Relative hypoxia at high altitudes increases the incidence of pheochromocytomas

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We read with great interest the recent paper reporting a high incidence of pheochromocytomas and paragangliomas in an unselected population from the western region of Canada (1). All cases were identified based on clinical data available over a 7 years period. Interestingly, Alberta has a higher altitude (3678 ft, <https://en-gb.topographic-map.com/maps/lrg4/Alberta/>) compared with other geographical areas from where a lower incidence was reported in previous papers (Table 1). Similarly, detailed epidemiological data from multiple geographical area are not easily available. Previous reports involving the entire USA population cannot be scrutinised as they lack ‘granular details’ regarding states with different altitudes. There is, however, a convincing trend that suggests that high altitude (as in Alberta) and its associated relative hypoxia modulate the risk of development of pheochromocytomas.

In support of this hypothesis, in an analysis of 58 subjects from 23 families with SDHD mutations, subjects with pheochromocytomas lived at higher altitudes and were exposed to higher altitude-years than those without them. Furthermore, those who were diagnosed with single tumours at their first clinical evaluation lived at lower average altitudes and were exposed to lower altitude-years than those with multiple tumours (7). Population-weighted elevations were approximately 260 m for the United States and 2 m for the central-Western Netherlands (P=0), suggesting that low altitudes in The Netherlands reduce penetrance and relax the natural selection on SDHD mutations (7).

Previous basic research data provide a mechanism that could explain this relation through the pseudohypoxia model. Hypoxia-induced factor (HIF2 α) is more intensely expressed in both noradrenergic sporadic and hereditary

von-Hippel Lindau (VHL)-related tumours than in sporadic and familial adrenergic tumours. HIF-2 α is also expressed in developing sympathetic neurones, where it regulates the expression of tyrosine hydroxylase (TH), the rate-limiting enzyme in catecholamine synthesis (8). Such expression might confer onto these cells a susceptibility to VHL-associated tumorigenesis, thereby explaining both the development of such tumours and their associated noradrenergic phenotype (9).

Robust data is available on the ability of hypoxia to modulate enzymatic activity needed for catecholamine production. Long-term hypoxia in ewes maintained at high altitude (3820 m) results in a selective reduction in plasma adrenaline following acute stress, due to a reduction in tyrosine hydroxylase (TH), dopamine beta-hydroxylase (DBH) and phenylethanolamine N-methyltransferase (PNMT) expression (10). In animals conceived, born and raised at high altitude (3800 m, 13% PO₂), the activities of the synthesizing enzymes, TH, DDC and PNMT, were variably affected at some time during the perinatal period. The activities of the catabolizing enzymes, MAO and COMT, at high altitude were increased on the last days of gestation but depressed after birth (11).

In laboratory settings, mouse pheochromocytoma cells (MP712 cells) showed a two-fold increase in PNMT mRNA after incubation in 5%O₂, with an inverse relationship between PNMT gene reporter gene expression and O₂ concentration between 10 and 1%. Anoxia evokes the most pronounced response, detectable within 15 min, becoming maximal at 45 min then subsiding to normoxic levels by 120 min (12).

Traditionally it is considered that noradrenaline (NA) and adrenaline (Adr) are stored in different types of intracellular granules. In a previous study using

Table 1 Regional variability in incidence of phaeochromocytoma.

Ref	Data source	Country	Average altitude	Age-standardized incidence rates (per 100 000 person-years)
2	Dutch pathology registry	Netherlands (1995–2015)	98 ft (30 m)	Phaeo: 0.29 (95% CI: 0.24–0.33) to 0.46 (95% CI: 0.39–0.53) PGL 0.08 (95% CI: 0.06–0.10) and 0.11 (95% CI: 0.09–0.13)
3	National Health Insurance Service Database	South Korea (2003–2014)	925 ft (282 m)	0.18
4	National cancer registry	Sweden (1958–1981)	1050 ft (320 m)	0.21
5	Epidemiology study	Rochester, Minnesota (1950–1979)	1100 ft (314 m)	0.8
6	Population study	South Galicia, Spain (1980–1992)	1296 ft	0.2 (range 0.0–0.39) per million.

electron microscopy we found no correlation between the proportion of adrenergic granules (range 7–89%) and the output of catecholamines as assessed by 24-h urine catecholamine levels (13). If the morphology of tumour granules is not directly correlated with its biochemical profile, it remains likely that intra-tumoural functional changes modulate the catecholamine output. When the histology reports from 92 phaeochromocytomas were scrutinised, we found that patients whose tumours contained areas of necrosis/haemorrhage (i.e. assumed to be ischaemic tumours) had a tendency for higher adrenaline secretion as reflected by higher metanephrine/

normetanephrine ratio (median: 0.432 (0.005–3.0820) vs 0.334 (0.004–16.073) (Fig. 1). It remains to be confirmed whether changes in hypoxia-induced PNMT activity modulate the pattern of catecholamine secretion from individual tumours.

In summary, the recent publication by Leung *et al.* in a recent issue of the *European Journal of Endocrinology* reinforces the concept that variability of phaeochromocytoma incidence in different parts of the world is, at least partially, due to the impact of physical factors represented by variable partial pressure of oxygen at different altitudes. This would be a translation to population level of the accepted hypoxic signature on cellular and tumoural secretion of catecholamines from phaeochromocytomas.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this letter.

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Figure 1

Metanephrine/normetanephrine ratios in 92 patients with phaeochromocytomas. Filled circles: with necrosis or haemorrhage; open circle: no necrosis and no haemorrhage.

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