Pulmonary and systemic vasodilator responses to the soluble guanylyl cyclase activator, BAY 60–2770, are not dependent on endogenous nitric oxide or reduced heme

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Pankey EA, Bhartiya M, Badejo AM, Jr, Haider U, Stasch J, Murthy SN, Nossaman BD, Kadowitz PJ. Pulmonary and systemic vasodilator responses to the soluble guanylyl cyclase activator BAY 60–2770, are not dependent on endogenous nitric oxide or reduced heme. Am J Physiol Heart Circ Physiol 300: H792–H802, 2011. First published January 7, 2011; doi:10.1152/ajpheart.00953.2010.—4-({(4-carboxybutyl)(2-(5-fluoro-2-\{4’-trifluoromethyl\}biphenyl-4-yl)methoxy}phenyl)ethyl}amino)methyl)benzoic acid; 2-{1-[2-(fluorophenyl)methyl]-1H-pyrazolo[3,4-b]pyridin-3-yl}-5(4-morpholinyl)-4,6-pyrimidinediamine. BAY 60–2770 and sodium nitroprusside decreased pulmonary and systemic arterial pressures in monocrotaline-induced pulmonary hypertension. The results of these studies show that BAY 60–2770 has a slowly developing, long-acting, vasodilator activity in the pulmonary and systemic vascular beds that is not impaired by treatment with monocrotaline and that the vasodilator activity is

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enhanced under elevated tone conditions or after NOS inhibition or treatment with ODQ.

METHODS

The Institutional Animal Care and Use Committee of the Tulane University School of Medicine approved the experimental protocol employed in these studies, and all procedures were conducted in accordance with institutional guidelines. In these experiments, adult male Sprague-Dawley rats (Charles Rivers) weighing 325–450 g were anesthetized with Inactin (100 mg/kg ip) (Sigma-Aldrich) and were placed in the supine position on an operating table. Supplemental doses of Inactin were administered intraperitoneally to maintain a uniform level of anesthesia. Body temperature was maintained with a heating lamp. The trachea was cannulated with a short segment of PE-240 tubing to maintain a patent airway. The animals spontaneously breathed room air. A femoral artery was catheterized with PE-50 tubing for measurement of systemic arterial pressure. The left jugular and femoral veins were catheterized with PE-50 tubing for intravenous injections and infusions of agents. For pulmonary arterial pressure measurement, a specially designed 3-Fr single-lumen catheter with a curved tip and with radio-opaque marker was passed from the right jugular vein in the main pulmonary artery under fluoroscopic guidance (Picker-Surveyor Fluoroscope) as previously described (2). Pulmonary and systemic arterial pressures were measured with Namic Perceptor DT transducers (Boston Scientific), digitized by a Biopac MP100 data acquisition system (Biopac Systems), and stored on a Dell personal computer (PC). Cardiac output was measured by the thermodilution technique with a Cardiomax II computer (Columbus Instruments). A known volume (0.2 ml) of room temperature 0.9% NaCl solution was injected in the jugular vein catheter with the tip near the right atrium, and changes in blood temperature were detected by a 1.5-Fr thermistor microprobe catheter (Columbus Instruments) positioned in the aortic arch from the left carotid artery. The indicator dilution curve data were stored on the PC.

Each experimental series was carried out in a separate group of rats, and, in the first set of experiments, the effects of intravenous injections of the sGC activator BAY 60–2770, in doses of 10, 30, and 100 μg/kg, were investigated on changes in peak pulmonary and systemic arterial pressures and on cardiac output in the anesthetized intact chest rat under baseline conditions. The time course of the changes in

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Fig. 1. A: bar graphs showing changes in pulmonary and systemic arterial pressures and changes in cardiac output in responses to iv injections of the soluble guanylyl cyclase (sGC) activator 4-(((4-carboxybutyl)[2-(5-fluoro-2-[[4'-{(trifluoromethyl)biphenyl-4-yl}methyl]amino}methyl]benzoic acid (BAY 60–2770) in doses of 10, 30, and 100 μg/kg iv under baseline conditions. *P < 0.05 compared with baseline. B: line graphs showing the time course changes in pulmonary and systemic arterial pressures and cardiac output in response to an iv injection of a midrange dose of BAY 60–2770 (30 μg/kg). n, No. of experiments. *P < 0.05 by ANOVA for repeated measures.
pulmonary and systemic arterial pressures and cardiac output in response to the midrange dose (30 μg/kg iv) of BAY 60–2770 was also investigated.

In the second set of experiments, responses to intravenous injections of BAY 60–2770 (10, 30, and 100 μg/kg) and the time course of the response to the midrange dose of the sGC activator (30 μg/kg iv) when baseline pulmonary arterial pressure was increased to ~30 mmHg by an iv infusion of U-46619. After an initial high priming rate (400 ng/min), the U-46619 infusion was adjusted (150–250 ng/min) to maintain pulmonary arterial pressure at ~30 mmHg. In these experiments, responses to the sGC stimulator 2-[1-[2-(fluorophenyl)methyl]-1H-pyrazolo[3,4-b]pyridin-3-yl]-5(4-morpholiny)-4,6-pyrimidinediamine (BAY 41–8543) and the sGC activator BAY 60–2770 were compared.

In the third set of experiments, the effect of the NOS inhibitor l-NAME (50 mg/kg iv) on responses to and the time course of the response to the midrange dose of BAY 60–2770 in the pulmonary and systemic vascular beds was investigated to determine the role of endogenous NO in mediating the response to the sGC activator.

In the fourth set of experiments, responses to and the time course of the response to the midrange dose of BAY 60–2770 were investigated in animals treated with the sGC inhibitor ODQ (5 mg/kg iv). In this series of experiments, the effects of ODQ were investigated on responses to a NO donor, sodium nitroprusside, and the heme-dependent sGC stimulator BAY 41–8543 (18, 19). ODQ inhibits sGC by oxidizing the heme iron on sGC, rendering the enzyme insensitive to NO (9, 10, 24, 29). BAY 41–8543 is a sGC stimulator that has vasodilator activity in the pulmonary and systemic vascular beds in Table 1.

Table 1. Effect of U-46619 on systemic and pulmonary arterial pressure and on cardiac output

<table>
<thead>
<tr>
<th></th>
<th>Systemic Arterial Pressure, mmHg</th>
<th>Pulmonary Arterial Pressure, mmHg</th>
<th>Cardiac Output, ml/min</th>
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<tbody>
<tr>
<td>Control</td>
<td>91 ± 3</td>
<td>22 ± 1</td>
<td>116 ± 9</td>
</tr>
<tr>
<td>U-46619</td>
<td>98 ± 4</td>
<td>33 ± 1*</td>
<td>80 ± 5*</td>
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Values are means ± SE; n = 13–16 rats in each group. *P < 0.05 compared with control.
the rat (2, 18, 19). In an additional set of experiments, the effects of combined treatment with L-NAME and ODQ on responses to BAY 60–2770 were investigated to evaluate the combined effect of NOS and sGC inhibition.

In the fifth series of experiments, decreases in pulmonary and systemic arterial pressures in response to the sGC activator were investigated in animals with monocrotaline-induced pulmonary hypertension. The animals were treated with monocrotaline, 60 mg/kg iv, and response to intravenous injections of BAY 60–2770 was determined on day 28 after administration of the plant alkaloid. Responses to intravenous injections of sodium nitroprusside were investigated in the monocrotaline-treated rats. The administration of monocrotaline (60 mg/kg iv) produced a large increase in pulmonary arterial pressure with minimal effects on systemic arterial pressure or on cardiac output, when values are measured on day 28.

Drugs. BAY 60–2770 and BAY 41–8543 were obtained from Dr. Johannes-Peter Stusch of the Institute of Cardiovascular Research, Pharma Research Centre, Bayer AG, Wuppertal, Germany, and were dissolved in Transcutol-Cremophor EL-0.9% NaCl solution (10:10:80) (20). U-46619 (Cayman Chemical) was dissolved in 95% ethyl alcohol and diluted in 0.9% NaCl solution. ODQ (Cayman Chemical), sodium nitroprusside, and L-NAME (Sigma-Aldrich) were dissolved in 0.9% NaCl. Monocrotaline (Sigma Aldrich) was dissolved in 1 N HCl neutralized with NaOH and diluted with PBS. The filtered solution was injected in the tail vein of male Sprague-Dawley rats in a dose of 60 mg/kg.

### Table 2. Effect of L-NAME on systemic and pulmonary arterial pressure and on cardiac output

<table>
<thead>
<tr>
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<th>Systemic Arterial Pressure, mmHg</th>
<th>Pulmonary Arterial Pressure, mmHg</th>
<th>Cardiac Output, ml/min</th>
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<tbody>
<tr>
<td>Control</td>
<td>99 ± 4</td>
<td>22 ± 1</td>
<td>130 ± 9</td>
</tr>
<tr>
<td>L-NAME (50 mg/kg)</td>
<td>138 ± 10*</td>
<td>31 ± 1*</td>
<td>77 ± 5*</td>
</tr>
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</table>

Values are means ± SE; n = 13–18 rats in each group. L-NAME, Nω-nitro-L-arginine methyl ester. *P < 0.05 compared with control.

Fig. 3. A: bar graphs showing the changes in pulmonary and systemic arterial pressures and changes in cardiac output in response to iv injections of BAY 60–2770 (10, 30, and 100 µg/kg) in animals treated with the NOS inhibitor Nω-nitro-L-arginine methyl ester hydrochloride (L-NAME, 50 mg/kg iv). *P < 0.05. B: line graphs showing time course of the changes in pulmonary and systemic arterial pressure and cardiac output in response to iv injection of the midrange dose of BAY 60–2770 (30 µg/kg) in L-NAME-treated animals. n, No. of experiments. *P < 0.05 by ANOVA for repeated measures.
The hemodynamic data are expressed as means ± SE and were analyzed using paired and group t-tests and ANOVA for repeated measures. The criteria used for statistical significance was $P < 0.05$.

**RESULTS**

**Hemodynamic responses to BAY 60–2770.** Responses to intravenous injections of the sGC activator BAY 60–2770 were investigated in the anesthetized rat under baseline conditions, and these results are summarized in Fig. 1. Changes in peak pulmonary and systemic arterial pressures and changes in cardiac output occurring at the change in peak pressure are shown in Fig. 1, left, and time course data for the response to the midrange dose (30 μg/kg iv) of the sGC activator are shown in Fig. 1, right. The intravenous injections of BAY 60–2770 in doses of 10, 30, and 100 μg/kg produced small decreases in pulmonary arterial pressure, larger dose-dependent decreases in systemic arterial pressure, and no change or small increases in cardiac output (Fig. 1A). The time course of the changes in pulmonary and systemic arterial pressures and in cardiac output in response to intravenous injection of the midrange dose of BAY 60–2770 (30 μg/kg iv) are shown in Fig. 1B. The decreases in pulmonary and systemic arterial pressure in response to BAY 60–2770 (30 μg/kg iv) were slow in onset and long in duration (Fig. 1B).

**Responses to BAY 60–2770 under elevated tone conditions.** Responses to BAY 60–2770 were investigated under elevated pulmonary vascular tone conditions, and these results are summarized in Fig. 2. The intravenous infusion of U-46619 produced a significant and sustained increase in pulmonary pressure and a significant decrease in cardiac output, with no change in systemic arterial pressure (Table 1). When pulmonary arterial pressure was increased to ~30 mmHg by the thromboxane mimic, the intravenous injections of BAY 60–2770 (10, 30, and 100 μg/kg) produced larger dose-dependent...
decreases in pulmonary arterial pressure, smaller decreases in systemic arterial pressure, and small increases in cardiac output (Fig. 2A) compared with responses in control animals (Fig. 1A). The time course of the changes in pulmonary and systemic arterial pressures and cardiac output in response to intravenous injection of the midrange dose of BAY 60–2770 (30 μg/kg iv) in U-46619-infused animals are shown in Fig. 2B. Systemic arterial pressure was not changed, the decrease in pulmonary arterial pressures was long in duration, and pressure was decreased up to 120 min after administration of BAY 60–2770 (30 μg/kg iv) (data not shown).

Effect of NOS inhibition with L-NAME. The administration of L-NAME in a dose of 50 mg/kg iv produced a significant increase in pulmonary and systemic arterial pressures and a significant decrease in cardiac output (Table 2). Following administration of the NOS inhibitor, the decreases in pulmonary arterial pressure in response to intravenous injections of BAY 60–2770 (10, 30, and 100 μg/kg) were significantly greater than responses obtained under baseline conditions (Figs. 1A and 3A) and were similar to responses obtained in U-46619-infused animals (Fig. 2A). The decreases in systemic arterial pressure were similar to, or greater than, responses in control animals, as shown in Fig. 1A, and were significantly greater than the decreases in systemic arterial pressure in response to BAY 60–2770 in U-46619-infused animals, and cardiac output was increased (Fig. 3A). The time course of the decreases in pulmonary and systemic arterial pressures and increases in cardiac output in response to the 30 μg/kg iv dose of BAY 60–2770 are shown in Fig. 3B. The decreases in pulmonary arterial pressures were long in duration, and pressures were decreased up to 120 min after administration of BAY 60–2770 (30 μg/kg iv) (data not shown).

Effect of ODQ. The effect of ODQ, an inhibitor of sGC that oxidizes the heme iron on the enzyme, on responses to BAY 60–2770 is shown in Fig. 4. The intravenous injection of ODQ (5 mg/kg iv) had no significant effect on pulmonary or systemic arterial pressure or on cardiac output (Table 3). Following administration of ODQ, the decreases in pulmonary and systemic arterial pressures in response to intravenous injections of BAY 60–2770 (10, 30, and 100 μg/kg) were significantly increased, and cardiac output was increased (Fig. 4A). The duration of the decreases in pulmonary and systemic arterial pressure in response to a midrange dose of BAY 60–2770 (30 μg/kg iv) after treatment with ODQ was long in duration (Fig. 4B) and was maintained for periods >120 min (data not shown). The decreases in systemic arterial pressure were very large in ODQ-treated animals. Following administration of ODQ, the decreases in pulmonary and systemic arterial pressures in response to intravenous injections of the NO donor

Table 3. Effect of ODQ on systemic and pulmonary arterial pressure and on cardiac output

<table>
<thead>
<tr>
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<th>Systemic Arterial Pressure, mmHg</th>
<th>Pulmonary Arterial Pressure, mmHg</th>
<th>Cardiac Output, ml/min</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>112 ± 4</td>
<td>22 ± 1</td>
<td>119 ± 5</td>
</tr>
<tr>
<td>ODQ (5 mg/kg)</td>
<td>114 ± 4</td>
<td>23 ± 1</td>
<td>115 ± 8</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 15–26 rats in each group. ODQ, 1H-[1,2,4]-oxadizaolo[4,3]-quinoxaline-1-one.
sodium nitroprusside (1 μg/kg) or to the sGC stimulator BAY 41–8543 (30 μg/kg) were significantly attenuated (Fig. 5).

**Effect of combined treatment.** The effect of combined treatment with L-NAME (50 mg/kg iv) and ODQ (5 mg/kg iv) on responses to BAY 60–2770 was investigated. Treatment with L-NAME and ODQ produced significant increases in pulmonary and systemic arterial pressures and a significant decrease in cardiac output (Table 4). Following combined treatment with L-NAME (50 mg/kg iv) and ODQ (5 mg/kg iv), intravenous injections of the midrange dose of BAY 60–2770 (30 μg/kg) produced large, long-lived decreases in pulmonary and systemic arterial pressures and an increase in cardiac output (Fig. 6). After combined treatment with L-NAME and ODQ, the decreases in pulmonary and systemic arterial pressure in response to intravenous injections of the midrange dose of BAY 60–2770 were significantly increased, and the decreases in pulmonary and systemic arterial pressures in response to intravenous injections of BAY 41–8543 (30 μg/kg) were significantly attenuated (Fig. 7) compared with responses in control animals (Fig. 1A).

**Responses in monocrotaline-treated animals.** The administration of monocrotaline in a dose of 60 mg/kg iv produced a large increase in pulmonary arterial pressure with small changes in cardiac output and systemic arterial pressure when hemodynamic measurements were made 28 days after administration of the plant alkaloid (Table 5). In animals with monocrotaline-induced pulmonary hypertension, the intravenous injection of a midrange dose of BAY 60–2770 (30 μg/kg) produced significant decreases in pulmonary and systemic arterial pressures and no change in cardiac output (Fig. 8). The decreases in pulmonary and systemic arterial pressures in response to BAY 60–2770 were not significantly different when compared on a percent decrease basis. The absence of an increase in cardiac output in response to BAY60–2770 in the monocrotaline-treated animals may be explained by the observation that baseline cardiac output was higher in this group of rats. The intravenous injection of sodium nitroprusside (1 μg/kg) produced a significant decrease in pulmonary and systemic arterial pressures and an increase in cardiac output (Fig. 8).

**DISCUSSION**

The heme protein sGC is the intracellular receptor for NO (1, 11). NO binds to the reduced heme iron moiety on the enzyme, increasing cGMP formation, which promotes vasodilation in the pulmonary and systemic vascular beds (8, 22, 26, 28). The oxidation of the heme iron group reduces the sensitivity of the enzyme to NO and decreases cGMP production (4, 5, 9). Novel agents have been developed that activate the oxidized or heme-deficient form of the enzyme to promote vasodilation (17). BAY 60–2770 is a NO-independent activator of sGC that increases the activity of the normally reduced heme-containing enzyme 50-fold and the heme-deficient en-

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**Table 4. Effect of L-NAME + ODQ on systemic and pulmonary arterial pressure and on cardiac output**

<table>
<thead>
<tr>
<th></th>
<th>Systemic Arterial Pressure, mmHg</th>
<th>Pulmonary Arterial Pressure, mmHg</th>
<th>Cardiac Output, ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>90 ± 3</td>
<td>20 ± 0.5</td>
<td>116 ± 5</td>
</tr>
<tr>
<td>L-NAME (50 mg/kg iv) + ODQ (5 mg/kg iv)</td>
<td>130 ± 4*</td>
<td>27 ± 1*</td>
<td>101 ± 6*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 16 rats in each group. *P < 0.05 compared with control.
zyme by >200-fold (13). The results of the present study show that intravenous injections of BAY 60–2770 under baseline tone conditions produce small decreases in pulmonary arterial and systemic arterial pressure and no change or small increases in cardiac output. The decreases in pulmonary arterial pressure in response to the sGC activator were markedly enhanced when baseline tone was increased with U-46619. During infusion of the thromboxane receptor agonist, decreases in systemic arterial pressure in response to BAY 60–2770 were attenuated. The results of the present study indicate that BAY 60–2770 has vasodilator activity in the pulmonary and systemic vascular beds and were similar to results with the sGC stimulator BAY 41–8543. These observations are in agreement with data on the stimulatory effect of these agents on the catalytic activity of normally reduced heme containing sGC (2, 13).

The role of endogenous NO and the effect of oxidation of heme iron on the enzyme in mediating vasodilator responses to BAY 60–2770 were investigated. The decreases in pulmonary and systemic arterial pressure in response to BAY 60–2770 were enhanced by treatment with the NOS inhibitor L-NAME and by ODQ, an agent that oxidizes the heme iron on the enzyme (10, 24, 29). Although the sGC stimulator BAY 41–8543 and the sGC activator BAY 60–2770 had similar activity in decreasing pulmonary and systemic arterial pressures, the effect of L-NAME and ODQ treatment on responses to the two agents greatly differed. Treatment with L-NAME markedly reduced vasodilator responses to BAY 41–8543 in the pulmonary and systemic vascular beds, whereas responses to BAY 60–2770 were enhanced with the NOS inhibitor (2). This finding may be indicative of an ability of endogenous NO to protect sGC against oxidation. In addition, the effect of ODQ on responses to the two agents was opposite. Treatment with ODQ attenuated responses to the NO donor sodium nitroprusside and reduced responses to the sGC stimulator BAY 41–8543, whereas responses to the sGC activator BAY 60–2770 were enhanced. These data suggest that pulmonary and systemic vasodilator responses to BAY 60–2770 are not dependent on the presence of endogenous NO or a reduced heme iron group on sGC and, in fact, are enhanced by NOS inhibition and heme oxidation, whereas responses to BAY 41–8543

Table 5. Effect of monocrotaline on systemic and pulmonary arterial pressure and on cardiac output

<table>
<thead>
<tr>
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<th>Pulmonary Arterial Pressure, mmHg</th>
<th>Cardiac Output, ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>99 ± 3</td>
<td>20 ± 1</td>
<td>110 ± 3</td>
</tr>
<tr>
<td>Monocrotaline (60 mg/kg iv)</td>
<td>105 ± 5</td>
<td>44 ± 3*</td>
<td>122 ± 8</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 12–18 rats in each group. *P < 0.05 compared with control.
were dependent on endogenous NO and the reduced heme iron on sGC.

The results of the present study are consistent with results in the pulmonary circulation of the fetal lamb where BAY 58–2667, a sGC activator used in clinical trials for acute decompen.sated heart failure, had potent and sustained vasodilator activity that was enhanced by ODQ (6, 13–16, 20). The results in the intact rat model are different in some respects from responses observed in the fetal lamb (6) where the sGC activator BAY 58–2667 was much more potent than the sGC stimulator BAY 41–2272, and both pulmonary and systemic arterial pressures were decreased in the intact chest rat model in the present study. The reason for the difference in results with the sGC stimulator and activator in these two studies is uncertain but may involve differences in species, methods, age of the animals, or agents used in these experiments (6).

The results with the sGC activator in the presence of ODQ may be interpreted to suggest that vasodilator responses could be enhanced in pathophysiological states in which the heme iron on sGC is oxidized or lost (3, 21, 27, 30). Although vasodilator responses to the NO donor sodium nitroprusside and to the sGC stimulator BAY 41–8543 were attenuated by ODQ, this agent had no significant effect on baseline pressures in the intact rat and in the fetal lamb models (6). The lack of effect on baseline pressures, which is similar to observations in the fetal lamb, can be explained by recent data that show basal activity of the sGC enzyme is not reduced by ODQ, whereas ODQ treatment markedly attenuated NO-stimulated activation (29).

Moreover, the recent observation that the vasodilator activity of kynurenine, an endogenous activator of oxidized or heme-deficient sGC, is enhanced by treatment with ODQ may explain the inability of ODQ to increase pulmonary and systemic arterial pressures in the present study (25).

The administration of monocrotaline produced a large increase in pulmonary arterial pressure with minimal effects on systemic arterial pressure or on cardiac output in the rat. The effect of BAY 60–2770 was investigated in the monocrotaline-treated rat, and the results of these studies show that both
systemic and pulmonary arterial pressures were decreased in a similar manner. These results show that BAY 60–2770 does not have selective pulmonary vasodilator activity in monocrotaline-treated animals. These data suggest that the population or amount of oxidized sGC is not increased in the pulmonary vascular bed in animals with monocrotaline-induced pulmonary hypertension. The hypothesis that sGC is not oxidized in monocrotaline-treated rats is supported by the observation that responses to the NO donor sodium nitroprusside were not impaired in monocrotaline-treated animals.

The observation that the decreases in systemic arterial pressure in response to intravenous injection of BAY 60–2770 were attenuated in U-46619-infused animals suggests that the sGC activator has selective pulmonary vasodilator activity when systemic thromboxane levels are increased. However, the mechanism of this effect is unknown.

In summary, the results of the present study show that the sGC activator BAY 60–2770 has significant slowly developing, long-lived vasodilator activity in the pulmonary and systemic vascular beds in the rat. Vasodilator responses to BAY 60–2770 were enhanced by inhibitors of NOS and by ODQ, which attenuated vasodilator responses to the NO donor sodium nitroprusside and the sGC stimulator BAY 41–8543. BAY 60–2770 and sodium nitroprusside decreased pulmonary and systemic arterial pressures in a nonselective manner in rats with monocrotaline-induced pulmonary hypertension, suggesting that sGC is not oxidized in monocrotaline-treated animals. These results indicate that BAY 60–2770 has significant vasodilator activity in the pulmonary and systemic vascular beds that is enhanced when NOS is inhibited or when sGC is oxidized. These results suggest that the pulmonary vasodilator activity of BAY 60–2770 may be selective when systemic thromboxane levels are elevated.

GRANTS
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DISCLOSURES
No conflicts of interest are declared by the authors.

REFERENCES


