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REVIEW

The sex difference in haemoglobin levels in adults — Mechanisms, causes, and consequences

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ABSTRACT

Men and women have different mean haemoglobin levels in health in venous blood — women have mean levels approximately 12% lower than men. A similar sex-related difference in haemoglobin levels in adult animals is found in many species of mammals, birds and reptiles, indicating that it is an important physiological phenomenon. It is probably a direct effect of sex hormones, both oestrogen and androgens, on erythropoiesis. However, since there is no difference in erythropoietin levels between the sexes, this effect most likely takes place in the kidney, rather than in the bone marrow. Oestrogens dilate and androgens constrict the renal microvasculature: dilation and vasoconstriction in vessels below 300 μm in diameter respectively increase and decrease the haematocrit in blood in arterioles, capillaries and venules, altering the oxygen delivery per unit red cell mass, and providing a mechanism for varying the red cell mass without compensatory changes in erythropoiesis.

1. Introduction

The long phylogenetic history of the sex difference in haemoglobin levels in vertebrates indicates that males and females evolved different mean venous haemoglobin levels for different purposes, or under different selection pressures. How and why these differences are maintained, and their relevance in medical practice, have not been fully defined to date, and are the subjects of this review.

Adult men and adult women have different haemoglobin levels in health [1–4]. This sex difference is independent of iron status — iron replete premenopausal women have mean haemoglobin levels approximately 12% lower than age & race matched men [1,4]. The mean circulating erythropoietin (Epo) level does not differ between men and women, and in women does not differ between pre and postmenopausal women [5,6], indicating that the sex difference is constitutive, and that women do not attempt to achieve male levels in health [5,7]. The sex difference in adult haemoglobin levels is conserved throughout *Mammalia* — a higher adult male haemoglobin level occurs in almost all mammal species studied to date, including non-menstruating and non-placental species: chimpanzees [8], rhesus macaques [9], vervet [10], cynomolgus [11] & capuchin monkeys [12], baboons [13], rodents [14], dogs [15], marsupials & monotremes [16], and in seals [17]. It also occurs in adults in many bird species [18], and in at least some reptiles at some stages of reproduction [19]. Whether the phenomenon occurs even further back in phylogenetics remains to be determined, but it is an ancient or recurring feature in evolution, which raises profound questions of what its importance may be.

A sex difference in haemoglobin levels has not been reported in juveniles in any species of mammal, bird or reptile: after the onset of adulthood male mammals and birds diverge from the juvenile state, raising their haemoglobin level by several percentage points. Females also increase their haemoglobin levels above the juvenile level, but not to the same extent as males.

2. Mechanisms producing the sex difference in venous haemoglobin levels in adult animals

In general, in healthy humans, the venous haemoglobin level correlates to a modest extent with the red cell mass, though the correlation is different for adult men and women, as discussed extensively below. The two values are determined by largely by the same factors (the tissue demand for oxygen determined at the juxtaglomerular apparatus), but are subject to some independent modulators — genetic and physiological, and are not directly interdependent. The physiological factors may be constitutive or chronic, such as puberty and menopause, acclimatisation to altitude, level of fitness or lean body mass, or acute such as posture or level of hydration. This lack of precise correlation exists both for individuals and for populations. Thus while red cell mass is on average lower per unit mass of tissue in females, the red cell mass in individuals in either sex cannot be estimated precisely from the venous haemoglobin level. Nevertheless for most clinical purposes venous

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haemoglobin levels can be used to imply red cell mass in individual patients, although the imprecision in this approach becomes apparent in the management of the apparent polycythaemia of chronic hypoxic lung or cardiac disease.

The haematocrit in healthy individuals varies predictably with the haemoglobin content of the blood it is measured in, and can be used interchangeably with haemoglobin level to compare the same value in populations of healthy individuals, and within individuals over short periods of measurement, though not reliably outside that.

The sex difference in mean venous haemoglobin levels and red cell mass is generally considered to be caused by a direct stimulatory effect of androgen in men in the bone marrow in association with erythropoietin, a stimulatory effect of androgen on erythropoietin production in the kidney, and an inhibitory effect of oestrogen on the bone marrow in women [20,21]. These effects have been demonstrated in vitro [22–24], and also work directly in vivo — androgens raise the haemoglobin level in males and females [25–29], and oestrogen lowers it [24,30]. However these direct and indirect effects of sex hormones on either marrow erythropoiesis or renal production of erythropoietin do not account for the absence of increased erythropoietic drive in females in response to their lower mean haemoglobin levels [5,7]. Testosterone in male animals may enable them to reach a desirable haemoglobin level more easily because of the synergistic effect of androgen on the bone marrow, with for example, a lower JGA mass. However this does not explain why females would not achieve the same effect in some other way, should there be an advantage in doing so. Females – adult human females at least – can raise their venous haemoglobin levels in response to additional erythropoietic stimuli. Andean women have higher haemoglobin levels at altitude than women of the same ethnicity living at lower levels, while preserving the sex difference with males at the same altitude, as do Tibetan women living at very high altitudes [31,32]. Female athletes can elevate their haemoglobin levels in response to exogenous rhuEPO in a manner similar to males [33,34]. Men, premenopausal women and postmenopausal women have similar plasma erythropoietin levels [5], indicating that women do not attempt to compensate for their lower haemoglobin levels by increasing erythropoietic drive. These observations show that the prevailing lower haemoglobin level in females cannot be ascribed to a lack of bone marrow or renal erythropoietic capability: they indicate that adult females maintain their venous haemoglobin levels at a lower level than adult males as a physiological steady state — they do not try under physiological conditions to maintain the same levels as adult males. Of course these factors may also indicate that males set their physiological haemoglobin levels higher than females, or rather that both sexes set their mean optimum level separately and to some degree independently. Anephric patients and patients with end stage renal failure do not exhibit a sex difference in baseline haemoglobin levels [35] demonstrating that the sex difference is mediated largely at the level of the kidney, rather than by direct erythropoietic action in the bone marrow. In addition, anephric patients did not have an erythropoietic response to therapeutic doses of androgens in a prospective randomised clinical trial of 103 men and 40 women, that included 15 patients who had undergone bilateral nephrectomy [36]. Perhaps it would be surprising if this were not the case, since the red cell mass itself is determined at the level of the kidney, and not at the level of the bone marrow.

It is hardly surprising that reptiles, birds and mammals have evolved different optimum levels of red cell mass and haemoglobin levels for males and females: red cells constitute a huge biological resource – one third by number of the body's cell complement, and with a relatively high turnover – that imposes enormous demands on the organism. Different drivers in males, such as competition for mates, and in females, such as parturition, could well have determined independent optimum investment in red cell mass in the sexes over the long course of vertebrate evolution. Huge phenotypic differences have existed between the sexes since the emergence of complex life forms — different venous haemoglobin levels evolved for different purposes would hardly be revolutionary. Indeed an absence of independently evolved haemoglobin levels might be more puzzling given the profound differences in the ecology and physiology of the sexes.

Erythropoietic drive in the intact adult animal is determined in very large part by the delivery of oxygen to the juxtaglomerular apparatus (JGA) of the kidney. Other mechanisms also play a part — including a baseline marrow erythroid activity that maintains a haemoglobin level around 70 g/L in anephric patients [35,37], a direct erythropoietic effect on the marrow of angiotensin II [38], and a modulation of oxygen consumption at the JGA by glomerular function [39]. Women with end stage renal disease are Epo resistant compared to age-matched males with end stage renal disease, requiring greater doses of Epo to achieve the same (sub-physiologic) haemoglobin level, consistent with the synergistic effect of androgen on erythropoietic dynamics in the bone marrow [40]. This however emphasises that females could achieve the same levels of haemoglobin by increasing Epo production — they "choose" not to, for whatever reason. Modulation of the JGA erythropoietic response to the level of red cell mass is the probable cause of the sex difference in haemoglobin levels, since as explained above, there is no compensatory response on the part of the JGA to the constitutively lower levels in healthy adult females.

The JGA could respond differently to the same total body red cell mass through several different mechanisms acting either singly or together. Red cells in adult females could deliver more oxygen per cell than in adult males. While there are subtle sex differences in red cells [41–44], a difference in oxygen dissociation has not been shown to exist, so that a difference in oxygen unloading is unlikely to account for the effect. However differences in flow dynamics in small arterioles caused by sex-related red cell differences remain possible. In addition the ability of the microvasculature to transfer oxygen from red cells to the tissues may differ between the sexes at the JGA. For example, sex differences in microvascular wall function, independent from vasodilation, that would allow females to deliver more oxygen per unit red cell mass than males to the cells of the JGA may exist, but have been not been reported to date. In addition, sex differences may exist in the molecular pathways of oxygen response in the kidney. While these effects cannot be ruled out, there are separate lines of evidence for a sex difference in blood flow in the microvasculature: a) adult females have a higher total body haematocrit than males at the same mean venous haemoglobin level; b) adult females have a higher mean microvascular haemoglobin level in the finger pulp for each value of venous haemoglobin level. A sex difference in microvascular blood flow provides a mechanism for differences in haemoglobin levels in adults, through modulation of the signal received at the JGA at a given level of red cell mass.

2.1. The Fåhraeus effect

Over eighty years ago Robin Fåhraeus observed a fall in the haematocrit of blood flowing into narrowing tubes below 300 μm in diameter [45]. The mean haematocrit in blood vessels below this size varies in proportion to the mean diameter of the vessels [46–49] (Fig. 1). In microvascular networks this effect is augmented by a separate differential segregation of red cells and plasma at vessel bifurcations. The net effect is that blood flowing through the microvasculature has a lower unit red cell content than blood in the larger veins and arteries, and that the haematocrit at a given point in a blood vessel is affected by the diameter of the vessel at that point.

A necessary consequence of the reduction in red cell content in the blood of the microvasculature is that the whole body haematocrit, determined by the simultaneous measurement of red cell mass and plasma volume, is less than the venous haematocrit. This was initially recorded by Chaplin et al. [50], who found that the mean whole body haematocrit was 10% lower than that of the venous blood, using simultaneous measurement of red cell mass by ^{51}chromium, and plasma