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EFFECTS OF ARTERIAL HYPOXIA ON THE CUTANEOUS CIRCULATION OF THE RABBIT

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SUMMARY

1. Changes in blood flow of the skin of the rabbit's ear and hind limb have been studied during arterial hypoxia by a calibrated heat conductivity method, together with changes in arterial pressure and aortic blood temperature.

2. There is little change in the blood flow of the hind-limb skin during the early phase of arterial hypoxia, reflecting a balance between the local dilator effects of hypoxia and the increased constrictor activity mediated through the sympathetic nerves as a result of arterial chemoreceptor excitation. During more prolonged arterial hypoxia there is a small gradual dilatation of the vessels of the hind-limb skin as a result of some diminution in the initial intensity of vasoconstrictor activity.

3. There is much more extensive vasodilatation in the ear than in the hind-limb skin during arterial hypoxia. Vasoconstrictor activity is slight in this region. Comparison of the ear responses to arterial and to primary tissue hypoxia suggests that in the former type of hypoxia stimulation of the arterial chemoreceptors inhibits thermoregulatory vasoconstriction to the ear, whilst in the latter type of hypoxia baroreceptor reflexes maintain or intensify it.

INTRODUCTION

Arterial hypoxia produces marked vasodilatation in the rabbit's ear (Krogh, 1922), but in man it causes vasoconstriction in the hand (Freeman, Shaw & Snyder, 1936; Abramson, Landt & Benjamin, 1943; Hintze & Thron, 1961). This difference in the response of the cutaneous circulation to arterial hypoxia demonstrates a difference in the mechanisms controlling heat loss in the two species, and the dilatation in the rabbit's skin contributes to the fall in body temperature, which is greater in the rabbit than in man (Korner, 1959; 1965*a*). The response of the vessels of the rabbit's ear during arterial hypoxia is anomalous in view of the strong

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circulatory chemoreceptor effects in this species (Korner, 1965*a*; Chalmers, Isbister, Korner & Mok, 1965). Cutaneous vasoconstriction rather than vasodilatation might be expected, particularly since stimulation of these receptors is known to produce vasoconstriction in the skin of the dog (Daly & Scott, 1962). The purpose of these experiments was to examine the circulatory changes in two different regions of skin (ear and hind limb) of the rabbit during graded arterial hypoxia, and to investigate the underlying mechanisms.

METHODS

Animals. New Zealand white rabbits cross-bred with the New Zealand Giant Strain (mean weight 2·7 kg; range 2·3–3·1 kg) were used in these experiments.

Operative procedures. The preliminary operations for the insertion of an aortic thermistor catheter, for transposition of the trachea, for bilateral adrenalectomy, for lumbar sympathectomy, and for section of the carotid sinus and aortic nerves were carried out as described elsewhere (Korner, 1965*b*; White, 1966; Korner & White, 1966; Chalmers, Korner & White, 1966). On the day of the experiment, catheterization of the central ear artery and insertion of a tracheotomy tube were carried out using local anaesthesia exactly as described previously (Korner, 1965*b*; Chalmers *et al.* 1966).

In two rabbits the left ear was denervated, through an incision made using local infiltration anaesthesia (0·5 % lignocaine HCl) of the base of the ear, by section of the greater auricular nerve and of the sympathetic fibres accompanying the central ear artery. A sham operation was carried out on the right ear and afterwards heat flow disks were applied to the two ears. In these animals mean arterial pressure was recorded through fine polyvinyl-chloride (PVC) catheters previously implanted into the lower abdominal aorta through the ilio-lumbar artery (Korner, 1965*b*).

Estimation of skin blood flow. The skin blood flow was determined by a heat conductivity method (Burton, 1948; Greenfield, 1956; Greenfield, Whitney & Mowbray, 1963) using a copper-tellurium heat flow disk (Hatfield, 1950; disks manufactured by Ernest Turner Ltd. Chiltern Works, High Wycombe, Bucks.). This method has been used to determine changes in skin blood flow (Jepson, 1954; Catchpole & Jepson, 1954, 1955; Holti, 1955; Roddie, Shepherd & Whelan, 1955; Greenfield, 1956). In the present experiments the heat flow of the rabbit's skin was measured and the blood flow estimated (see below), in the ear and lower parts of the hind leg. In both regions the proportion of muscle is small and almost all the blood flow passes to the skin.

The disks were built into the outer wall of a Perspex chamber (Fig. 1), connected in series with rubber tubing, and water at a constant temperature of 30° C was circulated through the system at a rate of 12 l./min by means of a Braun thermomix pump (Hartmann and Braun, Ltd.). The disks were applied to the rabbit's skin which was normally furred and not clipped, using petroleum jelly (to ensure a good contact) and adhesive strapping. The room temperature was maintained at 22–24° C and comparable environmental conditions were thus present in all experiments (Hertzman, 1953). The e.m.f. produced by the disks was fed into a Sanborn Low Level pre-amplifier, recorded photographically and converted to heat flow (cal/cm^2/min) using the appropriate calibration factor.

The relation between heat flow and blood flow in the skin was determined in perfusion experiments on isolated ear and lower hind-limb preparations. The experiments were carried out in rabbits anaesthetized with sodium pentobarbitone. In three animals PVC catheters were inserted into the central ear artery and vein and the collateral circulation occluded by means of clamps. The artery was perfused with blood entering the ear at the normal rabbit's body temperature of 40° C using a motor driven syringe pump and the effluent blood collected from the vein. In three other rabbits the anterior tibial artery and the lateral

cutaneous vein of the leg were cannulated at the level of the junction of the lower and middle thirds of the tibia using PVC catheters, and the collateral circulation was again occluded by means of strong clamps. The artery was perfused with blood at 40° C as described above and the venous effluent collected. At the end of the experiment the perfused organs were dissected and the component tissues weighed. The average weight of the isolated ear was 10 g of which 8 g was skin and the rest cartilage. The average weight of the isolated part of the hind limb was 50 g of which skin made up 25 g and muscle less than 3 g. The bulk of the perfused blood must have passed to skin, assuming that the flow in bone and cartilage was negligible (Cumming, 1962; Root, 1963). The relation between heat flow in cal/cm²/min and

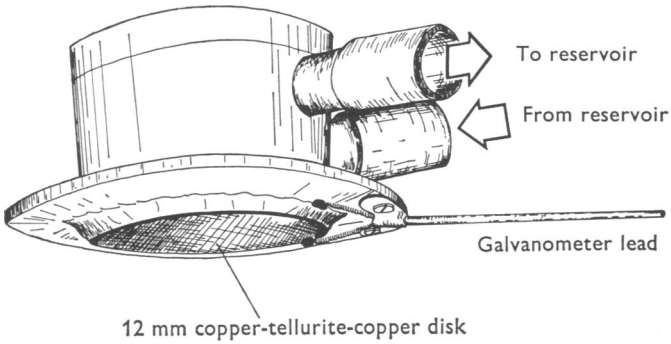

Fig. 1. Diagram of heat flow disk built into Perspex chamber. Further description in Methods.

skin blood flow in ml./100 g/min was approximately logarithmic, as indicated in Fig. 2. The relation was similar in the ear and hind-limb skin. The method is inaccurate at flow rates of less than 5 ml./100 g/min due to the increasing importance of conductive heat transfer (Burton, 1948) and, probably, also at very high flow rates where the changes in blood flow are accompanied by only small changes in heat flow. However, at any rate of blood flow the method will permit assessment of directional changes within animals, and its quantitative accuracy has been increased in the present experiments by averaging 2–3 measurements from each animal for each experimental time interval, and by pooling the results from a number of animals for each treatment.

Measurement of blood pressure, heart rate, arterial blood gas tensions and pH. Mean ear artery pressure and heart rate were recorded as described previously (Korner, 1965*b*). Oxygen and carbon dioxide tensions and pH were determined on 1·5 ml. of blood using a pH and blood analyser (model 113, Instrumentation Laboratory Inc.). Arterial P_{O_2} was determined polarographically with a Teflon covered oxygen microcathode, and P_{CO_2} using a Severinghaus-type glass electrode with a Teflon membrane of 0·001 in. (0·0025 cm) thickness (Severinghaus, 1959). Gas tensions were determined to an accuracy of ± 1 mm Hg. pH was determined to an accuracy of $\pm 0{\cdot}005$ units using a micro glass capillary electrode.

Administration of gas mixtures and drugs. Gas mixtures were freshly prepared from cylinders of air, N_2, CO_2, and 0·5 % CO + 21 % O_2 in N_2 and were administered through a respiratory valve as described previously (Edwards, Korner & Thorburn, 1959). In three rabbits systemic cholinergic block was produced with atropine sulphate with an initial dose of 2 mg I.V. followed by 1 mg I.V. at 15 min intervals.

Conduct of experiments. Following completion of the minor operative procedures on the day of the experiment the rabbit was placed inside a large, sound-proof Perspex box of 14 l. capacity, where it sat comfortably without restraint. The box was ventilated by drawing room air through it at a temperature of 22–24° C at the rate of 8 l./min, but the

animal inhaled the appropriate gas mixture through the usual inlet tube of its respiratory valve which entered the box through a flexible rubber gasket. Recording commenced 1 hr after placing the animal in the box. Each experiment consisted of a control period of 13 min (breathing room air), treatment period of 25 min (breathing the test gas), and a recovery period of 12 min (breathing room air). In some animals two or more experiments were carried out with an interval of at least 60 min between them. The timing of the various measurements was always similar in different animals, and 2–4 values of each of the parameters were obtained and averaged for each animal, during each of the selected time intervals, for example as shown in Fig. 3. In a given set of experiments the mean value for each time interval was determined for all the animals in the group. The standard error of the mean of each time interval of each parameter was estimated by analysis of variance (Mather, 1949) as described previously (Korner, 1965*a*; Chalmers *et al.* 1965; Korner & White, 1966) and is represented as ± 1 S.E. from the mean control value in the symbol on the left of each parameter. In the example in Fig. 3 the standard error of the difference between all initial control values (two time intervals), and all treatment values (four time intervals) at a given level of hypoxia is given by S.E. $\times (3/4n)^{\frac{1}{2}}$, where S.E. is the standard error of each time interval, and n the number of animals in the group.

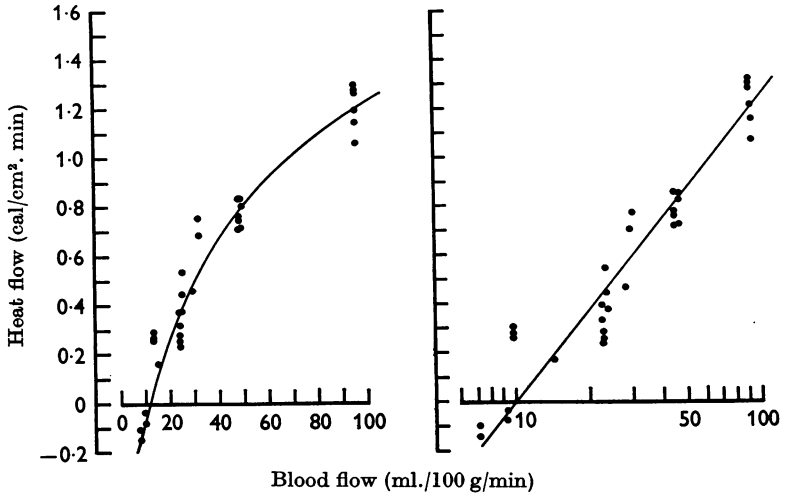

Fig. 2. Relation of blood flow and heat flow obtained in perfusion experiments on the isolated ear and lower hind limb in the rabbit. In right panel blood flow is plotted on a logarithmic scale.

RESULTS

Effects of breathing low O_2 mixtures in normal rabbits. The changes in ear and hind limb skin blood flow were studied in twelve animals in mild ($P_{O_2} > 35$ mm Hg), moderate (P_{O_2} 30–35 mm Hg), and severe ($P_{O_2} < 30$ mm Hg) arterial hypoxia produced by administration of low O_2 mixtures varying from 7·5 to 9·5% O_2 in N. The results are shown in Fig. 3 in relation to the changes in arterial pressure and aortic blood temperature. The changes in arterial blood gas tensions and pH are given in Table 1.

There was a large increase in the blood flow to the ear in all animals,

and this was greater during moderate and severe than in mild arterial hypoxia. The changes could not be accounted for by the associated blood pressure changes, and were thus the result of vasodilatation. The increase in flow was maximal during the first few minutes of hypoxia, at a time when the body temperature was falling rapidly. At the end of hypoxia the ear flow returned rapidly to control values.

The resting blood flow in the hind-limb skin was higher than in the ear, but the *changes* during hypoxia were much smaller. In mild hypoxia the

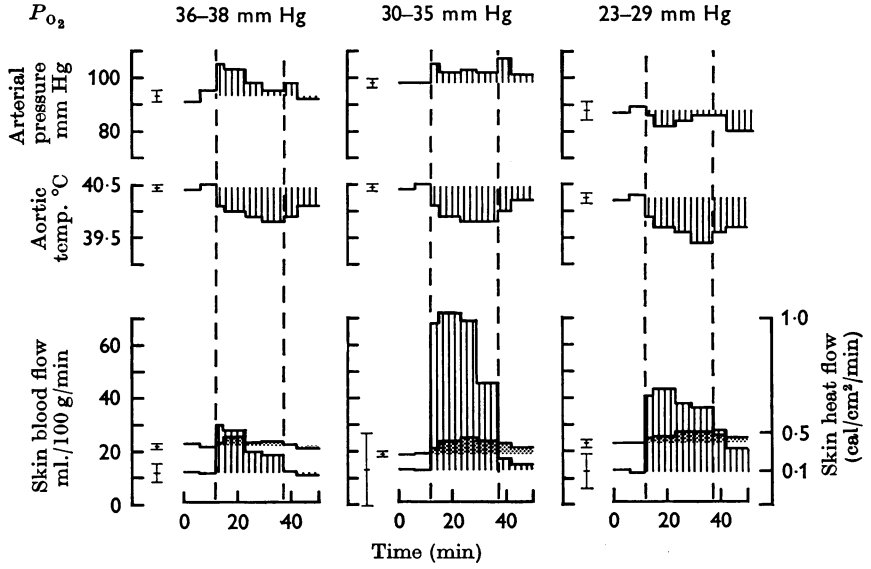

Fig. 3. Mean effects of mild arterial hypoxia in three rabbits (left panel), moderate arterial hypoxia in six rabbits (middle panel), and severe arterial hypoxia in three rabbits (right panel) on arterial pressure, aortic temperature, skin blood flow and skin heat flow. Low O_2 mixtures breathed between vertical interrupted lines in each panel, room air at other times. Hatching denotes deviation of test and recovery values from initial control values. Hind-limb skin flow—stippled hatching; ear blood flow—vertical hatching. Symbol on left of each parameter: mid point indicates mean initial control value with ±1 S.E. of mean of a single time interval as the distance above and below this point.

TABLE 1. Arterial blood gas tensions and pH in experiments on normal rabbits. *C* = control period breathing 21 % O_2; *T* = test period breathing low O_2 mixtures as described in text. S.E. Δ = standard error of difference between control and treatment means calculated from within animal comparisons

Degree of art. hypoxia	Number	P_{O_2} (mm Hg)			P_{CO_2} (mm Hg)			pH		
		C	*T*	S.E. Δ	*C*	*T*	S.E. Δ	*C*	*T*	S.E. Δ
Mild	3	98	37	±2·7	31	18	±3·7	7·48	7·59	±0·05
Moderate	6	99	32	±3·0	32	18	±1·5	7·47	7·59	±0·04
Severe	3	102	26	±6·0	33	21	±3·3	7·48	7·51	±0·110

blood flow changes could be accounted for by the changes in arterial pressure, and there was no significant change in cutaneous vascular resistance. During moderate and severe hypoxia the increase in blood flow was of more gradual onset than in the ear, and the vascular resistance fell slightly to about 85% of control. The hind-limb skin flows returned to normal during the recovery period.

Effect of section of carotid sinus and aortic nerves on hind-limb skin flows. The effects of arterial hypoxia were studied in two rabbits one day before, and one day after section of the carotid sinus and aortic nerves (Fig. 4).

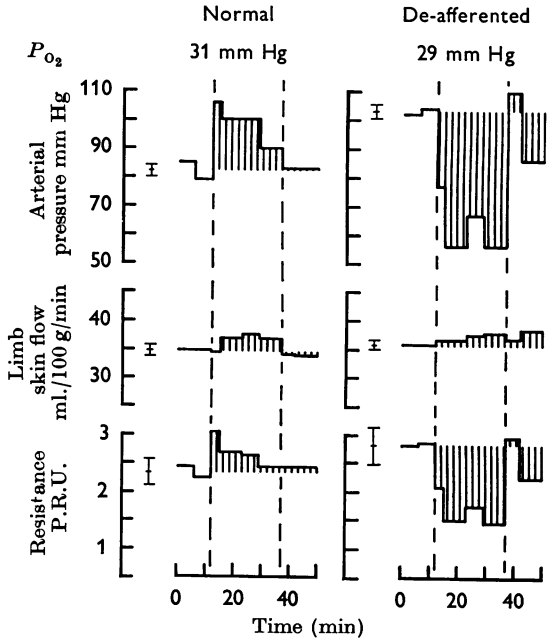

Fig. 4. Mean effects in two rabbits of similar degrees of reduction in arterial P_{O_2} on arterial pressure, limb skin flow and limb vascular resistance one day before (left panel) and one day after (right panel) section of the carotid sinus and aortic nerves. Notation as in Fig. 3.

Since de-afferentation of the carotid sinus region involved division of the sympathetic fibres to the ear accompanying the carotid artery, the skin flow was only estimated in the hind limb in these experiments. With intact buffer nerves there was no significant change in the vascular resistance to the hind-limb skin during arterial hypoxia. After section of these nerves there was marked vasodilatation with the vascular resistance falling to 53% of control during hypoxia. It is unlikely that the large vasodilatation reflects the differences in P_{CO_2} resulting from the abolition of the respiratory response to hypoxia, since in one of these animals the inhalation of

8% O_2+4% CO_2 before nerve section did not increase the usual small vasodilatation in the hind-limb skin.

Role of the vasomotor nerves on hind-limb skin flow. In three adrenalectomized animals with unilateral lumbar sympathectomy the resting skin flow was greater on the denervated side (Fig. 5). Severe arterial hypoxia (P_{O_2} 29–30 mm Hg) only produced a significant increase in flow on the innervated side (Fig. 5, left panel). There was a fall in hind-limb skin vascular resistance on both sides, and this fell to 75% of control on the innervated side but only to 88% on the denervated side. During inhalation of 8% O_2+4% CO_2 the dilatation was more gradual on the innervated limb, where the increase in skin flow was again greater than on the denervated side.

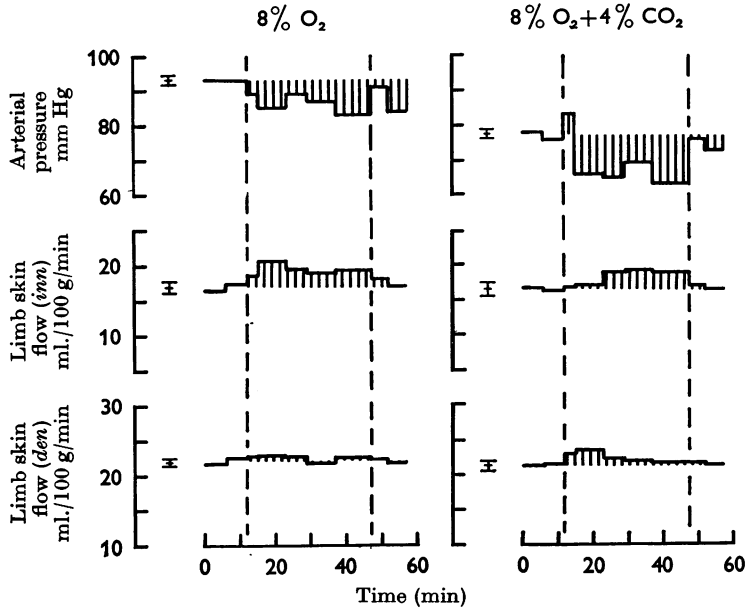

Fig. 5. Mean effects in three adrenalectomized rabbits with unilateral lumbar sympathectomy of breathing 8% O_2 (left panel), and 8% O_2+4% CO_2 (right panel) on arterial pressure and hind-limb skin flow in innervated (*inn*) and denervated (*den*) limbs. Notation as in Fig. 3.

These findings suggest that a gradual abatement of the normal increase in sympathetic constrictor tone in arterial hypoxia (Heymans & Neil, 1958; Daly & Scott, 1962; Korner, 1965*a*) helps to unmask the factors producing the dilatation in the hind-limb skin of the rabbit.

The vascular response of the ear. In this group of experiments the role of the sympathetic nerves in the vascular response to arterial hypoxia of the rabbit's ear was investigated. The possibility of cholinergically mediated

dilator effects was examined by comparing the response to hypoxia before and after administration of atropine. The role of the sympathetic constrictor nerves was investigated, first, by comparing the effects of arterial hypoxia in animals with spontaneous difference in the degree of vasoconstrictor tone of the ear and, secondly, by studying the response to hypoxia in the normally innervated and the denervated ear of the same animal. Finally, the response to arterial hypoxia was compared with the response to primary tissue hypoxia induced by inhalation of carbon monoxide. In the latter type of hypoxia increased sympathetic activity is mediated mainly through baroreceptor reflexes, in contrast with arterial hypoxia, where chemoreceptor reflexes are mainly involved (Korner, 1965*a*).

TABLE 2. Effects of breathing 8 % O_2 in three atropinized rabbits on ear blood flow (ml./100 g skin/min), and on arterial blood pressure (mm Hg). *C* = control values breathing 21 % O_2; *T* = treatment values after 5 min hypoxia (i.e. time of maximal ear dilatation, cf. Fig. 3)

	Ear blood flow (ml./100 g/min)		Arterial pressure (mm Hg)	
Rabbit	*C*	*T*	*C*	*T*
1	12·0	42·0	104	112
2	12·6	90·0	93	93
3	13·4	62·0	103	120
Mean	12·7	64·8	100	109

TABLE 3. Effect of mild arterial hypoxia (P_{O_2} 35–44 mm Hg), and severe arterial hypoxia (P_{O_2} 25–31 mm Hg) on ear blood flow (ml./100 g skin/min) and arterial pressure (mm Hg) in rabbits with spontaneously warm ears. Number in brackets in each group is the number of animals. S.E. = standard error of mean of each time interval

		Control (air)		Test (hypoxia)				Recovery (air)		
Time from start (min)...		6	12	15	23	29	37	42	50	S.E.
Mild (3)	B.P.	97	96	99	97	97	97	97	95	±1·9
	Ear flow	111	100	96	83	81	83	40	24	±19·7
Severe (4)	B.P.	97	95	101	98	91	91	94	92	±3·0
	Ear flow	136	166	173	155	141	131	93	109	±18·6

Administration of atropine did not prevent the normal dilatation in the ear in three animals, indicating that cholinergic dilator mechanisms were not involved in the response (Table 2). Since the usual marked vasodilatation was observed in the ears of three adrenalectomized animals breathing 8 % O_2, the effect could not be attributed to circulating catecholamines.

The effects of mild and severe arterial hypoxia were studied in seven rabbits whose ears were spontaneously warm (i.e. ears with relatively low vasoconstrictor tone) during the control period (Table 3). In these animals, with high resting ear flows, neither mild nor severe arterial hypoxia re-

sulted in further significant increase in blood flow. In only two of these seven animals was vasoconstriction in the ear observed during hypoxia.

Experiments were carried out in two rabbits immediately before and after denervation of one ear. One of these experiments is shown in Fig. 6. With both ears cold and probably having a high level of constrictor tone before nerve section, vasodilatation was observed on both sides, but the effect was greater in the left ear in the experiment shown. After nerve section the animal was warmed by means of remote heat to the body with

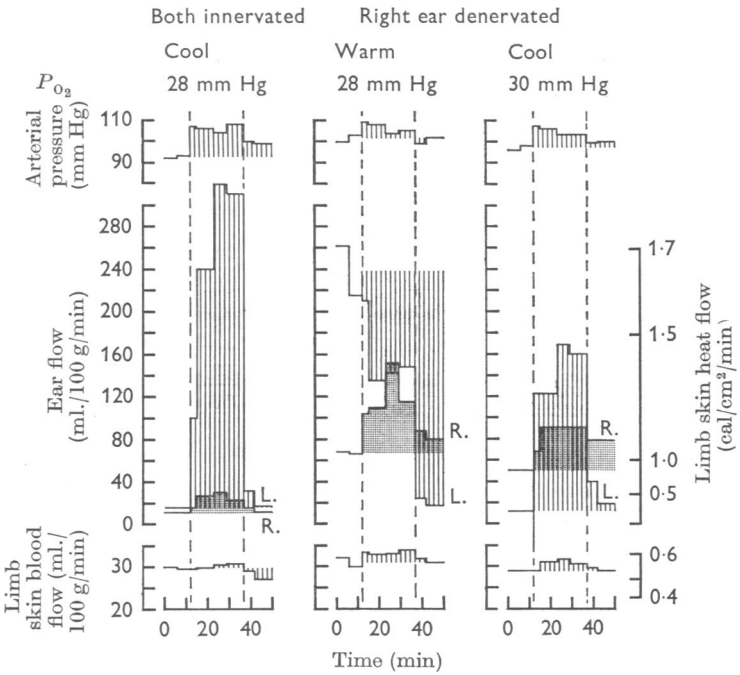

Fig. 6. Effects of arterial hypoxia in one rabbit on arterial pressure, ear flow and limb skin flow. Hypoxia induced with the animal at normal environmental temperature (cool, left panel), after applying indirect heat (warm, middle panel), and again at normal room temperature (cool, right panel). Nerve supply to both ears intact in experiment shown in left panel; experiments in middle and right panels carried out 1 hr after denervation of right ear. During each treatment period changes in blood flow in left ear denoted by vertical hatching, and in right ear by stippled hatching.

a 15 W electric light globe in order to diminish resting vasoconstrictor tone on the innervated side, and the resting flow in both ears increased with extremely high flows reached on the innervated side. During hypoxia the denervated ear dilated further, suggesting a local dilator effect of hypoxia, but there was immediate vasoconstriction on the innervated side, where the resting flow had been higher. At the end of this experiment

heating was discontinued and, with the innervated ear cool again, inhalation of 8% O_2 again produced dilatation in both ears. The findings were essentially similar in the second experiment.

These findings suggest that in arterial hypoxia the local effects of hypoxia on the ear predominate over the effects of any constrictor activity mediated through the vasomotor nerves. The effects of arterial hypoxia on the ear were compared with the effects of primary tissue hypoxia induced by the inhalation of 0·2% CO + 21% O_2 in N_2 (Table 4). It is apparent that arterial hypoxia produces far greater dilatation in the ear than does primary tissue hypoxia. This does not depend on the difference in arterial P_{CO_2} (Korner, 1965*a*), since abolition of the hypocapnia by the inhalation of 8% O_2 + 4% CO_2 did not diminish the dilator response in the ear during arterial hypoxia (Table 4).

TABLE 4. *A*. Comparison of effect of inhalation of 8% O_2 and 0·2% CO + 21% O_2 on ear blood flow (ml./100 g skin/min) and arterial pressure (mm Hg) in the same animals. *C* = control values breathing room air; *T* = average value of 25 min hypoxia; *R* = recovery value breathing room air. *B*. Comparison of effects of inhalation of 8% O_2 and 8% O_2 + 4% CO_2 on ear blood flow and arterial pressure in the same animals

A. Low O_2 – carbon monoxide comparison

	Low O_2						CO					
	Ear flow			Art. pressure			Ear flow			Art. pressure		
Rabbit	*C*	*T*	*R*	*C*	*T*	*R*	*C*	*T*	*R*	*C*	*T*	*R*
1	11·0	39·0	10·8	88	100	90	10·5	10·4	10·3	88	78	88
2	10·8	25·0	10·4	80	90	84	10·5	13·0	10·3	77	64	71
3	10·8	63·0	14·8	71	81	66	11·0	10·4	10·7	64	56	56
Mean	10·8	42·3	12·0	80	90	80	10·6	11·2	10·4	76	65	72

B. Low O_2 – low O_2 + CO_2 comparison

	Low O_2						Low O_2 + CO_2					
	Ear flow			Art. pressure			Ear flow			Art. pressure		
4	11·0	27·0	15·3	88	85	83	11·0	165·0	11·0	86	78	76
5	10·5	48·0	10·7	98	78	99	10·4	27·0	10·4	90	65	85
6	10·7	78·0	10·7	101	86	87	11·3	84·0	10·6	77	69	75
Mean	10·7	51·0	12·2	93	86	89	10·9	92·0	10·7	84	70	78

DISCUSSION

The estimated resting flows found in the rabbit's hind-limb skin and ear are much higher than the normal skin flow rates of 2–5 ml./100 ml. of skin in man (Fox & Edholm, 1963; Shepherd, 1963; Greenfield, 1963). The hind-limb skin is probably more representative of total body skin in view of the specialized thermoregulatory function of the rabbit's ear (Grant, 1930*a*, *b*; Grant & Bland, 1932; Hertzman, 1959). The high skin flow in

the rabbit reflects its high rate of resting metabolism (Korner & Darian-Smith, 1954; Edwards *et al.* 1959) and bears a relation to the resting cardiac output and muscle blood flow (Chalmers *et al.* 1966), which is similar to that in man.

In the skin of the rabbit's hind limb, arterial hypoxia produced only a small gradual vasodilatation. The results suggest that during the early phase of hypoxia there is even balance between the local dilator effects of arterial hypoxia, and the reflex increase in constrictor activity. Later on there is some diminution in the intensity of vasoconstrictor activity which unmasks the local dilator effects of hypoxia. This reflex increase in constrictor activity is mediated through the carotid and aortic receptor zones, and is abolished by de-afferentation. It is probably of chemoreceptor rather than baroreceptor origin, since in normal animals (Fig. 3) the response is similar whether the blood pressure rises or falls slightly during hypoxia. This vasoconstrictor activity is mediated through sympathetic nerves rather than adrenal medullary hormones, since the effects of hypoxia on the hind-limb skin were similar in normal animals and in the innervated skin of adrenalectomized animals.

In the ear, vasodilatation was much more marked than in the hind-limb skin, suggesting a predominance of the local effects of hypoxia over any reflex increase in constrictor activity. It was difficult to demonstrate vasoconstriction regularly during arterial hypoxia even when the basal constrictor tone to the ear vessels was reduced, as in the rabbits with moderately warm ears (cf. Table 3). Increased vasoconstrictor tone could only be demonstrated when the basal tone of the ear vessels was virtually abolished (Fig. 6). It seems probable therefore that the increase in sympathetic vasoconstrictor activity to the ear during arterial hypoxia must normally be small and much less marked than to the hind-limb skin, or to muscle (Chalmers *et al.* 1966).

In primary tissue hypoxia produced by the inhalation of carbon monoxide the local dilator effects of hypoxia did not predominate in this manner. In this type of hypoxia increased sympathetic activity is mediated through the arterial baroreceptors whilst in arterial hypoxia it is produced by excitation of the arterial chemoreceptors (Korner, 1965*a*). In the absence of reflex control the local effects of the two types of hypoxia are probably similar (Korner, 1965*a*; Korner & White, 1966), the findings thus indicating that reflex vasoconstrictor activity is more rapidly produced in the ear through baroreceptor reflexes than by means of excitation of the chemoreceptors. The experiments suggest that chemoreceptor excitation inhibits thermoregulatory vasoconstriction to the A–V anastomoses of the ear, but that increased sympathetic activity through baroreceptor reflexes intensifies it. This interpretation is in agreement with the demonstration by

Mott (1963) that chemoreceptor excitation inhibits reflex thermoregulatory shivering, and with the findings of Bostroem & Schneider (1953) that withdrawal of baroreceptor activity increases sympathetic constrictor activity and reduces the blood flow through arterio-venous anastomoses in the dog's paw, a structure with a similar vascular arrangement to the rabbit's ear (Hertzman, 1959; Greenfield, 1963; Folkow, 1964).

Folkow (1955) has suggested that the arterio-venous anastomoses in the skin are predominantly controlled from the hypothalamic heat loss centres and this could account for the different behaviour of the skin of the ear and hind limb during arterial hypoxia in the rabbit. The sympathetic supply to the limb skin vessels appears to be much more responsive to the excitatory effects of chemoreceptor stimulation than that of the ear.

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