capillary $PaCO_2$ in lung fall. Cerebral arteriolar PCO_2 may thereby be reduced by AZ, while PaO_2 is increased, both of which should reduce CBF. For example, Huang et al (52) utilized Doppler ultrasound in 8 volunteers to determine whether the usual AZ dose (250 mg three times daily) would increase CBF velocities in internal carotid and vertebral arteries. Although AZ decreased pHa, $PaCO_2$, and $P_{ET}CO_2$., both during normoxia and subacute hypoxia, they saw no effect on either baseline CBF or the CBF responses to acute hypoxia or hypercapnia. Kjaliquist and Siesjo (53) used fast freeze sampling of rat brain to show

that brain HCO_3^-. was increased about 9 mM kg^{-1} by AZ The rise of tissue. Pco_2 (~4mm Hg) could only have increased brain HCO_3^- by 0.7 mM- kg^{-1} .

One potential mechanism of AZ vasodilation was thought to be a blockade of the Bohr effect of metabolic CO_2 in tissue capillaries acting via pH to increase blood P O_2 and thus facilitate unloading of O_2. This possibility was excluded by Cotev et al (54) using brain surface PCO_2, pH and PO_2 electrodes When 25 mM kg^{-1} AZ in dogs increased CBF by 69% as estimated from arterial to saggital sinus blood O_2 content difference, cortex surface PO_2 increased by 16-20 mn Hg. They noted that surface pH fell from 7.22 to 7.12 within a few minutes, accompanied by a small rise of surface PCO_2 from 45 to 48 mm Hg, insuficient to explain the acid shift. In view of the rise of tissue HCO_3^- produced by AZ (53) they speculated that they were observing carbonic acidosis as if brain metabolism generates carbonic acid (i.e. H^+ and HCO_3^-), not gaseous $C0_2$, as the first products of decarboxylation. This was later confirmed directly in brain tissue homogenates (55). The isocapnic acidosis produced by AZ was confirmed by Bickler et al using flat cortical surface PCO_2 and pH electrodes (56). Following IV injection of 25 $mMkg^{-1}$ of AZ, ventilation was adjusted to hold brain surface PCO_2 constant. Brain surface pH fell approximately 0.1 pH within 3 min and brain oxygenation monitored by NADH fluorescence rose, even when animals were ventilated with 100% O_2 before giving AZ (57). The cortical surface location of the electrodes suggested that AZ rapidly penetrated the blood brain barrier.

Brain intracellular pH measured with MRS of phosphate does not fall after AZ administration according to Vorstrup et al (sensitivity of the method is limited to ±0.06 pH)(58). Cells respond to the rise in H_2CO_3 by more rapid export of H^+ than of $HC0_3^-$. Undissociated H_2CO_3 is fredy diffusible out of cells. During hypoxia at high altitude the overall effect of prolonged AZ treatment may be equivalent to a descent of several hundred metres It is probable that the increase of ventilation and oxygenation induced by use of AZ at high altitude obscures its inherent vasodilation, such that flouw would fall with time at altitude faster without than in the presence of AZ.

BRAIN PATHOLOGY AT EXTREME ALTITUDE

There is little evidence that hypoxia directly injures brain in climbers at extreme altitudes, but it is less clear whether in some way blood flow may be linked to brain injury. Hornbein and associates (59) performed neuropsychological and physiologic testing on 35 mountaineers before and 1 to 30 days after ascent to altitudes between 5488 and 8848 m, and on 6 subjects before and after simulation in an altitude chamber of a 40-day ascent to 8848 m. They reported a persistent decline in visual long-term memory A higher ventilatory response to hypoxia correlated with a reduction in verbal learrling ($r = -0.88$, $P < 0.05$) and with poor long-term verbal memory ($r = 0.99$, $P < 0.01$). An increase in the number of aphasic errors on the aphasia screening test also correlated with a higher ventilatory response to hypoxia in both the simulated-ascent group and a subgroup of 11 mountaineers. Because the functional decrements were greater in those who were believed to be less hypoxic, they suggested the possibility that the injury in climbers with strong HVR might have resulted from hypocapnic cerebral vasoconstnction, combined with the Bohr effecton capillary PO_2 ofthe extreme arterial alikalosis pH was predicted to be about 7 75 from the measured end tidal PCO_2 on Everest (60) but was measured at 7.57 and BE was -10 mM in the subjects in the Everest 11 chamber expenment (61), inducing a Bohr effect left shift of about 20%.

Song et al (62) reported cerebral thrornbi in several climbers who had gone higher than 5,000 m for longer than 3 weeks. They speculated that the cause was hemoconcentration resulting from secondary polycythemia and dehydration at altitude. In the fetus and infant, hypoxemia whether from high altitude or other causes, is associated with increased cerebrovascular morbidity. Longo et al (63) compared cerebral arteries obtained from normoxic and chronically hypoxic sheep adults and fetuses. Long-term hypoxemia was associated with generalized increase in base-soluble protein (5-5%), a depression of the maximum potassium-induced tensions (16-49%), and a depression of the relaxation responses to S-nitroso-N-acetylpenicillamine (1-11%), which releases nitric oxide into solution upon hydration. They concluded that chronic hypoxemia depresses cerebral vascular smooth muscle and endothelial hypoxic response to a greater- extent in the fetus than in adults

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