Impaired Leukocyte–Endothelial Cell Interaction in Spontaneously Hypertensive Rats

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Abstract Hypertension is associated with a progressive organ injury whose etiology remains largely speculative. An increasing database shows that activated leukocytes, while affording an important immune protection, may be a contributing factor to several of the pathogenetic features of the hypertension syndrome. The purpose of this study was to determine the extent to which the glucocorticoid pathway may be involved in the atypical elevation of arterial blood pressure, the spontaneously hypertensive rat (SHR) model provides a useful vehicle for analyzing the syndrome as it progresses from normotension to hypertension.

The basic mechanisms that predispose hypertensive individuals at regional and systemic levels to enhanced organ injury remain largely unresolved. Although the specific pathophysiological sequelae associated with the hypertensive state vary depending on the experimental manipulations used to induce a sustained elevation of arterial blood pressure, the spontaneously hypertensive rat (SHR) model provides a useful vehicle for analyzing the syndrome as it progresses from normotension to hypertension.

Leukocyte adhesion to endothelium and infiltration into tissue have been found to contribute to the tissue damage and impairment of local vascular behavior in a broad array of systemic diseases, including hypertension. It was therefore provocative to find in SHR, as well as in a number of other models of hypertension, that not only was the number of leukocytes in the circulating pool consistently above normal, but a significant fraction of neutrophils in SHR were in an "activated state" characteristic of cells primed to release oxygen radicals and thereby contribute to tissue damage. A challenge to this hypothesis arose in a recently reported study, using in vivo microscopy on the exteriorized mesentery of SHR, in which it was observed that the microvascular response to proinflammatory agents, such as platelet activating factor and leukotriene B₄, had no demonstrable effect on leukocyte adhesion and rolling, despite the fact that such stimulation caused a pronounced adhesion and rolling in normotensive Wistar-Kyoto (WKY) rats, indicating some form of inhibition in the SHR. We have also observed that histamine-induced leukocyte adhesion in WKY rats is attenuated in SHR. Although the blunted leukocyte–endothelial cell adhesive interaction following the proinflammatory stimuli in SHR may explain its neutrophilia, it still remained unknown what kind of factor could be responsible for blunting the leukocyte–endothelial cell adhesive interaction in SHR.

A number of reports in recent years have dealt with the role of the secretions of the adrenal cortex and their possible contribution to various forms of hypertension. Such data were of interest with respect to the leukocyte–endothelial cell adhesion phenomenon in view of the known anti-inflammatory action of adrenal corticosteroids. We therefore undertook to explore this interrelation between the blunted leukocyte–endothelial cell adhesive interaction and glucocorticoid in SHR through the use of a synthetic glucocorticoid inhibitor, RU 486 [mifepristone 17β-hydroxy-11β-(4-dimethylaminophenyl)-17α-(1-propynyl)-estra-4,9-dien-3-one], in conjunction with the response to a representative inflammatory mediator, histamine.

Methods

Animal Preparation

All animal procedures were reviewed and approved by the University of California, San Diego Animal Subject Commit-
controlled environment and maintained on a standard pellet diet at least 7 days before initiation of the experimental procedures. After general anesthesia with pentobarbital sodium (40 mg/kg IM), the femoral artery and vein were cannulated with PE-50 polyethylene tubing (Clay Adams) for monitoring of systemic arterial pressure and injection of reagents. Under such conditions, systemic blood pressure was maintained at a mean level of 140 to 150 mm Hg in SHR and 90 to 100 mm Hg in WKY rats. An infusion of 1.0 to 1.5 mL of normal saline per hour minimized any potential fluid deficits during such experimental procedures.

Rats were placed on a heating pad, covered with a blanket, and maintained at 37°C. The abdomen was opened along a small midline incision. The ileocecal portion of the mesentery was carefully exteriorized and mounted on a plastic support for intravital microscopy, as described previously. The exposed tissue was kept at 37°C and continuously superfused (1.0 mL/min) with a Krebs-Henseleit bicarbonate buffer saturated with a 95% N₂/5% CO₂ gas mixture. The oxygen saturation in the suffusion solution was kept at 0%.

**Intravital Microscopic Observation of the Mesentery**

The mesenteric microcirculation was visualized with an intravital microscope (×55 water immersion objective lens, Leitz) via a charge-coupled device (CCD) camera (model JE2362, Javelin). Leukocyte motion in venules was monitored together with arteriolar and venular erythrocyte velocities. Single unbranched venules with a diameter between 0.025 and 0.040 mm and approximately 0.15 mm in length were selected for detailed study. The images were recorded on a video cassette recorder (model AG-127OP, Panasonic). Venular diameters (D) were measured off-line with a video image-shearing meter (model 102, IPM). All diameters reported in the study refer to inner lumen diameter; no corrections were made for noncircular cross sections. Red blood cell centerline velocity (V̅RBC) was calculated based on the definition for a Newtonian fluid as $V̅_{RBC} = \frac{Centerline Velocity}{1.6}$. Venular shear rate was calculated based on the definition for a Newtonian fluid as $8(V̅_{RBC}/D)^2$.

The number of adherent leukocytes was determined during playback of the video images. A leukocyte was characterized as adherent to venular endothelium when it remained stationary for at least 30 seconds. We determined the number of adherent leukocytes over a vessel segment more than 0.1 mm in length. Rolling leukocytes on the endothelium were defined as white cells that were carried at a slower velocity than erythrocytes in the same radial vessel position and by the characteristic spherical shape of leukocytes. The leukocyte rolling velocity ($V_{WBC}$) was evaluated by determining the number of individual video frames required for a leukocyte to traverse a preselected distance along the venular wall. The distance over which a leukocyte showed rolling behavior as well as the time to traverse the same distance was measured, from which the mean leukocyte rolling velocity for individual leukocytes could be determined. Such measurements were carried out on at least 50 rolling cells for each experiment and were used to compose a histogram of the normalized leukocyte rolling velocity ($V_{WBC}/V_{RBC}$). $V_{WBC}/V_{RBC}$ serves as an index of the leukocyte membrane adhesive stress to the endothelium. The strength of the membrane adhesion during leukocyte rolling is inversely proportional to the velocity ratio $V_{WBC}/V_{RBC}$. A replay of approximately 3 minutes of video segments was usually required to complete 50 measurements.

**Experimental Protocols**

After the mesentery had been exteriorized and placed on the temperature-controlled plastic stage, the preparation was allowed to stabilize for at least 20 minutes. During this period, all hemodynamic parameters were monitored on-line (arterial pressure, red blood cell centerline velocity, venular diameter) and reached steady state. Venular leukocyte rolling mediated by P-selectin expression was essentially abolished. All images from the mesenteric preparation were continuously recorded on videotape.

For investigation of endothelial cell–dependent mechanisms of leukocyte rolling and adhesion, the superfusion solution was exchanged to Krebs-Henseleit bicarbonate buffer containing histamine dihydrochloride ($10^{-4}$ mol/L, Sigma Chemical Co). Before and after the start of histamine application, video images of the microvasculature were recorded at 10-minute intervals for 60 minutes.

In the histamine-treated group, the state of mast cell degranulation that might possibly be affected by the surgical exposure of the ileocecal mesentery was evaluated at the end of each experiment by superfusion of 0.1% toluidine blue (Sigma) solution for 30 minutes. With the use of this procedure, mast cells with degranulation could easily be identified by the presence of metachromatic granules in the extracellular space. Toluidine blue staining, the microscopic observation field and three or four contiguous fields were checked for mast cell degranulation. Measurements with more than 10% of mast cell degranulation were excluded to avoid the contribution of endogenous histamine release from degranulating mast cells either before or during the surgical procedure.

**Interventions**

In a separate set of experiments, the mesenteric preparation was pretreated with topically applied RU 486 (Roussel-Uclaf; $10^{-3}$ mol/L in the superfusate) 20 minutes before the addition of histamine to the solution. In other groups, a monoclonal antibody directed against P-selectin (PB1.3, 2.0 mg/kg, Cytel) and against intercellular adhesion molecule-1 (ICAM-1) (1A29, 2.0 mg/kg) on the endothelium was administered by intravenous injection for 20 minutes before the start of histamine application. In separate experiments, effects of a mouse IgG (Sigma) at the same dose were also evaluated as controls for PB1.3 or 1A29 in separate experiments.

For assessment of the effects of glucocorticoids on the leukocyte–endothelial cell adhesive interaction following histamine, a separate set of rats was pretreated intravenously with hydrocortisone 21-acetate (Sigma, 3.0 mg/kg in saline), one of the short-acting glucocorticoids, 40 minutes before the start of histamine application. After completion of the microvascular observations, blood samples were drawn into heparin (approximately 10 U/10 mL) for measurement of the total white blood cell count with a hemocytometer (Fisher Scientific) and the neutrophil count from the differential count on a blood smear.

**Systemic Application of RU 486**

For assessment of the systemic effect of RU 486, measurements of mean blood pressure and circulating leukocyte count as well as neutrophil count and activated leukocyte number (see below) were made 6 hours after intramuscular injection of RU 486 (33.3 mg/kg body wt) with rats under general anesthesia. The activation of neutrophils was determined by reduction of nitroblue tetrazolium (NBT) as a measure of spontaneous superoxide formation in neutrophils and monocytes and was carried out according to a modified method of Park et al. Briefly, 0.1 mL of freshly drawn, unseparated arterial blood was immediately transferred into a cleaned (with endotoxin detergent, Sigma), siliconized concave microslide and mixed with an equal amount of 0.1% NBT solution. Blood cell separation...
measurements were avoided because such handling can strongly influence spontaneous activation in predisposed animals. The blood-NBT mixture was incubated at 37°C for 10 minutes followed by 10 minutes at room temperature (approximately 22°C). After gentle stirring, coverslip smears were made and stained with Wright's stain, and 100 neutrophils were counted under X100 oil objective magnification. NBT-positive neutrophils showed a stippled cytoplasmic distribution of formazan deposit larger than the cell granules.

Statistical Analysis
The number of adherent leukocytes is expressed as mean±SD. Since the rolling velocity ratio $V_{WBC}/V_{RBC}$ usually exhibits a nonsymmetric frequency distribution, $V_{WBC}/V_{RBC}$ distribution and median value were determined for each intervention and time point, and $V_{WBC}/V_{RBC}$ was expressed as the mean value of medians for all animals in each group±SD. Statistical significance of the differences in the mean was determined by two-way layout ANOVA and a Schefte-type multiple comparison test. Statistical significance was set at a value of $P<.05$.

Results

Leukocyte Rolling
Fig 1 depicts the time course of the normalized leukocyte rolling velocity ($V_{WBC}/V_{RBC}$) in mesenteric venules after onset of histamine (10^{-6} mol/L) superfusion in Wistar-Kyoto (WKY) rats (a) and spontaneously hypertensive rats (SHR) (b). Seven groups were investigated: top: control, 10^{-6} mol/L RU 486, histamine, and histamine plus 10^{-5} mol/L RU 486; bottom: histamine plus 10^{-5} mol/L RU 486 with 2 mg/kg PB1.3, histamine plus 10^{-5} mol/L RU 486 with 2 mg/kg 1A29, and histamine plus 10^{-5} mol/L RU 486 with 2 mg/kg IgG2. In panel a, *$P<.05$ compared with control group (top); †$P<.05$ compared with histamine plus RU 486 group (bottom). In panel b, *$P<.05$ compared with control group (top); †$P<.05$ compared with histamine plus RU 486 group (bottom).
ments in preparations exposed to Krebs-Henseleit bicarbonate buffered solution as a control (open circles), to 10^{-5} \text{ mol/L} RU 486 (closed circles), to 10^{-5} \text{ mol/L} histamine (open squares), and to both 10^{-3} \text{ mol/L} RU 486 and 10^{-5} \text{ mol/L} histamine (closed squares) in a cohort of SHR and WKY rats. In neither the control nor the RU 486 group was there a statistically significant increase in the number of adherent leukocytes in SHR or WKY rats (Fig 2, open and closed circles). After topical histamine application, the number of adherent leukocytes showed an increase in WKY rats (Fig 2, top, open squares) but not in SHR (Fig 2, bottom, open squares). The number of adherent leukocytes after histamine application was significantly increased in WKY rats compared with SHR (P < 0.05). When RU 486 application was combined with histamine, the trend for the leukocyte adhesive reaction in SHR to be inhibited was abrogated, and a strikingly greater number of cells became adherent in SHR (Fig 2, bottom, closed squares) relative to the response observed in WKY rats (Fig 2, top, closed squares).

To explore the mechanism responsible for the reestablishment of leukocyte adhesion in the SHR after glucocorticoid inhibition, immunoprotection for P-selectin and ICAM-1 on endothelial cells was carried out. In WKY rats, RU 486 application had no effect on the number of adherent leukocytes at 60 minutes after 10^{-5} \text{ mol/L} histamine application, although the phenomenon was circumvented by pretreatment with either PB1.3 or 1A29 (Fig 3, left). In contrast, in the SHR group, the number of adherent leukocytes was significantly increased in the presence of RU 486 (Fig 3, right). The characteristic induced increase in leukocyte adhesion number was significantly counteracted by pretreatment with either PB1.3 (anti-P-selectin monoclonal antibody) or 1A29 (anti-ICAM-1 monoclonal antibody) (Fig 3, right). In contrast, leukocyte adhesion remained unaffected following pretreatment with IgG2 in SHR and WKY rats.

Relation Between Leukocyte Adhesion and Venular Shear Rate

Fig 4 compares the venular shear rate and number of adherent leukocytes on postcapillary venular endothelium measured 60 minutes after the onset of histamine superfusion in Wistar-Kyoto (WKY) rats (left) and spontaneously hypertensive rats (SHR) (right). Six groups are shown: control, histamine, histamine plus 10^{-5} \text{ mol/L} RU 486, histamine plus 10^{-5} \text{ mol/L} RU 486 with 2.0 mg/kg PB1.3, histamine plus 10^{-5} \text{ mol/L} RU 486 with 2.0 mg/kg 1A29, and histamine plus 10^{-5} \text{ mol/L} RU 486 with 2.0 mg/kg IgG2. Numbers at the bottom of each column indicate number of animals. For WKY rats, *P < 0.05 compared with control; †P < 0.05 compared with histamine group. For SHR, *P < 0.05 compared with control; †P < 0.05 compared with histamine plus RU 486 group.

The results of this study suggest that shear rate-dependent leukocyte recruitment could not be a major factor within the range of shear rates presented in this study. In WKY rats, although there was no significant correlation, histamine application itself resulted in an increase in adherent leukocyte number (Fig 4a). In SHR, although no significant linear correlation was observed, application of RU 486 in combination with histamine resulted in a measurable increase in adherent leukocyte number that tended to be associated with a reduction of venular
leukocytes adherent to venular endothelium (bottom). Hydrocortisone treatment alone had no significant influence on $V_{\text{WBC}}/V_{\text{RBC}}$ and the number of leukocytes adherent to venular endothelium in WKY rats as well as SHR. Although the normalized rolling velocity ($V_{\text{WBC}}/V_{\text{RBC}}$) was significantly decreased and the adherent leukocyte number was significantly increased after histamine, these trends were overridden by treatment with hydrocortisone in WKY rats. In contrast, in SHR no effect of hydrocortisone on leukocyte–endothelial cell interaction was detected (Fig 5, right).

**Effect of RU 486 on Circulating Leukocytes**

There were no significant changes in circulating leukocyte counts in WKY rats and SHR after the local superfusion of RU 486 during 80-minute mesenteric observation periods (data not shown).

Fig 6, top, shows the circulating leukocyte count in a cohort of WKY rats and SHR with or without RU 486 treatment (33.3 mg/kg body wt IM). Although in WKY rats the leukocyte count was not significantly decreased by the treatment with RU 486 (Fig 6, top), RU 486 established a leukocyte count in SHR similar to that in WKY rats (Fig 6, top). Fig 6 also depicts the number of circulating neutrophils (middle) and the number of activated circulating neutrophils assessed by NBT test (bottom) with or without RU 486 treatment. The neutrophil count as well as NBT-positive neutrophil number showed the same trends in both cohorts.

**Discussion**

**Leukocyte–Endothelial Cell Interaction and Glucocorticoid in SHR**

Leukocyte–endothelial cell adhesive interaction induced by a stimulation such as histamine appears to be suppressed in the mesenteric microcirculation of SHR. The present study demonstrates that atypical intercellular adhesion in the SHR can be restored by a synthetic glucocorticoid inhibitor, RU 486, and that conventional leukocyte adhesion following histamine in WKY rats can be blunted by hydrocortisone, one of the short-acting glucocorticoids. The fact that the neutralizing action of steroids on leukocyte adhesion could be overcome in SHR by RU 486 suggests that this agent acts by blocking steroid receptors without a major effect on the histamine receptors.

A growing body of evidence accumulated over the last decade suggests that activated blood leukocytes not only participate at a beneficial level in immune protection and tissue homeostasis but contribute to the parenchymal damage associated with various cardiovascular diseases. This includes syndromes associated with an increased incidence of hypertension, such as atherosclerosis or stroke. Our current results raise the possibility that elevated levels of adrenal corticosteroids in SHR may have an intermediate role in the exacerbation of hypertensive sequelae by interfering with conventional leukocyte kinetics in the microcirculation.

Oral administration of prednisone in humans significantly inhibits the adherence of peripheral neutrophils to nylon-wool columns when examined 4 hours after prednisone treatment. Histamine stimulates the adherence of rat peritoneal neutrophils to vascular endothelial
cells in human umbilical veins, a reaction that can be suppressed by dexamethasone. These separate results suggest that the leukocyte-endothelial cell adhesive interaction following histamine might be attenuated in SHR by elevated levels of glucocorticoid. This possibility is supported by the observation that in SHR hypertension, blockade of glucocorticoid receptors by RU 486 restored the ability of endothelial cells to express surface adhesive molecules and that in WKY controls, the treatment of hydrocortisone, one of the short-acting glucocorticoids, could significantly attenuate the leukocyte-endothelial cell adhesive interaction following histamine.

Stimuli that produce an excessive adrenal secretion of cortisol have been found to lead to hypertension. In such cases, the hypertension has been assumed to be associated in part with the glucocorticoid receptor pathway. Aoki has shown that adrenalectomy or hypophysectomy prevents the development of hypertension in SHR. It was further demonstrated that the cortical layers in the adrenal gland were hypertrophied in the SHR, suggesting a contributory role for the adrenals in the development of elevated blood pressure in SHR. Recently, Hashimoto et al reported that adrenalectomy prevented the development of hypertension in SHR but reported that corticosterone treatment restores the hypertension in this animal, again suggesting an involvement of adrenals in the development of elevated blood pressure in SHR. Cronstein et al found that pretreatment of human umbilical vein endothelial cells with dexamethasone suppresses the trend for endothelial cells to become more adhesive to neutrophils and diminishes the stimulated expression of ICAM-1 and endothelial cell-leukocyte adhesion molecule-1 (ELAM-1) induced by lipopolysaccharide. These authors also demonstrated that RU 486 (10^-5 mol/L) completely reversed the effect of dexamethasone on the lipopolysaccharide-stimulated expression of ELAM-1 and ICAM-1.

RU 486 appears to be the first synthetic glucocorticoid antagonist capable of antagonizing the short- and long-term effects of dexamethasone in vivo in different animal target tissues as well as in vitro without exhibiting any agonist activity even in large doses. RU 486 is known to stabilize the association of glucocorticoid receptors with heat-shock protein 90 in the presence of a ligand. Although the agent also cross-reacts with the progesterone receptor and to a slight degree with the androgen receptor, it has no cross-reactivity with mineralocorticoid receptors. Kalimi reported that RU 486 successfully counteracted the hypertension produced by the long-term administration of dexamethasone in male Sprague-Dawley rats.

Adhesion Molecules Related to Leukocyte-Endothelial Cell Interaction

We have previously suggested that the organ damage in SHR might be ascribed in part to the fact that the syndrome is associated not only with an elevated blood leukocyte count but with a higher proportion of circulating activated granulocytes in SHR compared with WKY. Arndt et al have reported a reduced level of surface CD11b/CD18 expression on leukocytes in SHR as well as a reduction in the number of leukocytes that...
In our SHR experiments, the trend toward an increase in the number of adherent leukocytes in SHR after RU 486 application was shown to be significantly attenuated by the treatment with either an anti-P-selectin or an anti-ICAM-1 monoclonal antibody (Fig 3). On the other hand, although the shift in leukocyte rolling velocity ($V_{WBC}/V_{RBC}$) in SHR following a combination of histamine and RU 486 was significantly blunted by an anti-P-selectin monoclonal antibody, it was not counteracted by an anti-ICAM-1 monoclonal antibody. This observation suggests that in SHR the endothelial surface expression of adhesion molecules, such as P-selectin and ICAM-1, could be modified by a glucocorticoid inhibitor. Although ICAM-1 may show a basal constitutive expression on the surface of endothelial cells in postcapillary venules, its expression is dramatically increased after exposure to proinflammatory factors, with maximal expression achieved within approximately 4 hours.22,23 Since the adhesion response in the present case was more rapid, the ICAM-1 that participates in leukocyte adherence to endothelial cells following histamine in WKY rats or following histamine plus RU 486 in SHR appears to represent the constitutive form rather than the induced form of the glycoprotein. However, the possibility remains that different levels of the constitutively expressed ICAM-1 may exist in SHR and WKY rats.

P-selectin normally resides in a preformed state in $\alpha$-granules of platelets and Weibel-Palade bodies of endothelial cells,24,25 P-selectin can be rapidly (1 to 2 minutes) translocated to the endothelial cell surface when the cells are exposed to stimuli such as thrombin, histamine, hydrogen peroxide, and others.26-28 It has been reported that coronary artery endothelium when stimulated by histamine exhibits comparable increases in neutrophil adherence, a phenomenon that is significantly inhibited by an anti-P-selectin monoclonal antibody (PB1.3).29 Neutrophils have been found to roll on such P-selectin–enriched lipid bilayers30 and on postcapillary venules. Leukocyte rolling in vivo appears to be mediated by an interaction between P-selectin on endothelial cells and specific oligosaccharide ligands that are constitutively expressed on the surface of leukocytes. The increased number of rolling (but not adherent) leukocytes at the low range of in vivo shear rates could be attenuated by PB1.3.31 PB1.3 also exerted a significant influence on the normalized leukocyte rolling velocity ($V_{WBC}/V_{RBC}$).31

The possibility also exists that platelets may influence the rolling in vivo. In line with this possibility, PB1.3 may exert a protective action by binding to platelets, thereby blunting platelet interaction with other cells. However, in vivo monitoring of fluorescence-labeled platelets does not provide evidence for platelet aggregation and platelet–endothelial cell interactions in the mesenteric microcirculation during the histamine application in a protocol similar to the current one (unpublished observation from our laboratory).

Monoclonal antibodies against L-selectin have been effective in abolishing spontaneous leukocyte rolling in rabbit mesenteric venules32 and rat mesentery.33 Although it has not been established with certainty which molecules form the leukocyte ligands to P-selectin,
recent evidence suggests that an L-selectin–associated oligosaccharide may be involved, specifically sialyl Lewis X. According to previous measurements, there were no L-selectin between SHR and WKY rats. Since in the current experiments RU 486 was topically superfused, primarily endothelial surface molecules could be affected. Thus, the current array of evidence supports the hypothesis that glucocorticoids modulate primarily endothelial cell surface conditions and translocation of Weibel-Palade bodies rather than leukocyte surface conditions involving the sialyl Lewis X and the L-selectin–associated oligosaccharide.

Venular Shear Rate and Leukocyte Adhesion

Bienvenu and Granger reported that shear rate–dependent recruitment of rolling leukocytes is not affected by monoclonal antibodies against CD11b/CD18 or ICAM-1. This observation suggests that a different family of adhesion glycoproteins participates in the low-affinity binding that is a requirement for such rolling. Low shear rates may serve to increase P-selectin expression either as a result of reduced washout of basally produced histamine or by the fact that rolling leukocytes liberate hydrogen peroxide when they are juxtaposed with the endothelial cell membrane. Lorant et al demonstrated a priming role for endothelial cell–associated P-selectin after contact with neutrophils. In our present experiments, although recruitment of rolling leukocytes was promoted by application of histamine in WKY rats, and it could also be restored in SHR by the addition of RU 486 despite a higher shear rate than that in the report of Bienvenu and Granger, the leukocyte rolling was not affected by a monoclonal antibody against ICAM-1.

In conclusion, elevated levels of glucocorticoid in SHR appear to inhibit the P-selectin–mediated leukocyte–endothelial cell interaction. After RU 486 superfusion, the impaired response in SHR is abrogated, and P-selectin continues to be expressed on the endothelial surface. Immunoneutralization of ICAM-1 inhibits the stronger attachment of adherent leukocytes after histamine application in WKY rats as well as in SHR after histamine and RU 486. Since P-selectin is an important rolling receptor for leukocytes, the inhibition of this surface expression may explain the reduced leukocyte margination in SHR and may contribute to the high circulating leukocyte count in this strain. The lack of P-selectin expression in SHR could be reversed with a glucocorticoid inhibitor.

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