The Responses of Pulmonary and Systemic Circulation and Airway to Allergic Mediators in Anesthetized Rats

Mofei Wang, a,b Toshishige Shibamoto, a,Yuhichi Kuda, a Mamoru Tanida, a Tao Zhang, c Jie Song, d Kiyotaka Mukai, e and Yasutaka Kurata e

a Department of Physiology II, Kanazawa Medical University; Uchinada, Ishikawa 920–0293, Japan; b Department of Diabetes Surgery, The Fourth Affiliated Hospital of China Medical University; Shenyang 110032, China; c Department of Coronary and Hernia Surgery, The Fourth Affiliated Hospital of China Medical University; Shenyang 110032, China; d Department of Anesthesiology, China–Japan Friendship Hospital; Beijing 100029, China; and e Department of Nephrology, Kanazawa Medical University; Uchinada, Ishikawa 920–0293, Japan.

Received November 2, 2015; accepted January 5, 2016

Lung allergic diseases sometimes accompany pulmonary vasomotor- and bronchoconstriction. Rats are currently used for the experimental study of lung allergies. However, their hemodynamic mechanisms are not fully understood. Therefore the effects of allergic mediators were determined systematically in vivo in rats in terms of pulmonary vascular resistance (PVR), airway pressure (AWP) and total peripheral resistance (TPR). We directly measured pulmonary arterial pressure, left atrial pressure, systemic arterial pressure, central venous pressure and aortic blood flow to determine PVR and TPR, as well as AWP, following injections of platelet-activating factor (PAF), histamine, serotonin, leukotriene (LT) C4, and prostaglandin (PG) D2 in anesthetized open-chest artificially ventilated Sprague-Dawley (SD) rats. PVR was dose-dependently increased by consecutive administration of PAF, LTC4, and PGD2, with the maximal responsiveness being PAF>LTC4>PGD2. However, neither histamine nor serotonin changed PVR. TPR was decreased by all agents except LTC4 which actually increased it. PAF and serotonin, but not the other agents, increased AWP. In conclusion, allergic mediators exert non-uniform actions on pulmonary and systemic circulation and airways in anesthetized SD rats: PAF, LTC4 and PGD2, but not histamine or serotonin, caused substantial pulmonary vasodilation; LTC4 yielded systemic vasoconstriction, while the others caused systemic vasodilatation; only two mediators, PAF and serotonin, induce airway constriction.

Key words peripheral resistance; pulmonary arterial pressure; anaphylaxis; left atrial pressure; vasodilation; pulmonary vasoconstriction

Rats are currently used for investigations on pulmonary allergic diseases. However, the studies on physiological characteristics of the rat pulmonary circulation were limited. The rat pulmonary vascular responses to various endogenous allergic mediators were previously examined in isolated perfused lungs: platelet-activating factor (PAF) and leukotriene (LT) C4 cause substantial vasoconstriction. In rat isolated pulmonary arteries, serotonin showed strong constriction. However, there is no systematic study in which the effects of allergic mediators on the rat pulmonary vascular resistance (PVR) and total peripheral resistance (TPR) were determined by measuring cardiac output (CO) and the inflow and outflow pressures of the systemic and pulmonary circulations. Therefore, we measured directly and continuously CO, pulmonary arterial pressure (PAP) and left atrial pressure (LAP), along with systemic arterial pressure (SAP) and central venous pressure (CVP), in order to determine the responses of PVR and TPR to allergic mediators including PAF, histamine, serotonin, LTC4, and prostaglandin (PG) D2 in anesthetized Sprague-Dawley (SD) rats. Airway pressure (AWP) was also measured to determine whether the allergic mediators cause bronchoconstriction. We hypothesized that these mediators do not exert the same directional actions on pulmonary and systemic circulation and airway.

MATERIALS AND METHODS

Animals Forty male SD rats (Japan SLC, Shizuoka, Japan) weighing 362±3g (9 week) were used in this study. Rats were maintained at 23°C and under pathogen-free conditions on a 12:12-h dark/light cycle and allowed food and water ad libitum. The experiments conducted in the present study were approved by the Animal Research Committee of Kanazawa Medical University.

Surgical Preparation Rats were anesthetized with pentobarbital sodium (60mg/kg, intraperitoneally (i.p.)), placed supinely on a heating pad with body temperature at 36–37°C, and mechanically ventilated with a tidal volume of 7mL/kg, a respiratory rate of 60/min and a positive end-expiratory pressure (PEEP) of 2.5 cmH2O. AWP and SAP were measured from the inspiratory line and left femoral artery, respectively. A thin inner tube tapered to around 0.1mm in diameter for allergic mediator injections. After a chest midline incision, polyethylene catheters (0.3mm i.d., 0.5mm o.d.) were inserted into the pulmonary artery via the right atrium, and into the left atrium for measurement of PAP and LAP, respectively. The pulsed Doppler flow probe (MC2PSS; Transonic Systems, Ithaca, NY, U.S.A.) was placed on the ascending aorta for measurement of aortic blood flow (ABF).

Experimental Protocol In anesthetized open-chest rats, SAP, PAP, LAP, CVP and AWP were continuously monitored. These variables were recorded at 40Hz by PowerLab (AD
Instruments, Australia). PVR and TPR were calculated as follows:

\[
\begin{align*}
PVR &= \frac{\text{mean PAP} - \text{mean LAP}}{\text{mean ABF}} \\
TPR &= \frac{\text{mean SAP} - \text{CVP}}{\text{mean ABF}}
\end{align*}
\]

At 20 min after surgery, the baseline measurements were performed. Then PAF, histamine, serotonin, LTC₄, or PGD₂ was intravenously administered via the jugular vein as a bolus consecutively basically from the starting dose of 0.01 nmol/kg, unless otherwise mentioned, with an injection volume of 50 μL. In addition, the effect of pretreatment with the thromboxane receptor antagonist SQ 29548 (0.1 mg/kg, intravenous (i.v.)) at 10 min before PAF injection on the PVR and AWP responses to PAF was studied for the post-SQ 29548 PAF group. When hemodynamic variables returned to the pre-injection levels within 10 min after preceding administration of a smaller dose, a subsequent higher dose was administered. Each animal received only one agent. We also performed the control studies in which 50 μL saline alone as the control for the histamine and serotonin groups, or 50 μL saline-diluted ethanol (20%) as the control for the PAF, post-SQ 29548 PAF, LTC₄, and PGD₂ groups was intravenously injected at 10 min intervals over 50 min. Five rats were assigned to each drug and control group.

**Drugs** All drugs except SQ 29548 were purchased from Sigma Chemical Company (St. Louis, MO, U.S.A.), and SQ 29548 from Cayman Chemicals (Ann Arbor, MI, U.S.A.). Histamine and serotonin were dissolved in saline. PAF, LTC₄, PGD₂, and SQ 29548 were dissolved in 95% ethanol for stock solution, which was diluted with saline for the working solution.

**Statistical Analysis** Results are expressed as the mean±standard error of the mean (S.E.M). Intragroup comparisons were performed using two-way ANOVA. Intergroup comparisons were performed using one-way ANOVA. When a significant difference was observed, post-hoc test was performed by using Bonferroni. The statistical analyses were performed by Stat View, version 5.0 (SAS Institute Inc., Cary, NC, U.S.A.).

**RESULTS**

**The Basal Levels of Variables in Pulmonary and Systemic Circulation** The basal hemodynamic values for each group were shown in Table 1. The summarized data of 40 rats were as follows: mean SAP, 107±5 mmHg; CVP, 3.6±0.5 mmHg; mean PAP, 18.2±0.8 mmHg; mean LAP, 4.9±0.1 mmHg; mean ABF, 44.5±3.2 mL/min; TPR, 2.4±0.2 mmHg·min/mL; PVR, 0.32±0.5 mmHg·min/mL; heart rate (HR), 412±10 beats/min; peak AWP, 10.3±0.6 cmH₂O.

**Effects of the Allergic Mediators**

PAF

Figure 1 shows representative recordings of the changes in the variables after injections of PAF at doses ranging from 0.01 to 100 nmol/kg in an anesthetized rat. Figure 2 shows the summarized data of maximal changes in PVR, TPR, and AWP in all groups studied. At 0.1–100 nmol/kg, both SAP and ABF decreased, resulting in decreases in TPR. At 100 nmol/kg, TPR decreased until 1 min, thereafter followed by a marked increase due to a progressive decrease in ABF. At 10 and 100 nmol/kg, PAP initially and transiently increased by 1.5±0.2 and 7.5±0.8 mmHg, respectively followed by a sustained decrease which accompanied the progressive decrease in ABF. Concomitantly with the initial PAP increase, PVR significantly increased to 167±13% and 268±21% baseline within 1 min after injection of 10 and 100 nmol/kg PAF, respectively. There followed a huge increase in PVR due to a large reduction of ABF at 100 nmol/kg (Fig. 1, bottom right). We adopted the PVR values at the initial phase, but not at the late phase, as the maximal PVR shown in Fig. 2. At 1 nmol/kg PAP showed only a depressor response along with a decrease in ABF. AWP increased dose-dependently at 10 and 100 nmol/kg (Figs. 1, 2C-1).

Next we determined, by pretreatment with SQ 29548, the roles of thromboxane in the responses of the pulmonary vessels and airway to PAF. As expected, the PAF-induced increases in PAP, TPR, and AWP, as observed in rats without SQ 29548 pretreatment (Fig. 1), were abolished by SQ 29548 (Fig. 3).

Histamine

Histamine produced significant decreases in both SAP and TPR, and an initial and transient increase in ABF at doses of 0.1 μmol/kg or higher (Figs. 2B-2, 4). At 1–100 μmol/kg, ABF showed a biphasic response of the initial increase followed by a slight decrease. PAP did not increase but decreased along with a decrease in ABF. Consequently, PVR did not change significantly at any doses studied (Figs. 2A-2, 4). AWP

<table>
<thead>
<tr>
<th>Groups</th>
<th>MAP (mmHg)</th>
<th>CVP (mmHg)</th>
<th>PAP (mmHg)</th>
<th>LAP (mmHg)</th>
<th>ABF (mL/min)</th>
<th>AWP (cmH₂O)</th>
<th>HR beats/min</th>
<th>TPR (mmHg·min/mL)</th>
<th>PVR (mmHg·min/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAF (n=5)</td>
<td>107±3</td>
<td>4.1±1.0</td>
<td>19.1±0.9</td>
<td>4.6±0.1</td>
<td>42.6±4.5</td>
<td>10.6±0.1</td>
<td>422±16</td>
<td>2.5±0.3</td>
<td>0.36±0.04</td>
</tr>
<tr>
<td>Post SQ 29548</td>
<td>108±4</td>
<td>3.6±0.4</td>
<td>18.8±1.1</td>
<td>4.8±0.2</td>
<td>49.5±5.2</td>
<td>10.5±0.5</td>
<td>415±11</td>
<td>2.2±0.2</td>
<td>0.29±0.04</td>
</tr>
<tr>
<td>Histamine (n=5)</td>
<td>112±5</td>
<td>3.6±0.5</td>
<td>18.7±1.0</td>
<td>4.9±0.2</td>
<td>44.9±5.3</td>
<td>10.5±0.5</td>
<td>428±5</td>
<td>2.6±0.5</td>
<td>0.35±0.07</td>
</tr>
<tr>
<td>Serotonin (n=5)</td>
<td>110±3</td>
<td>3.8±0.4</td>
<td>18.3±1.1</td>
<td>4.7±0.4</td>
<td>38.9±4.5</td>
<td>11.0±0.8</td>
<td>428±20</td>
<td>2.8±0.3</td>
<td>0.37±0.05</td>
</tr>
<tr>
<td>LTC₄ (n=5)</td>
<td>105±5</td>
<td>3.2±0.3</td>
<td>18.3±1.0</td>
<td>5.3±0.2</td>
<td>43.5±1.9</td>
<td>10.1±0.6</td>
<td>414±13</td>
<td>2.4±0.1</td>
<td>0.30±0.03</td>
</tr>
<tr>
<td>PGD₂ (n=5)</td>
<td>103±6</td>
<td>3.3±0.5</td>
<td>16.9±1.0</td>
<td>4.9±0.4</td>
<td>42.3±3.1</td>
<td>10.4±0.5</td>
<td>384±15</td>
<td>2.4±0.2</td>
<td>0.29±0.03</td>
</tr>
<tr>
<td>Saline control (n=5)</td>
<td>102±4</td>
<td>3.5±0.3</td>
<td>17.8±1.2</td>
<td>4.8±0.3</td>
<td>45.5±2.5</td>
<td>9.9±0.5</td>
<td>395±12</td>
<td>2.2±0.5</td>
<td>0.29±0.01</td>
</tr>
<tr>
<td>Ethanol control (n=5)</td>
<td>107±6</td>
<td>3.6±0.5</td>
<td>18.2±1.0</td>
<td>5.1±0.3</td>
<td>47.5±2.7</td>
<td>9.8±0.7</td>
<td>410±11</td>
<td>2.3±0.2</td>
<td>0.28±0.02</td>
</tr>
</tbody>
</table>

Values are the mean±S.E.M. MAP, mean systemic arterial pressure; CVP, central venous pressure; PAP, pulmonary arterial pressure; LAP, left atrial pressure; ABF, aortic blood flow; AWP, airway pressure; HR, heart rate; TPR, total peripheral resistance; PVR, pulmonary vascular resistance.
showed no significant change at any doses (Figs. 2C-2, 4).

Serotonin
Serotonin decreased SAP and TPR at 10–300 nmol/kg (Figs. 2B-3, 5). Shortly after injections of 100 and 300 nmol/kg, PAP increased significantly but only slightly by 2.8 ± 0.5 and 3.1 ± 0.8 mmHg, respectively. This increase of PAP was

Fig. 1. The Representative Recordings of the Left Atrial Pressure (LAP), Systemic Arterial Pressure (SAP), Heart Rate (HR), Pulmonary Arterial Pressure (PAP), Airway Pressure (AWP), Aortic Blood Flow (ABF), and Central Venous Pressure (CVP) after Successive Injections of PAF at 0.01, 0.1, 1, 10, and 100 nmol/kg in an Anesthetized Rat

Pulmonary vascular resistance (PVR) and total peripheral resistance (TPR) were also shown, which were automatically calculated by Figs. 1 and 2 with PowerLab. White and black arrow heads, and arrows indicate the time points when the changes in PVR, TPR, and AWP, respectively, were determined as the maximal ones.

Fig. 2. The Maximal Changes in Pulmonary Vascular Resistance (ΔPVR), Total Peripheral Resistance (ΔTPR), and Airway Pressure (ΔAWP) in the PAF (n=5), Post-SQ 29548 PAF (n=5), Histamine (n=5), Serotonin (n=5), LTC4 (n=5), PGD2 (n=5) Groups, as Well as the Saline Control (n=5) and Ethanol Control (n=5) Groups

*p<0.05, versus the baseline. The time points when the maximal changes were determined are indicated in the representative recordings (Figs. 1, 3–7) for each agent by white or black arrow heads, or arrows for PVR or TPR, or AWP, respectively. *p<0.05, versus the baseline; †p<0.017, versus the control group (black bars); †p<0.017, versus the PAF group.
concurrently accompanied by increases in LAP by 3.5±0.7 and 4.2±0.9 mmHg, respectively, but only small insignificant increases in ABF by 0.2±0.05 and 0.1±0.07 mL/min, respectively. Consequently, PVR did not significantly change (Figs. 2A-3, 5). AWP significantly increased at doses of 100 and 300 nmol/kg (Figs. 2C-3, 5).

LTC₄
In contrast to other mediators, LTC₄ increased SAP initially and transiently, and decreased it sustainably, along with a decrease in ABF, resulting in a dose-dependent increase in
TPR at 1, 10 and 30 nmol/kg (Figs. 2B-4, 6). At 1 nmol/kg and higher, PAP showed a dose-dependent decrease along with a decrease in ABF, although PAP at 10 and 30 nmol/kg an initial and transient elevation by 1.8±0.3 and 2.3±0.5 mmHg, respectively (Fig. 6). With 10 and 30 nmol/kg LTC$_4$, the corresponding increases in PVR at the initial phase were 5.0±0.7% and

---

**Fig. 5.** The Representative Recordings of the Hemodynamic Variables and Resistances after Intravenous Injections of Serotonin at 0.1, 1, 10, 100 and 300 nmol/kg in an Anesthetized Rat

Black arrow heads and arrows indicate the time points when the changes in TPR and AWP, respectively, were determined as the maximal ones.

---

**Fig. 6.** The Representative Recordings of the Hemodynamic Variables and Resistances after Intravenous Injections of LTC$_4$ at 0.01, 0.1, 1, 10 and 30 nmol/kg in an Anesthetized Rat

White and black arrow heads indicate the time points when the changes in PVR and TPR, respectively, were determined as the maximal ones.
51±7% but the increases observed at late low ABF phase were 56±8 and 64±11%, respectively. Of note, the initial increase in PVR, which was accompanied by the increase in PAP, was apparently due to pulmonary vasoconstriction, and their data were shown in Fig. 2A-4. AWP did not change significantly at any doses studied (Fig. 2C-4).

**DISCUSSION**

We determined the responses of systemic and pulmonary circulation, as well as AWP, to allergic mediators in anesthetized open-chest SD rats. There are three major findings: 1) PAF, LTC4 and PGD2, but not either histamine or serotonin, increased PVR, with the rank of the potency being PAF > LTC4 > PGD2; 2) Only LTC4 increased TPR, whereas the other agents decreased it; and 3) PAF and serotonin, but not the others, increased AWP in anesthetized SD rats.

PAF is a potent smooth muscle contract. Actually, in anesthetized rats, inhalation of PAF causes bronchoconstriction.11 Consistently, we confirmed the ability of PAF administered intravenously to increase AWP in vivo rats. In contrast, with respect to the action of PAF in pulmonary circulation, Clavijo et al. reported that PAP in in vivo rats did not increase but rather decreased along with systemic hypotension when PAF was intravenously infused.12 We here demonstrated that PAF definitely increased PVR in in vivo rats at the high doses of 10–100 nmol/kg, although the small dose of 1 nmol/kg caused only a decrease in PAP along with a decrease in ABF. Indeed, PAF-induced vasoconstriction was well known in isolated perfused rat lungs.13 On the other hand, the late increase in PVR at 100 nmol/kg might be simply due to a passive effect of lower blood flows,14,15 rather than pulmonary vasoconstriction: ABF decreased hugely, resulting in collapse of pulmonary vessels and finally development of a marked increase in PVR. Pulmonary vasoconstriction and bronchoconstriction induced by PAF in rats are reported to be largely mediated by thromboxane.13,16 Actually in in vivo rats, thromboxane analogue, U46619, causes substantially both pulmonary vasoconstriction and bronchoconstriction.10 We here reinforced this conception in in vivo rats by showing that the PAF-induced increases in PVR and AWP were abolished by pretreatment with the thromboxane receptor antagonist SQ 29548.

Histamine causes pulmonary vasoconstriction in animals such as rabbits,17,18 dogs,19 cats,20 guinea pigs,21 pigs,22 and horses.23 Histamine is also reported to exert pulmonary vasodilator actions preferentially during vasoconstriction and in other conditions of high PAP in animals18–20 including rats.20,24 However, our study showed no changes in PVR in response to histamine, indicating that histamine did not cause pulmonary vasoconstriction or vasodilatation in in vivo rat lungs. The lack of substantial pulmonary vasoconstrictive action for histamine in rats is consistent with the previous

---

**Fig. 7.** The Representative Recordings of the Hemodynamic Variables and Resistances after Intravenous Injections of PGD2 at 0.1, 1, 10, 100 and 300 nmol/kg in an Anesthetized Rat

White and black arrow heads indicate the time points when the changes in PVR and TPR, respectively, were determined as the maximal ones.
report. Furthermore, the present study demonstrates that histamine does not exert a vasodilatory action at the basal pulmonary vascular tone in in vivo rats. It is generally assumed that pulmonary vasodilatation is induced by activation of not only vascular smooth muscle H2 receptor but also endothelial H1 receptor which is associated with NO production, while pulmonary vasoconstriction by activation of vascular smooth muscle H1 receptor. Further study is required to determine how individual histamine receptor subtypes contribute to the absence of substantial pulmonary vasomotion of anesthetized rats.

In contrast to histamine, serotonin is currently reported to cause pulmonary vasoconstriction and bronchoconstriction in isolated pulmonary arteries and perfused lungs from rats. In the present in vivo rats serotonin at 100 and 300 nmol/kg significantly increased AWP and PAP. However the increase in PAP was as small as 3.1 mmHg at 300 nmol/kg, and PVR did not significantly increase due to the concurrent increase in LAP. This finding indicates that serotonin does not apparently cause pulmonary vasoconstriction in anesthetized rats. This finding is consistent with the previous report for anesthetized rats: a similar small increase in PAP of 3.0 mmHg was observed in response to an intravenous injection of serotonin at 30 µg/kg, i.e., 142 nmol/kg, the comparable dose to that used in the present study. The absence of pulmonary vasoconstriction in anesthetized rats is not in agreement with the previous reports on other mammals, in which activation of the 5-HT1B/1D and 5-HT2A receptors has been implicated in serotonin-induced pulmonary vasoconstriction. The reason for the absence of serotonin-induced pulmonary vasoconstriction in in vivo anesthetized rats is not known, and the further study is required.

The systemic pressor and pulmonary depressor actions of LTC4 in the rat were previously reported. However, this previous study was limited because of the lack of PVR determination; as the authors discussed, whether the pulmonary depressor response was due to the generation of a pulmonary vasodilator substance or resulted from a reduction in cardiac output could not be specifically determined. In contrast to this previous report, we clearly observed LTC4-induced pulmonary vasoconstriction, as evidenced by an increase in PVR along with an increase in PAP at the early phase (as indicated by white arrow heads in Fig. 6). The later increase in PVR was due to a reduction of ABF. The cysteinyll LT binds to the cysteinyll LT receptors 1, 2, and 3 or the cysteinyll LT receptor E4. Cysteinyll LTs evoke contradictory effects on vascular tone, depending on the species and the experimental preparations, via both endothelium- and smooth muscle-dependent actions. The functional roles of these cysteinyll LT receptors in regulation of pulmonary vessels still remain unknown.

PGD2 dose-dependently increased PVR, albeit to a small extent, in the present study. This finding is not consistent with the previous report that either PVR or the blood flow to lung did not change in response to a PGD2 receptor agonist in anesthetized rats. However, in this previous study, the blood flow was measured with the microsphere method only one time at the end of infusions of the agonist. Thus the maximal response of PVR might have been missed. In contrast, we measured continuously ABF as well as the inflow and outflow pressures of the lung to obtain PVR exactly. In agreement with the present result, PGD2 produces pulmonary vasoconstriction in adult gouts, dogs, sheep, and cats. On the other hand, PGD2-induced decreases in SAP were well known in rats as well as dogs and monkeys; the present study reinforced these observations by showing that hypotension is caused by a decrease in TPR in anesthetized rats. DP1 receptor, one of the PGD2 receptors leads to vasodilatation, which seem to be responsible for the decrease in TPR, while pulmonary vasoconstriction induced by PGD2 might be mediated by thromboxane receptors.

In summary, we determined the responses of PVR, TPR and AWP to allergic mediators in anesthetized open-chest SD rats. PAF, LTC4 and PGD2, but not either histamine or serotonin, increased PVR, with the rank of the potency being PAF>LTC4>PGD2. However, pulmonary hypertension induced by these pulmonary vasoconstrictors was small in magnitude. In contrast, systemic hypotension or TPR reduction was induced by all mediators studied except LTC4. AWP was increased by PAF and serotonin, but not by the other mediators in the present rat in vivo preparations. The PAF-induced increases in PVR and AWP were abolished by the thromboxane receptor antagonist. These results demonstrate that allergic mediators exert non-uniform actions on the pulmonary and systemic circulation and airway in anesthetized SD rats.

**Conflict of Interest** The authors declare no conflict of interest.

**REFERENCES**

vasoconstriction modulates the responses of pulmonary vasculature
and airway to vasoconstrictors in anesthetized rats. Exp. Lung Res.,
11) Misawa M, Takata T. Effects of platelet-activating factor on rat air-
12) Clavijo LC, Carter MB, Matheson PI, Wilson MA, Wead WB, Gar-
rison RN. PAF increases vascular permeability without inducing
pulmonary arterial pressure in the rat. J. Appl. Physiol., 90, 261–268
13) Uhlig S, Wollin L, Wende1 A. Contributions of thromboxane and
leukotrienes to PAF-induced impairment of lung function in the rat.
14) Mink SN, Becker A, Unruh H, Kepron W. Effects of anaphylaxis
mediators on partitioned pulmonary vascular resistance during rag-
15) West JB, Dollery CT, Naimark A. Distribution of blood flow in
isolated lung; relation to vascular and alveolar pressures. J. Appl.
16) Martin C, Göggel R, Ressmeyer AR, Uhlig S. Pressor responses to
platelet-activating factor and thromboxane are mediated by Rho-
(2004).
17) Halonen M, Lohman IC, Palmer JD. The role of histamine in the
physiologic alterations of IgE anaphylaxis in the rabbit. Immuno-
18) Morecroft I, MacLean MR. 5-Hydroxytryptamine receptors mediat-
ing vasoconstriction and vasodilation in perinatal and adult rabbit
19) Tucker A, Weir EK, Reeves JT, Grover RF. Histamine H1- and H2-
receptors in pulmonary and systemic vasculature of the dog. Am. J.
20) Thompson B, Barer GR, Shaw JW. The action of histamine on pul-
21) Albert RK, Lanim WJ, Henderson WR, Bolin RW. Effect of leuko-
trienes B4, C4, and D4 on segmental pulmonary vascular pressures.
22) Tsang JY, Ohtaka H, Ohgami M, Schellenberg RR. Indomethacin
enhances histamine-induced pulmonary hemodynamic changes.
23) Hanna CJ, Eyre P. Pharmacological studies on the pulmonary vein
24) Russell PC, Wright CE, Barer GR, Howard P. Histamine induced
pulmonary vasodilatation in the rat: site of action and changes in
25) Houge A. Role of histamine in hypoxic pulmonary hypertension
in the rat. I. Blockade and potentiation of endogenous amines,
26) Matsuki T, Ohhashi T. Endothelial and mechanical responses of isolated
monkey pulmonary veins to histamine. Am. J. Physiol., 259,
27) Tucker A, Weir EK, Reeves JT, Grover RF. Histamine H1- and H2-
receptors in pulmonary and systemic vasculature of the dog. Am. J.
28) Lau WH, Kwan YW, Au AL, Cheung WH. An in vitro study of
histamine on the pulmonary artery of the Wistar-Kyoto and sponta-
29) Voelkel NF, McMurtry IF, Reeves JT. Hypoxia impairs vasodilation
30) Belohlávková S, Simák J, Kokesová A, Hnilicková O, Hampí V.
Fenfluramine-induced pulmonary vasoconstriction: role of serotonin
receptors and potassium channels. J. Appl. Physiol., 91, 755–761
31) Casey DR, Badejo AM, Dahiwal JS, Sikora JL, Fokin A, Golwala
NH, Greco AJ, Murthy SN, Nossaman BD, Hyman AL, Kadowitz
PJ. Analysis of responses to the Rho-kinase inhibitor Y-27632 in
the pulmonary and systemic vascular bed of the rat. Am. J. Physiol.
and the pulmonary circulation: receptors, transporters and relevance
(2000).
33) Lanau JM, Herve P, Peoc’h K, Tournois C, Callebert J, Nebigil
CG, Etienne N, Drouet L, Humbert M, Simonneau G, Maroteaux
L. Function of the serotonin 5-hydroxytryptamine 2B receptor in
34) Iacopino VJ, Fitzpatrick TM, Ramwell PW, Rose JC, Kot PA.
Cardiovascular responses to leukotriene C4 in the rat. J. Pharmacol.
35) Lynch KR, O’Neill GP, Liu Q, Im DS, Sawyer N, Metters KM,
Coulombe N, Abramovitz M, Figueroa DJ, Zeng Z, Connolly BM,
Bai C, Austin CP, Chateauneuf A, Stocek R, Greg G, Kargman
S, Hooks SB, Housfield E, Williams DL Jr, Ford-Hutchinson AW,
Casky CT, Evans JF. Characterization of the human cysteiny1 leu-
36) Bearse CE, O’Dowd BF, Figueroa DJ, Sawyer N, Nguyen T, Im DS,
Characterization of the human cysteiny1 leukotriene 2 receptor. J.
Leukotriene E4 activates peroxisome proliferator-activated receptor
γ and induces prostaglandin D2 generation by human mast cells. J.
38) Walsh L, Norel X, Gascard JP, Brink C. Functional studies of
leukotriene receptors in vascular tissues. Am. J. Respir. Crit. Care
39) Koch KA, Wesselle JL, Moreland R, Reinhardt GA, Cox BF. Effects
of BW245C, a prostaglandin dp receptor agonist, on systemic and
regional haemodynamics in the anesthetized rat. Clin. Exp. Phar-
of prostaglandin D2 on perinatal circulation. Am. J. Physiol., 240,
41) Wendling MG, DuCharme DW. Cardiovascular effects of prosta-
glandins D3 and D2 in anesthetized dogs. Prostaglandins, 22,
42) King LS, Fukushima M, Banerjee M, Kang KH, Newman JH, Biag
PJ. Analysis of responses to the Rho-kinase inhibitor Y-27632 in
43) Kaye AJ, Nossaman BD, Santiago JA, DeWitt BJ, Ibrahim IN,
Kadowitz PJ. Differential effects of glibenclamide on responses to
thromboxane A2 mimics, U46619, in the pulmonary and hindquar-
(1997).
44) Hamid-Bloomfield S, Whittle BJ. Antagonism of PGD2 vasodepres-
sor responses in the rat in vivo by the novel, selective antagonist,
45) Whittle BJ, Monacada S, Mullane K, Vane JR. Platelet and
cardiovascular activity of the hydantoin BW245C, a potent prosta-
46) Woodward DF, Jones RL, Narumiya S. International union of basic
and clinical pharmacology. LXXXIII: Classification of prostanoid
receptors, updating 15 years of progress. Pharmacol. Rev., 63,