

Carotid bodies in animal models of human disease: what do they teach us?

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Animals suffer their own diseases and rarely afford us accurate pictures of human afflictions. The argument is cogent that we can only learn about human problems through the study of humans. However, had we never investigated animals there are things we certainly would never have known. I contend that we would not have discovered the respiratory function of the carotid body. In anaesthetised animals we can humanely cut and record from nerves, change gas tensions, give drugs and poisons. Animals can be exposed to environments which affect humans under controlled conditions, and then compared with normal animals of similar age, sex, and life experience. Then there is the morphological problem. Animal tissues can be taken at the moment of death or before, so that the autolytic problems which beset pathologists do not hold. All these points apply to research on the carotid body, to the interaction between physiologists and pathologists, and the arguments between them. Much has been learnt from the efforts of these two groups but few problems are wholly settled; the disputes between different disciplines often point the way forward to further research. In talking about "models" we should consider how far they reproduce both morphological and functional features of human conditions.

Historical

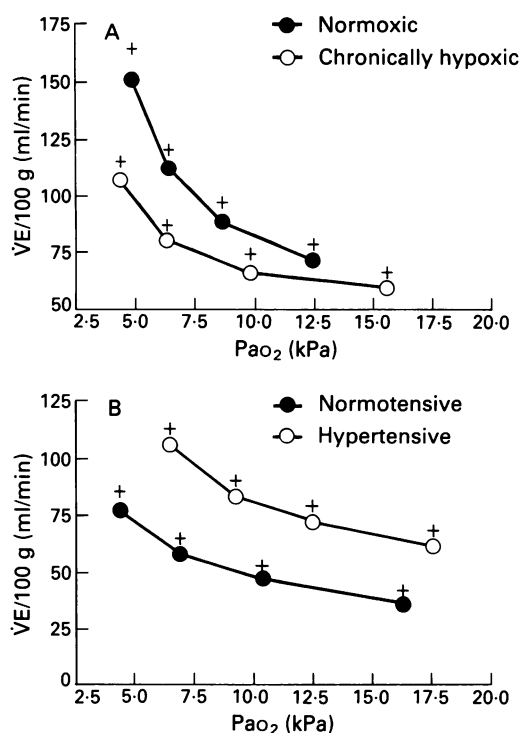
Study of the human carotid body gathered impetus when Arias-Stella found that it was unusually large in people in the high Andes who had lived all their lives in an hypoxic environment.¹ At this time Professor Heath was studying patients with chronic bronchitis and emphysema who were hypoxic because they could not take in sufficient air. He found changes in their pulmonary vessels similar to those found in high altitude dwellers. He began to look at their carotid bodies and found them also to be abnormally large. In Sheffield we were studying rats and mice made hypoxic in a hypobaric chamber and had sent Professor Heath some slides of their lungs. He replied with enthusiasm that their small lung vessels resembled those of his bronchitic patients. At a meeting of the Pathological Society in Sheffield in 1970 he gave a paper on human carotid bodies and we gave one on pulmonary vessels in our hypoxic mice.² We met and both decided to look at carotid bodies in animals kept in a low oxygen environment – in "animal models of hypoxic lung disease". Thus began a long friendship and collaboration.

Hypoxic carotid body in man and animal "models": morphology and physiology

In 1970 Heath and colleagues published a paper describing the carotid bodies in 40 consecutive necropsies. The weight of the carotid body was high in patients with emphysema, Pickwickian syndrome, and cor pulmonale, and a significant correlation was observed between the combined weights of the carotid bodies and the weight of both the right and, unexpectedly, the left ventricle.³ In 1971 a further paper confirmed these findings.⁴

In the following years the Liverpool group produced a series of fascinating papers on rats exposed chronically to hypoxia in a hypobaric chamber. They showed that the carotid body enlarged rapidly, developed vascular engorgement and cellular changes at both the light and electron microscopic levels, and returned to normal rapidly in air.⁵ Others confirmed these findings. In collaboration with Dr Edwards from the Liverpool group our Sheffield team showed similar morphological changes in rats kept in both hypobaric and normobaric hypoxic chambers.⁶ In Prague Herget, in collaboration with us, found enlargement of the carotid body in rats with experimental silicosis and emphysema, the size being proportional to the degree of hypoxia in life.⁷ In Sheffield we found functional changes attributable to the carotid body in our chronically hypoxic rats.⁶ When removed from the chamber and given low oxygen mixtures to breathe they increased their ventilation to a lesser degree than normal rats (figure). This excited us because high altitude dwellers in both the Andes and the Himalayas have a "blunted" ventilatory response to hypoxia, as do children hypoxic from congenital heart disease. The "blunting" in rats lasted only a few days into recovery in air, but the finding has been repeated many times. About this time it was shown by the group in Denver, Colorado that non-native residents at high altitude develop "blunting" after about 12 years' residence.⁸ More recently the Denver group have shown that "blunting" in women living at high altitudes in Peru is "reversible" in that a brisk ventilatory response to hypoxia returns to these normally blunted individuals during pregnancy.⁹ Thus blunting may be switched on and off. Flenley and colleagues showed that a proportion of patients with chronic hypoxic lung disease have a poor ventilatory response to hypoxia.¹⁰ To this point human and animal studies concurred, but more detailed morphological investigations led to a divergence.

In rats chronically exposed to hypoxia with or without hypercapnia morphometric analysis



Relation between ventilation/100 g body weight and arterial PO₂. Values are means (SE.) (A) Chronically hypoxic rats increase ventilation less than control rats with increasing hypoxia. (B) Hypertensive rats ventilate more than normotensive rats over a wide range of PO₂ but the increase in ventilation with increasing hypoxia is similar. Data derived from refs 21 and 29.

showed that the enlargement of the carotid body was partly due to vascular engorgement but also to proliferation of type 1 (often called chief) cells and connective tissue cells; there was also angiogenesis.¹¹ The dense-cored vesicles in type 1 cells, which contain dopamine, were changed morphologically and the number per carotid body was greatly increased. The proliferation of type 1 cells was at first disputed since they were thought to be neural in origin; hyperplasia was proved conclusively when mitoses were found after arrest of cell division with vincristine.¹² Autoradiographs taken after administration of tritiated thymidine showed numerous cell divisions 1–4 days into hypoxic exposure.¹³ No change was detected in the type 2 cells which normally envelop the nests of type 1 cells. The carotid body therefore appeared to be hyperplastic and active as one might expect under chronic stimulation.

By contrast, in the enlarged carotid body of patients dying from hypoxic lung disease Professor Heath's group found a hyperplasia which consisted of concentric whorls of "sustentacular" cells (resembling type 2 cells) surrounding and seemingly compressing a diminished number of type 1 cells.¹⁴ Among the sustentacular cells were numerous nerve fibres which at times resembled a neuroma; the appearance was similar to that seen when nerves are cut and subsequently "seek" the cells with which they should synapse. The type 1 cells were of several types, thought to be of different functional or developmental significance, whereas in rats they are uniform. One might say that the organ looked "worn out". A similar

appearance was found by Habeck in some of his hypoxic patients.¹⁵ The question was raised as to whether this appearance was related to the advanced age of many of the patients compared with the youth of the rats. A study of changes in the human carotid body with age showed that this was not so, although sustentacular proliferation became more common as life advanced.¹⁶ Nonetheless one cannot compare the carotid body of a human coming to necropsy after a lifetime of repeated illnesses and experiences with that of a rat dying after a sheltered healthy life and brief hypoxic exposure. This problem is unresolved.

Do chronically hypoxic rats, therefore, more closely resemble high altitude dwellers than hypoxic patients? This may be so. Arias-Stella and Valcarcel¹⁷ found that the carotid body of Quechua Indians contained larger and more numerous lobules than that of plain dwellers, due to proliferation of "chief cells" with thin intervening fibrous tissue. Recently Professor Heath's group have looked at carotid bodies of four high altitude dwellers from Ladhak in the Karacorams.¹⁸ The carotid body was abnormally heavy in the two oldest subjects. In three cases there were numerous clusters of chief cells with many of the "dark" variety, which have been found both in young and old cases of hypoxaemia. Only a 52 year old man had sustentacular cell proliferation. We must look at rats after repeated or very long hypoxic exposures to see if they develop sustentacular hyperplasia. It may eventually be proved, however, that rats and humans are fundamentally different.

Biochemical changes in the hypoxic carotid body: functional consequences

In the 1970s and 1980s electrochemical analyses showed that the catecholamine content of the carotid body in rats altered during hypoxia. During chronic hypoxia the noradrenaline and dopamine contents increased dramatically, and returned slowly to normal during recovery in air.¹⁹ The turnover of dopamine also increased.²⁰ Dopamine inhibits the response of the carotid body to hypoxia; it diminishes both the frequency of impulses travelling up the carotid nerve and the subsequent increase in ventilation. We wondered if the "blunting" seen in our rats could be due to the high content of dopamine in their carotid bodies. We found, indeed, that a dopamine inhibitor, domperidone, increased ventilation during hypoxia in both normal and chronically hypoxic rats but more so in the latter, so that their ventilation became equal to that of normal rats.²¹ Recently Bee has studied the effect of different lengths of hypoxic exposure on the ventilatory response to hypoxia in rats.²² She reasoned that, during the cell division period, dopamine would not be synthesised. The response to hypoxia was enhanced in the first few days of exposure, then became normal after seven days, and "blunted" after two weeks as previously shown.^{6,21} Dopamine inhibition is therefore one potential cause of blunting. Other workers, using different species, made different suggestions – for

example, central nervous system inhibition,²³ efferent inhibitory impulses in the carotid nerve.²⁴ Several potential causes of modulation of the ventilatory function of the carotid body are thus emerging from animal studies; it may become possible to test some of them in humans.

Carotid body, lung volume, and bronchoconstriction in hypoxia

In hypoxic lung disease the residual volume is high and there is bronchoconstriction. Animal experiments have shown that carotid body reflexes may contribute to these changes.^{25,26}

Carotid body and systemic hypertension in man, rat, and rabbit

In the late 1970s a connection was noted between the carotid body and systemic hypertension. Przybylski observed that spontaneously hypertensive rats of the Okamoto strain hyperventilated.²⁷ Then in Warsaw, Liverpool, and the German Democratic Republic separate groups found that the carotid bodies of this strain were larger than those of normal rats of a different strain;⁵ this result was confirmed later with genetically similar normotensive rats. Young men with borderline hypertension were found to hyperventilate and had signs of peripheral chemoreceptor hyperactivity,²⁸ so it was proposed that carotid body overactivity might actually cause hypertension. Later work in rats showed that enlargement of the carotid body occurred *after* hypertension had developed; it seemed to be secondary to vascular disease in the supplying arteries.^{5,28} The idea developed that carotid body overactivity was caused by ischaemia secondary to vascular obstruction. Several groups including that of Professor Heath (who had shown the first link between carotid body weight and left ventricular weight) found enlarged carotid bodies in hypertensive patients at necropsy; all showed vascular disease in carotid body vessels. The Liverpool group made the surprising observation that these carotid bodies closely resembled those of patients dying of hypoxic lung disease. Both showed diminished numbers of type 1 cells and an overgrowth of sustentacular cells.¹⁴ Again, therefore, despite carotid body enlargement and functional changes in both rat and man, closer study revealed differences between them. More extensive studies in both humans and animals have shown that high blood pressure is not invariably associated with enlargement nor, in rats, with hyperventilation.

Habeck showed that some relatively young hypertensive humans do not have large carotid bodies and neither do patients dying from renal hypertension, despite severe arterial disease in their carotid bodies.¹⁵ In rats, too, there were discrepancies. In Sheffield we studied the New Zealand strain of hypertensive rat for which genetically similar "normotensive" rats were available.²⁹ The carotid bodies of normotensive and hypertensive individuals were similar in size, though larger than those of other strains.

The hypertensive rats were, however, hyperventilating; at any partial pressure of oxygen they breathed more than their normotensive cousins and had a relative *hypocapnia* (figure).²⁹ The line relating ventilation to oxygen tension was parallel to that of controls, so there was no increase in sensitivity to hypoxia. They also had severe disease in small carotid body arterioles with obstruction of the lumens. Unlike chronically hypoxic rats, they had a reduced number of type 1 cells and diminished vascular volume rather than engorgement. The dopamine content of the carotid body was normal but the noradrenaline content was increased. The results could be explained if oxygen tension at the site of the oxygen sensor was reduced due to diminished blood flow and to the high metabolism of this organ. The Milan strain of hypertensive rat, currently being studied in Sheffield, is different again. There is severe hypertension, the carotid body is *smaller* than in normotensive controls, and there is no hyperventilation.³⁰ Vascular changes are smaller than in New Zealand rats and the ventilatory response to graded hypoxia differs; a steeper relation between ventilation and oxygen tension suggests increased sensitivity to hypoxia, an observation also made in the Okamoto strain.³¹ Habeck *et al* found the carotid bodies of Lyon hypertensive rats to be larger than one strain but similar to a second normotensive strain.³² In F₁ and F₂ hybrids from the Okamoto strain they found no relation between size and vascular or ventilatory changes.³³ Angell-James *et al*^{34,35} found no carotid body hypertrophy or ventilatory abnormalities in rabbits in whom carotid vessels were narrowed by atherosclerosis or in rabbits with renal hypertension, nor was severe vascular disease in renal hypertensive rats associated with carotid body enlargement.³⁶

The link between carotid body size and function in systemic hypertension is therefore unresolved. Neither in man, rat, nor rabbit is enlargement always present; animal work suggests that genetic differences may also affect size. Where hyperventilation attributable to the carotid body has been found, the consensus seems to be that it is secondary to restriction of the blood supply. The reduced number of type 1 cells in the New Zealand strain, compared with the increased number in chronically hypoxic rats, raises the question as to whether the type 1 cell population gives rise to overactivity or underactivity of the carotid body. In the New Zealand hypertensive rats the carotid body was apparently responding normally or excessively to hypoxia, whereas the chronically hypoxic rats were under-responding. Moreover, in hypoxic rats the dopamine content was increased whereas in the hypertensive rats it was normal. It is tempting to speculate that the difference is related to the inhibiting effect of the dopamine-containing type 1 cells.

Carotid body and renal function, especially in hypoxia

Hypoxia is associated with disturbances of fluid balance and oedema, both on mountains and

in hypoxic cor pulmonale. Climbers to very high altitudes are prone to pulmonary (and cerebral) oedema, and high altitude dwellers are subject to chronic mountain sickness with oedema. The oedematous episodes of chronic cor pulmonale were long considered to be caused by right heart failure, although the moderate pulmonary hypertension and well sustained cardiac output did not fit this explanation. In 1956 Stuart-Harris and colleagues in Sheffield showed that these patients have an unexplained low renal blood flow.³⁷ In Sheffield it has long been considered that the oedema might be caused by a disturbance of hormones which control fluid balance. Recently Anand *et al*³⁸ have found that healthy soldiers stationed at very high altitudes for many weeks have reduced renal blood flow, sodium and water retention, various hormonal changes, and ankle oedema, together with evidence of right ventricular preponderance and raised pulmonary artery pressure. These men, engaged in heavy exercise, were certainly not in cardiac failure. The similarity between their fluid balance and renal changes and those of patients with hypoxic cor pulmonale, despite vigorous health on the one hand and severe illness on the other, supports a hormonal explanation.

A link between hypoxia and the carotid body has only recently been detected in fluid balance problems. Honig,²⁸ reviewing observations made both in man and animals, concluded that moderate hypoxia was associated with diuresis and natriuresis, whereas more severe hypoxia was associated with water and sodium retention. In experiments on cats his group found that hypoxia limited to the carotid body/sinus regions caused reflex diuresis and natriuresis.²⁸ The efferent limb of this reflex appeared to be due to an increase or decrease of an unidentified bloodborne factor, a hormone; it was not dependent on renal nerves and there was no reduction in renal blood flow. Almitrine, a drug which mimics the effect of hypoxia on the carotid body, also caused diuresis and natriuresis in cats.³⁹ Karim and colleagues found that severe hypoxia in dogs caused a reduction in renal blood flow and sodium retention due to increased activity in the renal sympathetic nerves.⁴⁰ In Sheffield it was shown in rats that small doses of almitrine caused diuresis and natriuresis without change in renal blood flow; section of the carotid nerve abolished the response and it survived in a transplanted, denervated kidney.^{41,42} So far we have been unable to cause sodium retention in chronically hypoxic rats so we do not yet have an animal "model" of human hypoxic oedema, but the experiments just described open up new possibilities to be explored.

Carotid body in sudden infant death syndrome

The sudden infant death syndrome (cot death) may have many causes but there is a clear link with previous long periods of sleep apnoea. A failure of respiratory control has long been suspected, especially the carotid body response

to hypoxia. Several groups have looked for morphological changes in the carotid body but no clear picture has emerged. Naeye *et al*⁴³ described abnormalities of the carotid body in a large series of cases, but Dinsdale *et al*⁴⁴ and several other groups could find no consistent changes, although Cole *et al* described a reduction in the numbers of type 1 cells and dense-cored vesicles.⁵ It is a major problem to find suitable "controls". Perrin found significantly raised dopamine and noradrenaline levels in the carotid bodies of 13 cases of sudden infant death syndrome compared with age matched controls.⁴⁵ In two of three cases of sudden infant death syndrome Heath *et al* found proliferation of the "dark" chief cell variant, while the third showed gross sustentacular cell overgrowth and areas where chief cells were almost absent; both these changes are seen in hypoxaemia.⁴⁶ Can animal "models" help us with this problem? It is known from work on lambs that the peripheral chemoreceptor apparatus is fully developed but not functional in the preterm fetus; it comes into action after birth and must, therefore, have been suppressed. Our chronically hypoxic rats have taught us that the hypoxic ventilatory response is variable. It is enhanced after short term hypoxia but "blunted" after longer exposure, associated with an increased dopamine content in the carotid body. In Sheffield Bee *et al*⁴⁷ are looking at newborn rabbits to see whether there is a time when the response to hypoxia is depressed which might correspond to the peak danger period for sudden infant death syndrome in babies. The ventilatory response to hypoxia was tested in 10 awake rabbit pups from week 1 to week 8 after birth. They fell into two groups. In five pups there was a profound depression of the response at about five weeks, while in the other five there were two troughs at about two and seven weeks. This work not only provides an illuminating analogy with human babies, but it may indicate genetic variation.

Conclusions

Have these animal "models" taught us anything useful? Yes, I believe they have. We have learnt that the carotid body is an active organ which changes, grows, and regresses with the events of life. Moreover, its functional properties are also variable. They have afforded us new ideas which may help to solve human problems. Yet human studies warn us to be careful because there may be species differences and both animal and human studies suggest that there may be genetic differences within a species. Above all, the interaction between physiologists and pathologists has been most fruitful. Long may this continue.

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