102. DO CHANGES IN LOCAL \( \text{Ca}^{2+} \) CONCENTRATION AFFECT BLOOD FLOW IN THE BRAIN?

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The mechanism which links local changes in cerebral blood flow to neuronal activity is far from clear (Cameron, 1977, *Clinical Science and Molecular Medicine*, 52, 549–554). Changes in the local concentration of \( \text{H}^+ \), \( \text{K}^+ \) and adenosine may be responsible. Recently, Nicholson et al. (1977, *Proceedings of the National Academy of Sciences of the U.S.*, 74, 1287–1290) demonstrated that repetitive stimulation of neurons is accompanied by a fall in local \( \text{Ca}^{2+} \). Betz, Enzenross & Vlahov (1974, *Epilepsia*, 343, 79–88) have shown that an increase in local \( \text{Ca}^{2+} \) causes a constriction of pial arterioles and a reduction in dilatation. We have attempted to show that local changes within brain parenchyma will affect local flow and that changes in \( \text{Ca}^{2+} \) may be important, therefore, in the matching of blood flow to brain activity.

Hypothalamic blood flow (HBF) was measured using a local \( \text{13}^\text{3} \text{Xe} \) clearance technique in rabbits anesthetized with pentobarbitone. Cannulae were placed on either side of the hypothalamus using a stereotaxic headplate technique. On one side of the hypothalamus \( \text{13}^\text{3} \text{Xe} \) was injected in a mock CSF containing \( \text{Ca}^{2+} \) (1 mmol/l) and on the other side containing \( \text{Ca}^{2+} \) (6 mmol/l). The volume injected was 5–20 μl. Blood flow was derived from the monoexponential clearance curve obtained with an external counter. A mean value for HBF was obtained, therefore, in each rabbit in the presence of 1 and 6 mmol/l \( \text{Ca}^{2+} \). In the presence of 6 mmol/l \( \text{Ca}^{2+} \) HBF was reduced by 17% compared with that measured in the presence of 1 mmol/l \( \text{Ca}^{2+} \) (P < 0.025). Arterial \( \text{PCO}_2 \), varied by ventilating the rabbits with various \( \text{CO}_2 \) mixtures and HBF was again measured in the presence of 1 and 6 mmol/l \( \text{Ca}^{2+} \). The increase in HBF observed with \( \text{CO}_2 \) inhalation was not significantly different (0.084 ± 0.007 ml min⁻¹ 100 g⁻¹ kPa \( \text{PCO}_2 \); 1 mmol/l \( \text{Ca}^{2+} \), mean ± SEM and 0.076 ± 0.007 ml min⁻¹ 100 g⁻¹ kPa \( \text{PCO}_2 \); 6 mmol/l \( \text{Ca}^{2+} \), P > 0.4).

Injection of a \( \text{Ca}^{2+} \)-free solution did not produce a significant rise in HBF, nor could an increase in local flow be demonstrated after injection of EGTA (1 mmol/l). An increase in local \( \text{Ca}^{2+} \) reduces HBF but does not influence the increase in flow observed with a rise in arterial \( \text{PCO}_2 \). We have failed to show an increase in flow with reduction of local \( \text{Ca}^{2+} \).

103. ANALYSIS OF MUSCLE WEAKNESS IN OSTEOMALACIA

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The unexplained proximal weakness of osteomalacia has been analysed in terms of the composition and function of the quadriceps muscle of 18 patients. Needle biopsy was used to examine the muscle chemistry (Edwards, Maudner, Lewis & Pearse, 1973, *Lancet*, ii, 1070; Edwards, Jones, Maudner & Batra, 1975, *Lancet*, ii, 736). Indices of contractility were measured during percutaneous electrical stimulation (Edwards, Young, Hosking & Jones, 1977, *Clinical Science and Molecular Medicine*, 52, 283).

Weakness could not be attributed to failure of neuromuscular transmission or to contracture coupling or energy supply. Plasma levels of creatine phosphokinase were normal and there was no histological evidence of denervation or of replacement of quadriceps muscle cells by fat or fibrous tissue. The most striking histological feature was atrophy, affecting both fibre types, but the type II fibres being the more severely affected.

Treatment with vitamin D₂ or with 1α-hydroxycholecalciferol required at least a week before there was a significant improvement in the force of a maximum voluntary contraction of the quadriceps. The time course of relaxation from a brief, electrically stimulated tetanus (prolonged in 12 of the 18 patients) was also slow to change. Increases in strength corresponded to increases in muscle fibre size.

The weakness of osteomalacia appears to be due principally to atrophy of muscle fibres. Recovery is correspondingly slow and may not be complete even after several months of treatment.

104. PATHOGENESIS OF ISCHAEMIC DISC SWELLING

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The optic disc commonly swells when the ocular circulation is impaired as in temporal arteritis, ischaemic optic neuropathy or accelerated hypertension. At the level of the optic nerve-head, retinal ganglion-cell axons are supplied by lateral and medial posterior ciliary branches of the ophthalmic artery. It has been postulated (McLeod, 1976, *British Journal of Ophthalmology*, 60, 551) that the disc swelling results from ischaemic obstruction of the normal bidirectional axoplasmic transport organelles following posterior ciliary artery occlusion.

In order to test this hypothesis, lateral orbitotomies were performed in monkeys and the lateral posterior ciliary arteries (which supply the temporal choroid and optic nerve-head) were occluded. Ischaemic vacuolation of axons developed in the laminar and retrolaminar regions of the optic nerve-head temporally, and axonal swelling was demonstrated on each side of the ischaemic zone. Electron microscopy revealed an accumulation of cytoplasmic organelles within the swollen axons.

Axoplasmic transport was studied in these animals by radioautography following an intravitreal injection of \( ^3\text{H}\)leucine; this is normally incorporated within retinal ganglion cells and transported along the optic nerve. When \( ^3\text{H}\)leucine was injected at the same time as lateral posterior ciliary artery occlusion, a build-up of label subsequently developed within distended axons in the prelaminar region temporally and transport of label into the temporal part of the optic nerve was reduced when compared with the medial side. Obstruction of orthograde axoplasmic transport was thus demonstrated. When \( ^3\text{H}\)leucine was injected some days prior to arterial occlusion (allowing time for its distribution throughout the axons), a build-up of label also occurred in distended axons in the optic nerve central to the ischaemic area, reflecting obstruction of retrograde axoplasmic transport.

These experiments confirm that ischaemic disc swelling represents an intra-axonal aggregation of cytoplasmic material resulting from obstruction of axoplasmic transport in ganglion-cell axons, and is thus a cotton-wool spot of the optic disc.

105. RELAXATION RATE OF TYPE I and TYPE II FIBRES IN HUMAN SKELETAL MUSCLE

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Human skeletal muscle comprises two main fibre types distinguished by their histochemical staining characteristics (Dubowitz & Brooke, 1973, *Molecular Biology: A Modern Approach*, Saunders, London). Animal studies indicate that type I fibres have slow, and type II fast, twitch characteristics (Close, 1972, *Physiological Reviews*, 52, 129). It is of interest to define the mechanical properties of the fibre types in human muscle since there is often a selective involvement in disease.

Motor units comprising type I fibres (low myosin ATPase activity) are alone recruited for low force contractions. Type