Oxygen tension distributions for normoxia and for hypoxia (P_a = 46.5 mm Hg) are demonstrated (Figure 2). During respiratory hypoxia the oxygen supply of some regions is not sufficient. From the oxygen tension distribution of the different capillary systems the histograms were derived. Oxygen tension histograms are illustrated for con- and countercurrent as well as capillary network systems (Figure 3). Furthermore, in the same figure an oxygen tension histogram for the hypoxia case is shown.

The figures demonstrate typical differences between oxygen tension histograms of the different capillary tissue models: the concurrent histogram is characterized by a homogeneous oxygen tension distribution with a oxygen tension spectrum between 23 mm Hg and arterial oxygen tension value of 100 mm Hg. Tissue points with values below the venous oxygen tension ar rarely seen. In the range between the venous and the arterial oxygen tension the frequency of oxygen tension values decreases more rapidly than in the concurrent histogram.

An extreme difference exists between homogeneously perfused con- or countercurrent systems and the inhomogeneously perfused capillary network. The capillary network has a broad spectrum ranging between zero mm Hg and the arterial oxygen tension of 100 mm Hg.

The analysis led to the conclusion that the frequently observed low oxygen tension values in brain tension (HEIDENREICH, ERDMANN, METZGER and THEWS[10] and METZGER[11]) might be caused by inhomogeneities in cerebral blood flow. A number of restrictions of this analysis should be kept in mind: homogeneity of oxygen consumption, isotropy of oxygen diffusion, equal solubility in all compartments, two-dimensional tissue area. Nevertheless, the present study of oxygen tension histograms help to better understand the experimental microelectrode results. This investigation demonstrates the tremondous influence of microcirculation and capillary architecture on oxygen tension distribution and histogram. A final proof of this conclusion will be obtained in a study on three-dimensional capillary arrangements.

Zusammenfassung. Mit Sauerstoff-Mikroelektroden werden die lokalen Werte des Sauerstoffpartialdruckes im Mikrobereich der Organe gemessen und graphisch als Häufigkeitsverteilungen (Histogramme) dargestellt. Theoretisch wird der Einfluss der Kapillaranordnung (Gleich-, Gegenstromsystem und Kapillarnetzwerk) auf die Häufigkeitsverteilung der P_{O_2} Werte untersucht. Die für zweidimensionale Modelle durchgeführte Analyse zeigt, dass Unterschiede in der Durchblutung, wie sie in den einzelnen Zweigen der Kapillarnetzwerke auftreten, einen starken Einfluss auf die Histogramme haben.

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Notations and constants: c = relative O_2 concentration or O_2 partial pressure. x, y = coordinates in tissue. n, s = capillary coordinates. l = capillary length = 60 µm. d = capillary side length = 6 µm. α = oxygen solubility coefficient = 0.025 ml/ml × Atm. diffusion coefficient = 2.10^{-5} cm²/sec. P_a = arterial oxygen tension = 100 mm Hg. P_v = venous oxygen tension = 34 mm Hg. P_K = critical oxygen tension = 1 mm Hg. m = Hill exponent = 2.83. K = Hill constant = 0.87×10^{-3}. c_{Hb} = hemoglobin concentration = 14 $g\%$. A = metabolic rate (grey matter) = ml/100 g × min. Δs = change of saturation of hemoglobin = 0.53. AG = 3.18. CH = 0.01. AK = 18 $AG \times K P_a^m m \times 100/\Delta s = 0.59 \times 10^{-4}$.

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The Impairment of the Thermoregulatory 'Set-Point' of a Sheep in the Apparent Absence of Any Interference with the Pathways Between Temperature Sensors and Thermoregulatory Effectors

Core temperature of homeothermic mammals appears to be regulated at or near to an inherent but variable set-point, the neuronal nature of which remains obscure. VENDRIK[1], inspired by BAZETT[2], has suggested that this set-point function may depend on the activity/temperature characteristics of temperature-sensitive neurones in the preoptic area of the anterior hypothalamus (POAH), and some hypothalamic neurones have activity/temperature relations which are consistent with this proposal[3]. An alternative hypothesis, based on the existence of temperature-insensitive neurones in the POAH[4], is that these cells may exert an inhibitory influence on the temperature sensor to thermoregulatory effector pathways[5,6] thus creating threshold levels above which heat loss effectors, and below which heat production effectors, are activated. (For a more detailed discussion of these ideas see BLIGH[7]).

To study the effects on thermoregulation of interactions between changes in hypothalamic temperature (T_{hy}) and injections into a lateral cerebral ventricle of putative transmitter substances, a multiple thermode assembly was introduced into the POAH of sheep[8]. This inevitably involves some local brain damage but does not usually impair the capacity to thermoregulate. One sheep was unable, post-operatively, to regulate body temperature at the normal level for this species. The observations made on this animal indicate that the set-point mechanism may be distinct from the temperature-sensor to thermoregulatory-effector pathways.

The first indication of a post-operative disturbance was a high rectal temperature (T_{re}) of 41.5°C, which could have

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been evidence of a fever. However, in contrast to the fever syndrome in which respiratory frequency (RF) is greatly depressed, the RF of this sheep at 20°C ambient temperature (T_a) was within the normal range (60–80 breaths/min). A local increase of T_{hy} by 1.5°C evoked panting (200 breaths/min) and a fall in T_{re} to about 40.5°C. Cessation of hypothalamic heating was followed by a fall in respiratory frequency to its pre-heating level, but T_{re} remained at its new level. A second period of hypothalamic heating again caused panting and a fall in T_{re} to 39.5°C at which level it remained even after hypothalamic heating was stopped. This observation indicated a disturbance to the set-point mechanism but no disturbance to the pathway from warm-sensors to heat-loss effectors.

A neuronal model of the pathways between temperature sensors and thermoregulatory effectors has been based on the thermoregulatory effects of intraventricular injections of putative transmitter and related substances[9, 8, 10]. The effects in this sheep of 2 of these substances, 5-hydroxytryptamine (5-HT) and eserine, were unaltered by the lesion but there was no recovery from the displacements of T_{re} which they produced. An intraventricular injection of 300 µg 5-HT caused the expected peripheral vasodilatation, increase in RF and a fall in T_{re} which persisted after the other effects of 5-HT had passed. An intraventricular injection of 300 µg eserine caused the expected peripheral vasodilatation, onset of shivering, decrease in RF and a rise in T_{re} which again persisted after the other effects of the injection had passed. These observations were considered to be evidence of the integrity of hypothalamic synapses in the neural pathways from temperature sensors to thermoregulatory effectors, and of the pathways from these synapses to the effectors.

Since pyrogens are considered to interfere with set-point mechanism and the set-point mechanism appeared to be impaired in this animal, we gave an i.v. dose of TAB vaccine sufficient to evoke a fever response in a normal sheep. No fever developed. In fact, the response was the converse to fever: RF increased and T_{re} fell slightly.

For this syndrome to be attributable simply to the inactivation of the temperature set-point mechanism, the initial observation of a high T_{re} must be explained. The critical T_a of the fully fleeced sheep is below 5°C, so at the temperature of the animal house (15–20°C) a normal sheep is probably actively losing heat to remain in thermal balance. In the absence of an effective set-point mechanism and little or not active heat loss, core temperature might be expected to rise until passive heat loss equals heat production. To test this explanation, the sheep was shorn. In this condition, T_a of 15–20°C is below thermoneutrality, and some shivering was present, but not sufficient to prevent T_{re} from falling below the normal range. When T_{hy} was raised the shorn animal ceased to shiver and there was a further fall in T_{re} to below 38°C. There was no active recovery of T_{re} after hypothalamic heating had ceased.

On the 68th day after the surgery, the sheep died quite suddenly although, apart from the impairment of temperature control, the animal had seemed in good health. A post mortem examination revealed extensive lesions in the anterior hypothalamus immediately caudal to the rear pair of thermodes.

Our conclusion is that by a chance circumstance which may not be readily repeatable, we had produced a hypothalamic lesion which inactivated or seriously disturbed the temperature set-point mechanism without causing a detectable interference with the pathways from temperature sensors to thermoregulatory effectors. This indicates that the normal set-point mechanism, and the pyrogen induced interference with normal body temperature, depend on structures other than the primary hypothalamic temperature sensors and the pathways from these sensors to thermoregulatory effectors. However, this syndrome is not consistent with the concept of a set-point signal which exerts an inhibitory influence on the sensor-effector pathways, since the removal of such an influence would be expected to increase rather than decrease the responsiveness of the thermoregulatory processes to changes in body temperature.

Zusammenfassung. Aus diesem Versuch wird geschlossen, unbeabsichtigte hypothalamische Läsion durch Thermoden-Implantation verursacht zu haben, die beim Schaf auffallende thermoregulatorische Störungen hervorriefen, so dass der thermoregulatorische Sollwert-Mechanismus ausgeschaltet wurde, die Bahnen zwischen den hypothalamischen Thermosensoren und den thermoregulatorsichen Effektoren hingegen durch die Läsion nicht beeinträchtigt waren, was eine anatomische Differenzierung zwischen Sollwert-Mechanismus und Sensor-Effektor-Bahnen erlaubt.

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Isolation of Large Sheets of Frog Skin Epidermis

Studies of active transport using intact isolated frog skin[1] have been hampered by the presence of the corium which constitutes not only a diffusion barrier[2], but also a metabolically active store of electrolytes. Previous efforts[1, 3–6] to split off the epidermis of frog skin has resulted in only small pieces. We have isolated large sheets of epidermis by trypsin hydrolysis. The problem was the tela subcutanea which is virtually impermeable to bovine serum albumin (Lindley and Hoshiko, unpublished).

Methods. The tela subcutanea of abdominal skin of *R. pipiens* was lightly scored with a scalpel to make a grid of fine cuts. The skin was mounted in an open cylindrical chamber (with the corium facing into the chamber) much like a piece of cloth in an embroidery hoop. The chamber was placed with the epithelial surface down in a petri dish containing sulfate solution (55 mEq/l Na_2SO_4, 5 mEq/l K_2SO_4, 5 m*M tris* buffer, pH 7.8) bubbled with compressed air. The corium was covered with sulfate solution contain-