

Endocrine Aspects of High Altitude Acclimatization and Acute Mountain Sickness

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Abstract

The acute acclimatization to high altitude is underpinned by a diuresis (and to a lesser extent a natriuresis) that facilitates a reduction in plasma volume. This allows a haemoconcentration to occur that increases the oxygen carrying capacity of a given volume of blood, a vital effect in the presence of a reduced partial pressure of oxygen. This critical acclimatization process is orchestrated by the endocrine system. This review will present the key evidence regarding the changes in several important hormones that affect this process.

Introduction

The exact pathophysiological mechanisms underlying both acclimatization and the development of Acute Mountain Sickness (AMS) are not fully understood and remain under active investigation. Alterations in the hormonal milieu are implicated in both high altitude (HA) acclimatization and AMS. This article presents and reviews the most relevant data regarding the endocrine changes at HA.

Fluid balance in acclimatization and AMS

The most commonly appreciated response to HA exposure is the increase in concentration of haemoglobin mediated by a hypoxia-driven increase in erythropoietin. However, this response takes several days to take effect and lags behind the crucial early changes in fluid homeostasis.

In the acute stages of HA exposure, changes in fluid balance with a marked natriuresis and diuresis are key to initial acclimatization [1, 2]. This process reduces total body water by up to 3 litres and leads to a reduction in plasma volume which increases the concentration of haemoglobin per volume of blood. This effect increases the oxygen carrying capacity of a given volume of blood compared to sea-level and partially compensates for the reduced partial pressure of oxygen that occurs at HA.

A frequently reported feature of AMS reported in the literature is a failure of this diuresis to occur [3-7] highlighting the central importance of fluid balance and the endocrine response to HA in both acclimatization and the pathogenesis of AMS. For that reason, and although other acute changes such as an increase in cardiac output and the hypoxic ventilatory response occur at HA, this review will focus on the endocrine changes occurring at HA relating to fluid balance in the context of acclimatization and AMS.

The Renin-Angiotensin-Aldosterone System

Aldosterone, arginine vasopressin (AVP), and atrial natriuretic peptide (ANP) are the major hormones controlling fluid balance at rest at sea level (SL) whilst contributions from other hormones

such as brain natriuretic peptide (BNP) are more relevant in pathological states such as heart failure. Most workers have demonstrated a reduction in plasma renin activity (PRA) at rest with HA exposure [1,8-12]. In addition a reduced resting plasma aldosterone concentration (PAC) at HA has frequently been recorded [1,10,13,14]. A relatively greater drop in PAC to PRA increases the PRA:PAC ratio and reflects a reduced aldosterone response to renin. This may be partly due to, *in vitro* at least, direct inhibition of aldosterone synthesis in the adrenal cortex by hypoxia [15]. As aldosterone has a primary role in water and sodium reabsorption this reduction in PAC is a beneficial adaptation that facilitates the natriuresis and diuresis required for the initial haemoconcentration to occur. Indeed, it is a relatively consistent finding that if this response does not occur and plasma aldosterone is elevated then this is associated with increased fluid retention and AMS [10,16,17]. It is the significant inter-individual variation in this endocrine response that may underpin the variable susceptibility to both poor acclimatization and AMS.

While variations in the endocrine response to HA at rest are important it is also vital to consider the response to exercise, an omnipresent feature of most trips to HA, if we are to gain a true insight into the pathophysiological mechanisms at play. Exercise at SL is a powerful stimulus for the release of PRA and aldosterone. While exercise at HA still produces a rise in PRA and PAC [13,18-20] the aldosterone response is blunted [1,21,22] and under hypoxaemic conditions there is also dissociation from PRA [23]. The reduced aldosterone response to exercise at HA therefore facilitates a reduction in the exercise-related sodium and fluid retention that may otherwise occur and potentially contribute to AMS and pulmonary interstitial oedema [10, 24]. Indeed a higher resting and exercise stimulated aldosterone at HA (though suppressed compared to sea-level) is associated with AMS and with lower oxygen saturation both before and during exercise [10].

At this juncture it is important to consider that the physiological and endocrine response to HA is both a variable and dynamic response with different responses depending on the duration of HA exposure. It is interesting to note therefore, that resting PRA and aldosterone appear to return to SL values after prolonged HA exposure such as four weeks at an altitude of 5050 m or above [1]. A similar effect has been recorded by other workers with the previously reduced PAC/PRA ratio seen at HA normalized after 20 days [13]. This may be due to the fact that

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increased erythropoietin has increased overall red cell mass and haemoconcentration is no longer the primary means of increasing tissue oxygen delivery. Interestingly the subdued response of PAC to exercise may still persist [25] but there are even data that suggest the PAC response to exercise at HA is more subdued with acute, rather than chronic (14-16 days), exposure [20].

The dual natriuretic peptides of the heart: ANP and BNP

In humans Atrial Natriuretic Peptide (ANP) and Brain Natriuretic Peptide (BNP) constitute the dual natriuretic peptide system of the heart. ANP is known to rise acutely under hypoxic conditions in both animal and human models. ANP is structurally related to BNP (they share a 17-amino acid internal ring) and both hormones have a role in fluid homeostasis, oppose the renin-angiotensin-aldosterone system and are secreted from cardiomyocytes [26]. Isolated rat hearts increase ANP and BNP with an acute (30 minutes) hypoxic exposure [27]. Indeed, even just 10 minutes of hypoxic exposure can induce ANP release in both isolated rat atrial tissue [28] and in anaesthetized rats [29].

In humans ANP has been found to rise acutely after breathing a hypoxic gas mixture (10% oxygen) for only 10 minutes [30] while other human studies have shown a rise in ANP after 30 minutes [31] and 1 hour [32] of hypoxia. As introduced above, exercise-associated changes in hormones at HA are often critical to the process of acclimatization or the development of AMS. One human study found no rise in ANP breathing hypoxic air (11% oxygen) at rest but a significant rise after brief (5 minutes) exercise [33]. While moderate exercise under acute hypoxic conditions induces a rise in ANP [19, 33] it is fascinating that once acclimatization at HA has occurred even exhaustive exercise does not appear to stimulate ANP [20]. It would therefore seem that acute exposure to HA or hypoxia induces a temporary response in the natriuretic peptide ANP to facilitate the diuresis and natriuresis needed to acclimatize initially but that this response accommodates with increased exposure perhaps, as suggested above, as an increase in red cell mass takes precedence. Elevated ANP has also been associated with AMS [9] and high altitude pulmonary odema (HAPE) [34].

The role of BNP, a cardiac hormone related to ANP, has been less thoroughly studied at HA. However, it is also capable of inducing a natriuresis and diuresis (albeit mild) and reducing renin and aldosterone secretion [35], all effects that should be beneficial at HA. BNP also has pulmonary vasorelaxant activity, attenuating acute hypoxic pulmonary vasoconstriction and reducing pulmonary hypertension [31] an effect that could protect against the development of HAPE which is associated with an increase in capillary pressure and pulmonary vasoconstriction [36]. All of these actions make it a likely candidate hormone to be involved in acclimatization.

BNP is stored in cardiomyocytes as proBNP. Once release is stimulated proBNP is cleaved into the active hormone BNP and the inactive peptide NT-proBNP. Although BNP is primarily released secondary to cardiomyocyte stretch [35] it is increasingly appreciated that BNP secretion may also be stimulated by hypoxia. Cultured adult rat cardiomyocytes have demonstrated an increase in BNP mRNA expression after the induction of systemic hypoxia [37], as have rats exposed to hypobaric hypoxia equivalent to an altitude of 5500 metres [38]. Human ventricular myocytes cultured under hypoxic conditions also increase the synthesis and secretion of BNP [39]. Studies in humans have

been less consistent. In one report involving 10 human subjects there was no apparent rise in BNP despite oxygen saturations of 75-80% being induced [40]. To the contrary in a more recent study with humans exposed to acute hypoxia, inducing oxygen saturations (SpO₂) of around 82% over 60 minutes, a 9% rise in NT-pro BNP was reported [41].

Considering these findings, and that there are BNP receptors on the adrenal gland [42] and that BNP causes a reduction in aldosterone secretion from the adrenals [35, 43] (which as discussed above has beneficial effects at HA) it is not surprising that there has been recent investigations regarding BNP at HA. Given that BNP rises with prolonged exercise under normoxic conditions [44] and given the effect of acute hypoxia on ANP, a related peptide, and acute hypoxia on BNP in the laboratory, it would seem likely that HA would lead to a rise in BNP. However, two recent studies have found no increase in BNP or NT-proBNP measured during rest at high altitude. Feddersen and colleagues [45] found no rise in BNP at rest measured the day after arrival at a new altitude with ascent up to 5050 m and SpO₂ of 84.5±1.3%. Similarly, another recent study [46] found no rise in NT-proBNP in 10 healthy subjects at 5200 m. These subjects had ascended to 5200 m by vehicle following a 5 day acclimatization period at 3650 m. Samples were again taken at rest with a mean SpO₂ on the day of sampling of 77.6% i.e. lower than that associated with a rise in NT-proBNP with acute hypoxia [41].

Moderate exercise at SL is generally not associated with a rise in BNP or NT-proBNP [47-49] and neither is high intensity short duration exercise [44]. However, prolonged endurance exercise at SL such as running an ultramarathon [44, 50] or prolonged cycling [51] may cause a rise in BNP or NT-proBNP. It is notable that NT-pro BNP levels measured the day after intense cycling have returned to baseline pre-exercise levels [51], a fact that could explain the negative findings of Feddersen and colleagues [45] at HA. Similarly, the acclimatization at 3650 m followed by vehicular ascent to 5200 m with samples taken at rest the next day could explain the findings of Toshner and colleagues [46].

As alluded to above changes in hormones following exercise at HA and not simply at rest are often crucial to acclimatization and the development or otherwise of AMS. Hence, any effect of HA on BNP needs to be evaluated following exercise. This is currently under investigation on Defence Medical Services (DMS) HA expeditions.

Vasopressin

Vasopressin (AVP) is the key hormone involved in reducing free water excretion at the kidney and is crucial in determining fluid balance at SL. Normally at SL a rise in osmolality or a marked decrease in plasma volume would lead to a rise in AVP secretion from the posterior pituitary and a reduction in free water loss at the kidney thereby maintaining osmolality. The response of AVP to HA is controversial.

Plasma osmolality rises at HA, secondary to the diuresis that has been discussed above [12,52-54]. Despite this, and somewhat paradoxically, most of the literature reports no accompanying rise in AVP in the normal process of acclimatization. In the presence of a documented rise in osmolality from 291 mosmol/kgH₂O at SL to 299 mosmol/kgH₂O at 4300m (after two days) and 302 (after 20 days) plasma AVP did not change [52]. Another report demonstrated a rise in osmolality from 290 mosmol/kgH₂O to 295 mosmol/kgH₂O at 5400m and 302 at 6300m (with an average 26.5 days above 5400m) with no accompanying rise in AVP [53,

54]. Such evidence suggests a reset osmotic threshold for AVP release that again facilitates the diuretic process at HA that allows a reduction in plasma volume and hence increase in oxygen carrying capacity of a given volume of blood. Other studies support the notion that at HA a given vasopressin concentration requires a higher osmolality compared with SL. Bestle and colleagues [12] found that over eight days at 4559m AVP was suppressed compared to SL despite an increase in plasma osmolality from 291 mosmol/kgH₂O to 296 mosmol/kgH₂O associated with a reduced urine volume in the first two days. These subjects were transported to this altitude and all had AMS on arrival. Some studies have even found a reduction in AVP on acute exposure to moderate altitude (2000m) [55]. Interestingly, high-altitude natives (2,600 m) have a greater resting AVP than sea-level natives [56], again suggesting a dynamic hormonal response dependent on length of HA exposure.

One study has gone further and examined the AVP response to water deprivation (which would normally stimulate a rise in AVP) at HA. The response to water deprivation appears to remain intact at HA. A 24 hr water deprivation test (WDT) with acute altitude exposure (day 2 at 4300m) and prolonged altitude exposure (day 20 at 4300m) still caused a rise in AVP in response to a rise in osmolality [52]. Interestingly though the rise in AVP with acute altitude exposure peaked at 16 hours and then fell to baseline during WDT but persistently rose throughout WDT after prolonged altitude exposure. Further the increase in AVP to higher osmolalities (>300 mosmol/kgH₂O) was greater after more prolonged exposure, again reflecting a change in the relationship between AVP and osmolality dependent on acclimatization. This may reflect the greater osmolality achieved in the latter WDT but could also reflect a dynamic change in AVP response to plasma osmolality according to acclimatization. In other words, despite the WDT inducing an acute rise in AVP the AVP response is "capped" with acute altitude exposure to restrict water retention. However, with further acclimatization this effect is lost, presumably because the desperate need to reduce plasma volume to maintain oxygen delivery per given volume of blood has been overridden by other factors, such as a primary increase in red cell mass. Although it is suggested that plasma volume re-expands with chronic exposure to HA the osmolality in this study was 291 mosmol/kgH₂O, 299 mosmol/kgH₂O and 302 mosmol/kgH₂O at SL, Day 2 and Day 20 respectively. Rather than a re-expansion of plasma volume with prolonged exposure there may simply be a levelling off once initial acclimatization has occurred.

Similar to the renin-angiotensin-aldosterone system, AVP has also been implicated in AMS [10, 14, 16, 53, 54]. With acute (8-12hr) exposure to a simulated 4880m altitude, subjects with high AMS scores (n=16) versus those with low AMS scores (n=16) demonstrated a rise in AVP at rest within 90 minutes of exposure. This was followed by a reduced urine output within three hours and subsequent fluid retention. In those subjects with AMS a positive fluid balance of 1.2 litres was recorded versus a negative balance of 0.7 litres in those without AMS. The low AMS score subjects with the negative fluid balance appear likely to be due to the fall in AVP that was recorded in those subjects [14]. These findings are very supportive of the central role an early diuresis has in acclimatization, albeit in a very acute setting, and the influence the AVP response has is critical to this. Earlier evidence is supportive of this concept: a more pronounced AVP response

in subjects with AMS symptoms after 3-4 h of simulated HA has previously been recorded [57]; and a tendency for higher AVP in HAPE sufferers versus controls has also been suggested [34].

As we have considered previously, the AVP response to exercise may also be important. Indeed AVP increases with exercise at altitude [10, 58] and may contribute to water retention. Again, this effect may have pathological consequences: 30 minutes of exercise on arrival at HA (4559 m) induces a greater rise in AVP in those with AMS than those without [10].

Cortisol

Cortisol is released from the adrenal gland under the control of ACTH and is a stress hormone that may contribute to fluid retention if elevated. The natriuretic peptides are also specifically involved in the regulation of the hypothalamic-pituitary-adrenocortical (HPA) system with ANP inhibiting the HPA system at all regulatory levels. There is also a strong correlation between aldosterone and cortisol at HA [22] and BNP is known to inhibit production of both hormones [26].

Most workers have found a rise in cortisol at rest at HA [1,59-65] although not necessarily on Day 1: Smith et al reported no rise in salivary cortisol at 4300m compared to SL initially but a steady increase peaking at Day 7 [66]. A further rise in cortisol at HA may also occur following relatively short duration maximal exercise at 5050 m [1]. Not all workers have found this rise in cortisol at HA [22, 67, 68] especially after prolonged residence [69]. Indeed Maher et al [18] found no change in resting cortisol levels between SL and 4300m with no rise following moderate exercise. Although a reduction in cortisol compared to SL has been reported at 4450m [22] at rest the same workers reported a rise in cortisol following 25 minutes of exercise. With a prolonged sojourn of over two months at an altitude of 5200m or over, no change in cortisol or ACTH compared to SL was found after an attempt to climb Everest with climbers reaching altitudes of between 7500-8852m [68]. This return to baseline of cortisol with prolonged exposure is supported by others who found an initial rise in resting cortisol maintained on Day 21 at 3500m which returned to SL values by Day 30, at 5080 m [60].

Again therefore, in parallel to the hormone systems discussed above, the response of cortisol to HA exposure is a dynamic one influenced both by duration of exposure and exertion. It would therefore seem appropriate that, as before, variations in cortisol response may have a pathological influence on AMS development. Indeed, AMS is a physiological stress. As such an elevated cortisol has been positively correlated with AMS scores [62]. Cortisol has also been noted to be highest in those with more severe AMS although the numbers involved (n=3) are insufficient on which to base any sound conclusion [59].

Conclusion

We have therefore seen how the acute response to HA is a diuresis (and to a lesser extent a natriuresis) that allows a reduction in plasma volume and haemoconcentration which therefore facilitates oxygen delivery in the presence of a reduced partial pressure of oxygen. This is a crucial process in initial acclimatization. It is driven by the endocrine system with changes in the renin-angiotensin-aldosterone system and the natriuretic peptide system facilitated by a somewhat subdued AVP response, all working apparently synchronously. It is a dynamic process, influenced by exercise and HA duration, in each of the hormone systems described. Failure to mount an appropriate response at

the appropriate time, including that to an exercise stimulus, may have pathological consequences in the development of AMS. With chronic HA exposure these responses seem less pivotal to acclimatization, perhaps as other acclimatization processes such as an increase in red cell mass become predominant. The research challenges for the future lie in exploring these changes in more detail, evaluating how to utilize the changes to predict AMS, and then evolving management strategies to improve acclimatization and reduce AMS.

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