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Renovascular adaptive changes in chronic hypoxic polycythemia

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Background. Chronic hypoxia in rats produces polycythemia, and the plasma fraction falls, reducing renal plasma flow (RPF) relative to renal blood flow (RBF). Polycythemia also causes increased blood viscosity, which tends to reduce RBF and renal oxygen delivery. We studied how renal regulation of electrolyte balance and renal tissue oxygenation (which is crucial for erythropoietin regulation) are maintained in rats during hypoxic exposure.

Methods. Rats of two strains with differing polycythemic responses, with surgically implanted catheters in the urinary bladder, femoral artery, and left renal and right external jugular veins, were exposed to a simulated high altitude (0.5 atm) for 0, 1, 3, 14, and 30 days, after which RPF (para-aminohippurate clearance), glomerular filtration rate (GFR, polyfructosan clearance), hematocrit and blood gases were measured, and RBF, renal vascular resistance and hindrance (resistance/viscosity), renal oxygen delivery, and renal oxygen consumption were calculated.

Results. During chronic hypoxia RBF increased, but RPF decreased because of the polycythemia. GFR remained normal because the filtration fraction (FF) increased. Renal vascular resistance decreased, and renal vascular hindrance decreased more markedly. Renal oxygen delivery and consumption both increased.

Conclusions. During chronic hypoxia GFR homeostasis apparently took precedence over RBF autoregulation. The large decrease in renal vascular hindrance suggested that renal vascular remodeling contributes to GFR regulation. The reduced hindrance also prevented a vicious cycle of increasing polycythemia and blood viscosity, decreasing RBF, and increasing renal hypoxia and erythropoietin release.

The kidney, as the organ of homeostatic control of electrolyte balance and red blood cell mass, faces two serious functional challenges during chronic hypoxic exposure. Control of electrolyte balance depends upon maintenance of the glomerular filtration rate (GFR), which could be compromised by the polycythemia of chronic hypoxia in two ways: the increased viscosity of polycythemic blood tends to reduce renal blood flow (RBF), and the reduced plasma fraction reduces renal plasma flow (RPF) relative to RBF. On the other hand, renal regulation of the rate of synthesis and release of erythropoietin (EPO) responds to changes in renal tissue P_{O2} [1, 2]. The response to renal hypoxia, with increased cellularity and viscosity of the blood, may cause a reduction in RBF that cannot be fully compensated by the higher oxygen-carrying capacity of the blood, so that renal oxygen delivery is reduced, exacerbating renal hypoxia and producing a vicious cycle of increasing polycythemia and increasing renal hypoxia.

Erslev, Caro and Besarab have suggested that this vicious cycle is prevented because decreased RBF reduces the filtered load of sodium for reabsorption and thereby reduces renal oxygen consumption, mitigating renal hypoxia [3]. However, RBF is not reduced, but is rather substantially increased in rats with hypoxia-induced polycythemia, and the glomerular filtration rate (GFR) is maintained within the normal range [4]. Therefore, in these animals the mechanism suggested by Erslev et al [3] does not appear to operate.

The increase in RBF therefore appears to be important for homeostatic control of both electrolyte balance and red blood cell mass in chronic hypoxia. Arterial blood pressure does not increase appreciably during chronic hypoxic exposure [4, 5], and therefore the increase in RBF implies that renal vascular resistance decreases sufficiently to account for the increased blood flow despite the increased blood viscosity. Renal vascular adaptive changes are therefore important in sustaining normal homeostatic function of the kidney in the presence of chronic hypoxia and polycythemia.

The present investigation extends our previous study [4]. We have studied two Sprague-Dawley rat strains with differing polycythemic responses to hypoxia: Hilltop rats develop excessive polycythemia whereas Madison rats develop only moderate polycythemia [2, 4, 6, 7]. These strain differences in the polycythemic responses to chronic hypoxia allowed us to evaluate the effect of polycythemia on the renal circulation and renal function with respect to electrolyte regulation and EPO regulation. Here we report the effects of hypoxia and polycythemia on RBF, RPF, filtration fraction (FF), GFR, renal oxygen delivery and

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renal oxygen consumption. The effects of hypoxia and polycythemia on EPO gene expression, EPO protein production, renal venous P_{O2}, sodium excretion and sodium reabsorption are described in a separate paper [2].

METHODS

Animals

Male Sprague-Dawley rats weighing 270 to 320 g from Hilltop (Scottsdale, PA, USA; altitude susceptible strain) and Madison (Madison, WI, USA) breeding laboratories were used. Five groups of at least five rats from each strain were exposed to simulated high altitude (0.5 atm) for 0, 1, 3, 14, and 30 days. At the end of each of these exposure periods, RBF, RPF, GFR, hematocrit and blood gases were measured or calculated. A total of 32 Hilltop rats and 33 Madison rats were used for RBF and RPF determinations, and 11 Hilltop and 9 Madison rats were used for GFR and FF levels.

Surgical preparations

Five to seven days prior to measurement, each animal was anesthetized with a combination of ketamine (60 mg/kg body wt, i.m.) and pentobarbital (20 mg/kg body wt, i.p.) and catheters were implanted in the urinary bladder, femoral artery and left renal and right external jugular veins as previously described [4, 8]. After surgery, the rats were treated with penicillin (100,000 U daily, i.m.) for five days and were allowed free access to water and laboratory rat chow. For the next two days, the animals were acclimated to a plastic restraining cage employed for renal function measurements. The animals recovered from surgery uneventfully, and the majority had gained weight by the time of measurements.

Experimental procedures

During measurements, each rat was housed in a restraining cage. A Plexiglas hood fit over the front of the restraining cage so that the desired gas mixture could be flushed through the hood. Measurements were made under hypoxic conditions (10.5% O_2) for the hypoxic rats and under normoxic conditions (20.9% O_2) for the sea level control rats.

The GFR was measured by the clearance of polyfructosan (Inutest; Laevasan, Linz-Donau, Austria), and RPF was determined from the extraction of para-aminohippurate (PAH; Merck Sharp & Dohme, West Point, PA, USA). The jugular venous catheter was connected to a variable-speed infusion pump (Sage Instruments; Orion Research Inc., Cambridge, MA, USA), and following a priming injection (0.25 ml/100 g body wt), an infusion of 10% polyfructosan and 1% PAH in sterile saline was started at a rate of 10 μl/min/100 g body wt. The exposed end of the bladder catheter was extended with a short length of polyethylene tubing to allow collection of urine underneath the restraining cage. Urine volume was measured by weight. After a 30 to 60 minute period of equilibration to the restraining cage, at least two duplicate samples of urine and arterial and renal venous blood were obtained from each animal under appropriate oxygen tension conditions. To avoid possible adverse effects of repeated blood sampling, which might change the hematocrit, each rat was studied only once. Each animal was killed, and the location of the renal venous catheter was determined. Data were accepted only when the renal venous catheter was midway between the inferior vena cava and the left kidney.

Analytical techniques

The following determinations were made in all plasma and urine samples: polyfructosan by the anthrone method [9], and PAH by the method of Bratton and Marshall as modified by Smith et al [10]. Hematocrit was determined by a micromethod. Urine flow and clearance rates are expressed per 100 g body wt. Arterial and venous blood gas samples were obtained anaerobically by withdrawing 300 μl from the rat; only the last 160 μl were used for analysis. The residue was returned to the rat. pH, P_{O2}, and P_{CO2} were measured with microelectrodes at 37°C (Model BMS 3 MK2; Radiometer America, Cleveland, OH, USA). The oxygen content in arterial and venous blood was estimated from a published rat oxy-hemoglobin dissociation curve [11]. Renal oxygen delivery and consumption were calculated by multiplying renal blood flow by the arterial oxygen content or renal arteriovenous oxygen content difference, respectively.

Statistical analysis

Least squares linear regression and analysis of covariance were done according to Snedecor and Cochran [12]. $P < 0.05$ was considered significant.

RESULTS

The hematocrit increased with time of hypoxic exposure from the sea level control value of 42.6 ± 1.4 to a peak value of 73.0 ± 0.9 in Hilltop rats and from 41.2 ± 3.0 to 61.0 ± 1.0 in Madison rats after 30 days of hypoxia.

Figure 1 shows the changes in RBF (Fig. 1A), FF (Fig. 1B), RPF (Fig. 1C) and GFR (Fig. 1D) as functions of the hematocrit. All four variables were approximately linear functions of hematocrit. Analysis of covariance showed no significant differences between the regression lines for Madison and Hilltop rats. RBF increased linearly as the hematocrit rose [slope = 91.2 ± 8.8 μl/min/100 g body wt/% hematocrit (Hct)], $P < 0.001$) and exceeded the sea level control values by approximately 50% at the highest hematocrit. Similarly, the FF increased by about 30% from a control value of 0.360 ± 0.003 to a value of 0.470 ± 0.007 at a hematocrit of 70% (slope = 0.0036 to 0.0010, $P <$ 0.002). In contrast, RPF fell slightly, but significantly