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Influence of gender and endogenous sex steroids on catecholaminergic structures involved in physiological adaptation to hypoxia

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Abstract Mechanisms underlying sex-related differences in adaptation to high altitude were investigated by assessing the turnover of dopamine and noradrenaline in structures of the chemoafferent pathway, i.e. carotid body and brainstem noradrenergic cell groups (A_1, A_5, A_6, A_2 to which chemosensory fibres project). The influence of gender was assessed in male and female rats reared at an altitude of 3600 m, whereas the influence of endogenous sex hormones was evaluated by castration. Haematocrit, red blood cell count and plasma erythropoietin levels were lower in females than in males (–5%, –15%, –53%, respectively). Dopamine and noradrenaline turnover were higher in female structures (carotid body: +51%; A_2: +140%; A_1: +54%; A_5: +27%). Dopamine and noradrenaline turnover in carotid body and brainstem cell groups were differently affected by castration, i.e. enhanced by orchidectomy (carotid body: +134%; A_2: +120%; A_1: +69%; A_5: +67%) but inhibited by ovariectomy (carotid body: –33%; A_2: –92%). Orchidectomy elicited a reduction in haematocrit (–10%), haemoglobin concentration (–8%) and red blood cell count (–24%), whereas haematological status remained unaltered after ovariectomy. Therefore, both gender and endogenous sex steroids may control catecholamine activity differently in structures involved in the chemoafferent pathway, thus providing a neurochemical basis for sex-related differences in adaptation to hypoxia.

Key words Carotid body · Chemoreceptor pathway · Nucleus tractus solitarius · Noradrenergic brainstem cell groups · Dopamine · Polycythaemia · Acclimatization to altitude

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Introduction

Several studies have shown gender-related differences in the susceptibility to hypoxia in humans [1] and in various species including swine [19], mouse [32] and rat [23]. The mortality rates and the pathophysiological processes developed during exposure to hypoxia, i.e. polycythaemia, pulmonary hypertension, right ventricular hypertrophy and hypoxaemia, are less marked in females than in males. Female sex hormones are thought to contribute to the higher resistance of females to hypoxia because they can suppress the polycythaemic and cardiopulmonary responses to long-term hypoxic exposure in rats [23]. The mechanisms underlying the facilitatory effects of ovarian steroids on adaptation to hypoxia have not been elucidated. The ovarian steroids are potent ventilatory stimulants [30] and it is possible that they reduce erythropoeitin (EPO) production by improving tissue oxygenation. More recently, Hannhart et al. [10] found that the female hormone progesterone, particularly when combined with oestrogen, raises ventilation and hypoxic ventilatory responsiveness by a combination of peripheral (carotid body) and unidentified central sites of action.

The carotid body chemosensory afferents terminate within the nucleus tractus solitarius (NTS), caudal to the obex, in a discrete region that contains noradrenergic neurons belonging to the caudal portion of the A_2 cell group [13, 31]. The noradrenergic A_2 neurons are adjacent to the dorsal respiratory group. In addition, noradrenergic neurons located in the ventrolateral medulla, an area that is reciprocally connected with the NTS, constitute the A_1 cell group and are intricate with neurons of the ventral respiratory group. The neural activity of both cell groups can be altered by exposure to hypoxia [27, 29, 31]. Other medullary noradrenergic cell groups, the locus coeruleus (A_6) and A_5 in the pons medulla are reciprocally connected with the NTS and are also affected by carotid chemoreceptor stimulation [9, 31]. At least during long-term exposure to moderate hypoxia, the changes in neural activity within brainstem noradrenergic cell groups are dependent on intact chemoafferents [31].

The medullary noradrenergic regions play a key role in integrating a variety of reflex inputs and participate in the regulation of sympathetic outflow, arousal, respiratory, cardiovascular and neuroendocrine functions. A role in ventilatory acclimatization to hypoxia has been assigned to catecholamines released from the carotid body and medullary cell groups [29, 35] as neurotransmitters involved in the modulation of peripheral arterial chemosensitivity, integration of chemosensory inputs and regulation of the central respiratory rhythm-generating network [3, 6, 12, 33]. It is thus reasonable to hypothesize that brainstem noradrenaline -containing neurons are part of a network involved in the chemoreflex responses to hypoxia.

The brainstem noradrenergic cell groups contain oestrogen receptors and, thus, are targets for female sex hormones [11]. Accordingly, one possible mechanism by which female sex hormones alter hypoxic ventilatory responsiveness could involve changes in the neural activity of peripheral and central structures participating in the chemoafferent pathway. The first aim of this study was to evaluate the putative influence of gender on the chemoreflex pathway in rats exposed to chronic hypoxia. For this purpose, we compared the catecholamine (dopamine: DA, noradrenaline: NE) activity of the carotid chemoreceptors and brainstem noradrenergic cell groups (A_1, A_2, A_5 and A_6: locus coeruleus) in males and females. Secondly, we evaluated the influence of endogenous sex steroid removal by castration on catecholamine activity in those organs. The study was performed using adult, intact and neutered male and female rats chronically exposed to high altitude from birth.

Materials and methods

Animal care

The study was carried out at the Instituto Boliviano de Biologia de Altura (La Paz, Bolivia; mean altitude=3600 m; PB≈66.7 kPa or 500 mmHg). Sprague-Dawley rats, bred at altitude for at least four generations, were housed in a climatized room (24 ± 1°C) with a 12-h light–dark cycle and allowed free access to food and water. All experiments were carried out in accordance with the ethical principles laid down by the French (Ministère de l'Agriculture) and EU Council Directives for care of laboratory animals. A total of 100 rats (50 females and 50 males) were submitted to the experimental protocol. They were reared in La Paz without any treatment until weaning (3 weeks of age). At this age, males and females were segregated and half of them (25 males and 25 females) were castrated under halothane (2% in O_2) anaesthesia.

Determination of catecholamine turnover

Rats were sacrificed by cervical dislocation at 12 weeks of age. The carotid bodies and the brain were rapidly removed, frozen in liquid nitrogen and stored at –80°C. The brainstem was cut into serial frontal slices 480 µm in thickness. The noradrenergic cell groups A_1, A_2, A_5 and A_6 were punched out according to the dissection procedure described by Soulier et al. [31]. In order to separate the area receiving chemosensory inputs from the area to which barosensory fibres project [13], the A_2 cell group was divided into two portions, respectively caudal (A_{2C}) and rostral (A_{2R}) to the calamus scriptorius [31].Tissue samples were placed in 100 µl of 0.4 M (punches) or 0.1 M (carotid bodies) perchloric acid containing 2.7 mM ethylenediaminetetraacetic acid (EDTA). In punch samples, the excess perchloric acid was removed by addition of 8 µl of 6.4 M potassium formiate to the supernatant. Catecholamines were assayed by high-performance liquid chromatography coupled with electrochemical detection [31].

α-Methyl-para-tyrosine (α-MPT, Sigma, St Quentin Fallavier, France), injected twice intraperitoneally at a dose of 250 mg kg^{-1}, 4 and 2 h before sacrifice, allowed determination of catecholamine turnover by blocking catecholamine biosynthesis. Each experimental group (n=25) was divided into two subgroups, one receiving α-MPT and the other receiving the corresponding volume of vehicle alone (0.9% NaCl), and the catecholamine (DA and NE in the carotid body, NE in the brainstem cell groups) content in these groups measured. After injection of α-MPT, the level of catecholamines decreased exponentially. After semiexponential linear regression, the rate of decrease of the catecholamine content was determined and was then multiplied by the respective mean amine content of saline-treated rats in order to obtain the turnover rate [29].

Catecholamine content and turnover are specific markers of the catecholaminergic systems and the conditions of punching removal and carotid body dissection correspond to a dissection by excess, including all catecholamine-synthesizing cells of the structure. Thus, the expression of catecholamine turnover per structure is more descriptive of the absolute value of monoamine activity in catecholaminergic tissues, which is independent of surrounding non-catecholaminergic tissue punched out together with the brainstem cell groups or that belonging to the carotid body organ. On the other hand, the total protein content and structure mass can fluctuate unspecifically in physiological conditions. Accordingly, the expression of the catecholamine activity per structure is more adequate than expression of results per milligram of protein or milligram of tissue, in order to avoid artefactual variations of the catecholamine turnover following modifications of total protein levels in the structure.

Haematological status

Using the blood obtained by exsanguination, the haematocrit (Hct) was measured by a microtechnique method. The haemoglobin concentration, [Hb], was determined by using a kit (525A-Sigma), the red blood cell (RBC) count was evaluated using standard Thoma pipettes and Hayem's solution as the diluting fluid. Plasma EPO concentration was determined by radioimmunoassay with a standard kit (Biomérieux, France).

Statistics

All the values reported are means ± SEM. For statistical comparisons of group means, a two-way ANOVA was used followed by a post-hoc test (Protected Least Significant Difference of Fisher). The level of significance was set at 5%. The turnover rates of catecholamines were compared using Dunnett's test for the comparisons of several means to the corresponding values for one set of control conditions.

Results

Influence of gender

The catecholaminergic activity in carotid body, as assessed by NE ($[NE]_{TO}$) and DA ($[DA]_{TO}$) turnover, was significantly higher in female than in male rats ($[NE]_{TO}$: +333%; $[DA]_{TO}$: +51%; Table 1). A higher noradrenergic activity was also evident in the A_2 cell group (caudal and

Table 1 Noradrenaline *([NE]$_{TO}$)* and dopamine *([DA]$_{TO}$)* turnover in the carotid body and noradrenergic brainstem cell groups in male and female intact rats. Results are means±SEM from 12 animals in each group. (A_{2C} Caudal A_2 subset, A_{2R} rostral A_2 subset)

* Significantly different from intact males

Cell group	Intact males		Intact females	
	$[NE]_{TO}$ (pmol · structure^{-1} · h^{-1})	$[DA]_{TO}$	$[NE]_{TO}$ (pmol · structure^{-1} · h^{-1})	$[DA]_{TO}$
Carotid body	25.4±4.4	42.4±3.7	110.0±19.5*	64.2±12.8*
Noradrenergic brainstem cell groups:				
A_{2C}	1.0±0.1	–	2.4±0.2*	–
A_{2R}	1.2±0.1	–	2.2±0.3*	–
A_1	1.3±0.1	–	2.0±0.1*	–
A_5	1.5±0.1	–	1.9±0.2*	–
A_6	3.8±0.5	–	3.8±0.4	–

Table 2 Haematological parameters in male and female rats either intact or castrated. Results are means±SEM. No. of animals in *parentheses.* (*Hc* Haematocrit, *[Hb]* haemoglobin concentration, *RBC* red blood cell count, *EPO* plasma erythropoietin level)

Parameter	Intact males	Orchidectomized males	Inntact females	Ovariectomized females
Hct (%)	58.0±0.7 (24)	52.2±0.7** (22)	54.9±1.7* (22)	54.7±0.8* (22)
[Hb] (g · dl^{-1})	18.1±0.4 (24)	16.7±0.2** (22)	17.4±0.7 (21)	17.2±0.2 (22)
RBC (10^{-6})	11.2±0.55 (24)	8.47±0.11** (22)	9.52±0.49* (20)	8.70±0.16* (22)
EPO (mU · ml^{-1})	10.4±2.0 (12)	10.4±1.4 (10)	4.9±0.8* (12)	6.1±1.0*** (10)

* Significantly different from intact males, ** significantly different from intact counterparts; *** significantly different from orchidectomized males

Table 3 $[NE]_{TO}$ and $[DA]_{TO}$ in the carotid body and noradrenergic brainstem cell groups in male and female castrated rats. Results are means±SEM from 12 animals in each group. (A_{2C} caudal A_2 subset, A_{2R} rostral A_2 subset)

* Significantly different from intact animals (data shown in Table 1); ** significantly different from orchidectomized males

Cell group	Orchidectomized males		Ovariectomized females	
	$[NE]_{TO}$ (pmol · structure^{-1} · h^{-1})	$[DA]_{TO}$	$[NE]_{TO}$ (pmol · structure^{-1} · h^{-1})	$[DA]_{TO}$
Carotid body	50.7±9.1*	99.3±8.3*	≈0*, **	42.9±5.4*, **
Noradrenergic brainstem cell groups:				
A_{2C}	2.2±0.3*	–	0.2±0.1*, **	–
A_{2R}	2.7±0.3*	–	2.8±0.2	–
A_1	2.2±0.1	–	1.5±0.1**	–
A_5	2.5±0.2*	–	1.4±0.1**	–
A_6	4.4±0.7	–	6.4±0.7*	–

rostral portions – A_{2C} and A_{2R}: +140%, and +83%, respectively) and in other brainstem cell groups (A_1, A_5: +54% and +27%, respectively) but not in the locus coeruleus (A_6) (Table 1).

The haematological status of female rats was distinct from that of males. Thus, Hct, RBC and plasma EPO levels were significantly lower in females than in males (–5%, –15% and –53%, respectively, female rats versus male rats; Table 2).

Influence of castration

As a whole, orchidectomy induced a marked increase in the catecholamine turnover in the carotid body ($[NE]_{TO}$: +100%; $[DA]_{TO}$: +134%; Table 1), in the A_2 noradrenergic cell group (A_{2C}: +120%; A_{2R}: +125%) within the NTS, and in the A_1, A_5 brainstem cell groups (+69% and +67%, respectively; Table 3, Fig. 1). Similar but insignificant changes were noted for A_6 (Table 3, Fig. 1).

As compared to orchidectomized rats, ovariectomized rats displayed various kinds of neurochemical alterations. Firstly, castration had an opposite effect in females and males in structures primarily implicated in the chemoafferent pathway, i.e. the carotid body and the caudal A_2 subset (A_{2C}). In these structures, ovariectomy inhibited the catecholamine turnover ($[NE]_{TO}$: –100%, and $[DA]_{TO}$: –33% in the carotid body; $[NE]_{TO}$: –92% in A_{2C}; Table 3, Fig. 1). In contrast, ovariectomized females displayed a higher rate of NE turnover than the intact females in the A_6 cell group (+68%). Finally, ovariectomy failed to alter $[NE]_{TO}$ in the rostral A_2 subset (A_{2R}), the A_1 and A_5 cell groups (Table 3, Fig. 1). The catecholamine turnover in several structures, including the carotid body, the caudal A_2 subset, the A_1 and A_5 cell groups, was significantly lower in ovariectomized females than in orchidectomized males ($[NE]_{TO}$: –100%, $[DA]_{TO}$: –57% in the carotid body; $[NE]_{TO}$: –91%, –32%, and –44% in A_{2C}, A_1 and A_5, respectively; ovariectomized females versus orchidectomized males; Table 3).

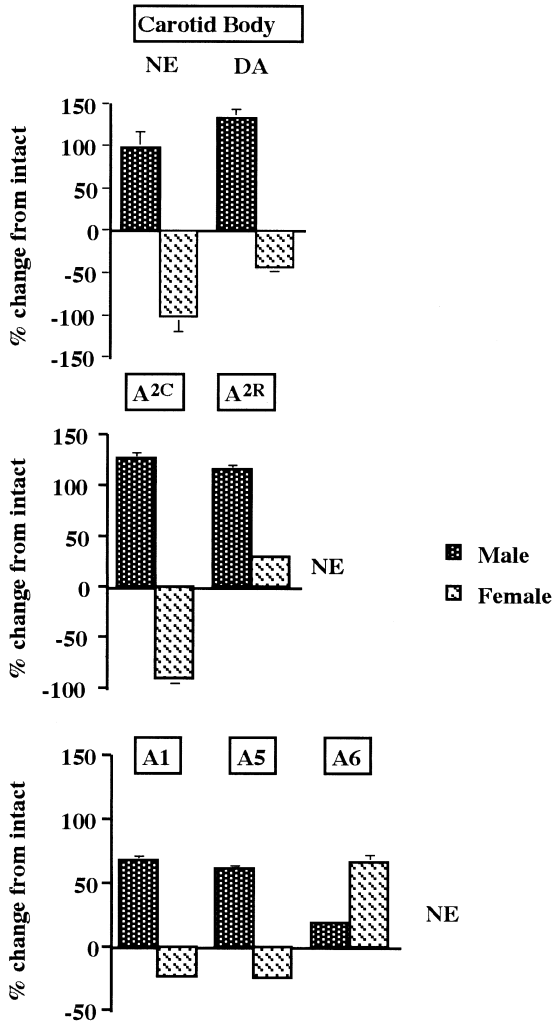

Fig. 1 Castration-induced changes in turnover rate of dopamine (*DA*) and noradrenaline (*NE*) in the carotid body, and of *NE* in brainstem noradrenergic cell groups (A_2 subdivided into caudal and rostral subsets, respectively, A_{2C} and A_{2R}, A_1, A_5 and A_6, locus coeruleus) in male and female rats. Data are expressed as % variations above or below the level of intact male and female rats corresponding to baseline. Results are means ± SEM. * Significantly different from intact animals

Orchidectomy was characterized by a significant decrease in Hct (–10%), [Hb] (–8%) and RBC (–24%) without any change in plasma EPO levels. All haematological parameters remained unaltered after ovariectomy (Table 2).

Discussion

Neurochemical studies

Long-term or chronic hypoxia induces haematological changes, the magnitudes of which are related to gender [23]. The female rats born and reared in La Paz (3600 m) developed a lesser polycythaemia than did their male counterparts, probably due in part to a lower erythropoiesis because sex differences in EPO levels were noted. Because ovarian steroids are potent chemosensory stimulants, we hypothesized that sex-related differences in acclimatization to hypoxia could be related to alterations of the chemoreceptor pathway leading to enhanced ventilatory responsiveness [10] and subsequent improved tissue oxygenation. Our study demonstrates that in areas involved in the chemoafferent circuitry the rate of catecholamine turnover, an index of neuronal activity, differed between male and female rats living under conditions of chronic hypoxia. Castration modified the catecholaminergic activity in the two groups, thereby showing that gonadal steroids may control the catecholamine metabolism in the carotid body and in central areas integrating chemosensory inputs.

Sex-related differences in catecholamine distribution and release have long been described to occur either under basal conditions or in response to acute stress [4, 7, 18]. Noticeably, the present data were obtained under stimulation of the chemoreflex pathway by chronic hypoxia, a situation expected to enhance neural differences that could be not detected under basal normoxic conditions. Indeed, although sex hormones are able to alter resting ventilation, it has been previously reported that no gender-related differences in ventilation could be evidenced under normoxic conditions [34]. The stimulus employed here was chronic hypoxia and not acute hypoxia because the primary aim was to look for adaptive mechanisms involved in the hypoxia-induced polycythaemia that develops under long-term exposure.

Ovarian steroids can modulate noradrenergic and dopaminergic neurotransmission in the central nervous system by altering the catecholamine biosynthesis and thereby the amount of neurotransmitter available for release [7, 24]. Gonadal steroids are able to modify the activity of tyrosine hydroxylase, the rate-limiting enzyme in catecholamine biosynthesis, and this effect may be manifest at the gene level [24, 26]. A further mechanism involved in modulation of catecholamine release lies in the capacity of oestrogen to inhibit the extraneuronal uptake of catecholamines and their catabolism by catechol-*O*-methyl-transferase [18]. In all but a few studies, the central influence of sex steroids was investigated in hypothalamic nuclei and pathways. However, a report by Liaw et al. [16] indicated that orchidectomy or oestrogen treatment in castrated males can modify the expression of tyrosine hydroxylase at the gene level in noradrenergic cell groups of the brainstem. The present studies confirm and extend the latter findings by showing gender-related differences in NE turnover in these central discrete areas and in the carotid bodies. The influence of sex hormones on catecholamine metabolism has been related to their action on specific receptors. Many catecholaminergic neurons are targets for ovarian sex steroids, in particular in the NTS (A_2 cell group), the caudal ventrolateral medulla (A_1) and the pons medulla (A_5 and A_6) [11]. Specific receptors for testosterone are also located in most brainstem noradrenergic cell groups except for the A_1 and A_2 noradrenergic cell bodies [11]. However, the

androgen metabolite 17β-oestradiol formed within brain cells may be one active agent in these areas.

In order to define the respective influence of male and female sex hormones, the rats were neutered and, clearly, removal of hormone production by orchidectomy or ovariectomy elicited distinct alterations of the catecholamine turnover in the carotid body and discrete brainstem areas. The overall effect of orchidectomy was an enhanced catecholaminergic activity, suggesting that testosterone can inhibit the neuronal activity in every region examined here. On the other hand, ovariectomy produced distinct neurochemical responses that differed according to the structure. The influence of ovariectomy was restricted to certain noradrenergic cell groups. In contrast to orchidectomy, ovariectomy inhibited the catecholamine turnover in structures involved in the primary chemoafferent pathway, i.e. the carotid body and the caudal portion of the A_2 cell group, the site to which the chemosensory afferents project [13, 31]. On the other hand, ovariectomy stimulated the catecholamine activity in the locus coeruleus (A_6) and did not produce significant changes in the rostral A_2 subset, the A_1 and A_5 cell groups. Thus, compared to that of androgens, the regional specificity of the influence of ovarian steroids on some structures of the chemoreceptor circuitry is noticeable, suggesting that there are sex-related differences in the neural mechanisms that are involved in the integration of chemosensory inputs and in the regulation of physiological adaptations to hypoxia.

Progesterone can act directly on the carotid body to raise ventilatory responsiveness to hypoxia, independently of descending central neural influences [10]. Consistent with this finding, ovariectomy inhibited, in the carotid body, the turnover of DA and NE, two major neurotransmitters involved in regulation of peripheral arterial chemosensitivity [8]. Afferent fibres of the carotid chemoreceptors terminate primarily within the commissural and medial subnuclei, a discrete area located caudal to the obex within the NTS that agrees well with the caudal A_2 subset [13, 31]. Neurons located in this region integrate primary afferent signals from the carotid chemoreceptor fibres [13, 21]. Here, ovariectomy inhibited selectively the activity of noradrenergic neurons in the caudal A_2 subset, whereas NE activity was unaffected in the rostral A_2. Previous studies from our laboratory support a functional subdivision of noradrenergic neurons within the NTS. The caudal A_2 subset is indeed selectively affected by carotid chemosensory inputs, whereas the rostral part of A_2 is affected by pharmacological handling of arterial blood pressure [27–29, 31]. In this context, the ovariectomy-induced alterations of noradrenergic activity in the caudal A_2 portion might be consecutive to stimulation of primary chemosensory afferents rather than to a direct effect of female steroids on NTS neurons. Thus, the present neurochemical data provide evidence that ovarian steroids can alter the neural activity of the chemoafferent pathway, both at the peripheral and central levels. This finding provides a neural basis to the study by Hannhart et al. [10] showing that progesterone, associated with oestrogen, acts at a combination of peripheral (carotid body) and central sites to raise the hypoxic ventilatory responsiveness. There is mounting evidence that the A_2 cell group seems to be involved in respiratory regulation. A_2 is adjacent to the dorsal respiratory group and a neuromodulatory role in control of ventilation has been assigned to A_2 neurons through the depressant effect of NE release on the firing activity of brainstem respiratory neurons [3]. Accordingly, stimulation of catecholamine-containing cells located in the carotid bodies and in the projection site of chemosensory afferents within the NTS might participate in modulation of the effects of ovarian steroids on breathing [10]. Noticeably, studies from our laboratory and others have indicated that the gradual rise in ventilation observed under long-term hypoxia was associated with increased catecholamine metabolism in the carotid body and in the NTS [22, 25, 30]. Given that catecholamines both at the carotid body and the brainstem level have been recognized as potent neuromodulators of peripheral chemosensitivity and central ventilatory control [3, 8], it remains to be determined whether the gender-related and castration-induced changes in catecholamine activity within key structures of the chemoafferent pathway are associated with modifications of ventilatory responsiveness to hypoxia.

Pronounced neural differences between ovariectomized females and orchidectomized males persisted long after castration, suggesting that the sexual dimorphism may be partly independent of the hormonal milieu. The data point out the possibility of structural differences in adult male and female neurons, which could be responsible for gender-related differences in respiratory control independently of the circulating levels of gonadal hormones [34]. In fact, the development of sex-specific neuronal properties may take place early at the embryonic stage independently of sex differences in the steroid environment [26]. Later, during the neonatal life, a period critical for neural development, sex steroids could have exerted modulatory, permanent influences on the organization of central neural structures that control respiration [2, 18].

Haematological studies

It has been noted for some time that sexually mature females of various species have lower [Hb] and Hct values compared to males. This gender-related difference in haematological status has been attributed to the role of sex hormones in the regulation of EPO production by the kidney [14]. Thus, administration of testosterone stimulates renal EPO production [17], whereas oestrogens inhibit erythropoiesis [5]. The role of sex hormones in the haematopoietic responsiveness during hypoxic acclimatization has recently been re-evaluated in rats [23] and it was concluded that the male sex hormones play no role in the development of excessive polycythaemia, whereas the female sex hormones suppressed both the polycythaemic and cardiopulmonary responses in vivo during

chronic hypoxia [23]. It is not known, however, if the sex-related haematopoietic response to hypoxia subsides or vanishes in mammals born and living at high altitude. Here, female rats displayed lower Hct, RBC and plasma EPO level as compared to males. In order to delineate whether the gender-related difference in haematological status is related to endogenous sex hormone plasma levels or not, we examined both males and females after prepubertal castration. It was found that orchidectomy reduced Hct, [Hb] and RBC without any change in plasma EPO level, whereas ovariectomy remained ineffective in altering the haematological status of female rats. These data are in contrast to those reported by Ou et al. [23], who reported that the rat haematopoietic response to hypoxia was not modified by orchidectomy or enhanced by ovariectomy. The discrepancies among the studies may be attributable to differences among the study designs. Firstly, in the present study, castration was performed before puberty whereas the rats from Ou et al. [23] were sexually mature with normal circulating sex hormones before castration and the sex hormones may have already influenced, or contributed in defining, the haematological status of the rats. Secondly, the role of sex hormones in adaptation to hypoxia was evaluated using a hypoxia-susceptible strain of rats (Hilltop strain) [23], whereas we used a Sprague-Dawley strain that develops only moderate haematological responses to hypoxia. Thirdly, in the present study, our rat strain had lived at high altitude for several generations and endocrine adaptation to life-long altitude exposure may have occurred, whereas Ou et al. [23] examined the sex hormone influence during altitude acclimatization. Surprisingly, we found haematological alterations in orchidectomized rats in the absence of plasma EPO changes. This would suggest that endogenous sex male hormones can affect erythropoiesis independently of EPO. In this respect, androgenic steroids have been shown to enhance the proliferation of erythrocytic progenitors [14]. Even though ovarian steroids have been claimed to inhibit erythropoiesis both at the kidney [20] and bone marrow level [15], ovariectomy did not produce a significant alteration in haematological status. The gender-related difference in RBC appears to be related in part to the effects of androgens on the proliferation and maturation of erythoid progenitor cells.

In conclusion, both gender and endogenous sex steroids can affect the catecholamine neurotransmitter metabolism within the carotid bodies and the brainstem noradrenergic cell groups. This neuromodulation may be part of the mechanisms involved in the sex-related differences of adaptation to hypoxia. The present data also provide evidence for mechanisms independent of sex hormones, probably linked to the blunting influence of high altitude on neuronal development and arterial chemoreflex.

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