Reduced Hypotensive Action of Arachidonic Acid in the Spontaneously Hypertensive Rat

PETER LUKACSKO, PH.D., EDWARD J. MESSINA, PH.D., AND GABOR KALEY, PH.D.

SUMMARY Prostaglandins (PG) E₂ and I₁ are potent vasodepressor agents and their endogenous release may contribute to the regulation of blood pressure (BP). We investigated whether a decreased response to or a decreased capacity of the vasculature to synthesize vasodepressor PGs could contribute to the increased vascular resistance characteristic of hypertension. The change in mean arterial blood pressure (MAP) to intraaortic (i.a.) injection of PGE₂ and PGI₁ at 0.01, 0.1, 1.0, and 10.0 and of sodium nitroprusside (NaNP) at 0.1, 1.0 and 10.0 nmol/100 g body weight (gbw) was measured in anesthetized, 30-week-old male rats of the spontaneously hypertensive (SHR), normotensive Wistar-Kyoto (WKY) and Wistar (W) strains. The percent decrease in MAP to equivalent doses of NaNP did not differ among the three strains of rats except at 1.0 nmol/100 gbw, a dose to which W rats showed a greater depressor response than either SHR or WKY rats. Similarly, no major differences were found among the strains in their response to the administration of PGI₁ except to a dose of 0.1 nmol/100 gbw to which both SHR and W rats responded with a greater percent decrease in MAP than WKY rats. In contrast, the percent decrease in MAP to PGE₂ was generally greater in SHR than WKY rats but was found not to differ between SHR and W rats at any dose.

The i.a. injection of arachidonic acid (AA), while causing dose-dependent percent decreases in MAP in all strains, produced significantly smaller hypotensive responses at doses of 10 and 100 nmol/100 gbw in SHR as compared to WKY or W rats. At doses of 300 nmol AA or greater, hypotensive responses did not differ significantly between SHR or WKY rats whereas the W rat exhibited percent reductions in MAP that were significantly larger than those obtained in the other two strains of rats. We conclude that SHRs do not have a reduced ability to respond to exogenous PGE₂, PGI₁, or NaNP; however, SHRs appear to have a decreased capacity to utilize AA for the synthesis of vasodepressor PGs. (Hypertension 2: 657-663, 1980)

KEY WORDS • hypotension • prostaglandins • arachidonic acid • indomethacin • sodium nitroprusside • spontaneous hypertension • rats

PROSTAGLANDINS (PGs), a group of biologically active substances, have potent vascular effects. Prostaglandin E₂ and the recently discovered prostacyclin (PGI₁) have been shown to be especially effective in producing a hypotensive response when injected into the circulation of different species. Microscopic observation of microvascular beds has provided more direct evidence of the vasodilator effect of PGE₂ and PGI₁ that may account for the reduction in blood pressure (BP) following their administration.

Studies using isolated vascular strips and microsomal fractions from blood vessels provide convincing evidence that arteries and veins have the ability to synthesize PGE₂ and PGI₁. Furthermore, the same PGs are also made by cultured vascular smooth muscle and vascular endothelial cells. Additional, though circumstantial, proof that blood vessels can release vasodilator PGs is provided by the reduction in blood pressure that follows the intravenous (i.v.) or intraarterial (i.a.) administration of precursors of PGs, the endoperoxides PGG₂ and PGH₂, or arachidonic acid (AA). That the dose-related change in BP is due to the conversion of AA to PGs is indicated by the finding that indomethacin, as well as other inhibitors or cyclooxygenase, eliminate fully the AA-induced effects. Microcirculatory beds also seem to have the capacity to synthesize vasodilator PGs as evidenced by the fact that superfusion of AA results in a dilation of arterioles in rat cremaster muscle that is inhibited by pretreatment with indomethacin. Moreover, there is ample evidence to suggest that PGs, especially PGE, and PGE₂, modulate vascular reactivity to diverse vasoconstrictor stimuli and inhibit norepinephrine release from sympathetic nerve terminals as well.

Although no direct proof exists as yet, it would seem plausible that endogenous vasodilator PGs contribute to the regulation of blood pressure by modulating vascular tone. It could be postulated that either a
decreased response to or a decreased capacity of blood vessels to synthesize vasodepressor PGs accounts for the increased vascular resistance characteristic of hypertensive states. 17, 18 Certain aspects of this hypothesis were examined by observing changes in systemic arterial BP in response to i.a. injection of PGE2, PGI2, and AA in spontaneously hypertensive and normotensive rats.

Methods

Three strains of adult male rats, ranging from 210 to 225 days of age, were used. The spontaneously hypertensive rats (SHR) 19 and two groups of normotensive controls, Wistar-Kyoto (WKY) and Wistar (W) rats, were purchased from Charles-River Farms at 25 days of age and housed in our animal quarters.

Anesthesia was initially induced by means of sodium pentobarbital (50 mg/kg, i.p.) and maintained with subsequent injections (15 mg/kg, i.m.) as required. A carotid artery was cannulated with polyethylene tubing (PE 90) for the measurement of arterial BP by means of a Statham transducer coupled to a Beckman R 611 dynograph.

To study more directly the systemic effects of the agents to be tested and to avoid responses that could be caused by their differential degradation by the lungs, a catheter (PE 10) was introduced into the left pulmonary artery for the purpose of retrograde injection.

After a minimum equilibration period of 30 minutes, some animals of each strain received bolus injections of PGE2, PGI2, and sodium nitroprusside (NaNP) while others received NaNP, AA, oleic, linolenic or di-homo-γ-linolenic acid, and indomethacin. Doses and order of administration of the PGs and NaNP were randomized in contrast to the fatty acids, which were tested starting with low doses. All vasoactive compounds were administered to each animal at least twice, and the responses to a given dose were averaged. All agents, except indomethacin, were given in a total volume of 0.1 ml, and at least a 10-minute period of equilibration was allowed after recovery from each successive dose. The mean arterial blood pressure (MAP) immediately prior to injection was used to calculate the reduction in arterial BP.

Prostaglandins E2 and I2 were injected in doses of 0.01, 0.1, 1.0, and 10.0 nmoles/100 gbw. A stock solution of PGE2 was prepared by dissolving 1.0 mg in 0.1 ml 95% ethanol and 0.9 ml of 2.0 mM Na2CO3. Prostaglandin I2 was prepared fresh daily as a stock solution (1 mg/ml) by dissolving crystals of PGI2 in 1 M TRIS (pH 9.6). Sodium nitroprusside was dissolved in isotonic saline (1 mg/ml) as a stock solution and injected in doses of 0.1, 1.0 and 10.0 nmoles/100 gbw. All stock solutions were stored on ice and diluted with isotonic saline at room temperature immediately prior to injection. The PG vehicles when diluted with an appropriate volume of saline did not affect the MAP.

Arachidonic acid, the precursor for PGs of the "2" series, was dissolved in 100 mM Na2CO3 and administered as the Na salt at 10, 100, 300, 500, and 1000 nmoles/100 gbw. Di-homo-γ-linolenic acid, the precursor for PGs of the "1" series, was injected as the Na salt in a dose of 1000 nmoles/100 gbw to assess whether PGs of the "1" series were synthesized to any significant degree by any of the strains of rats. Oleic and linolenic acids, neither of them PG precursors, were likewise injected as the Na salt at all of the above doses to determine the nonspecific effect of fatty acids on BP. Only animals that did not respond to the NaNP vehicle were used.

A working solution (5 mg/ml) of indomethacin was prepared by dissolving the drug in isotonic saline made alkaline (pH 8) by the addition of NaHCO3. The drug was administered at a dose of 5 mg/kg (0.1 ml of the working solution/100 gbw) in divided doses over a 30-minute period. At least 20 minutes were allowed after the final injection of indomethacin before AA was injected at the largest dose used to verify complete inhibition of PG synthesis.

The data obtained were evaluated by unpaired Student's t test and considered significant at p < 0.05. All regression lines were calculated according to the least squares method and tested for significance by linear correlation coefficients.

Results

The MAP of the three groups of age-matched rats and the actual reduction (ΔMAP) and percent reduction (%ΔMAP) in BP to the administration of PGE2 and PGI2 at 0.01, 0.1, 1.0 and 10.0 nmoles/100 gbw are summarized in table 1. The administration of PGE2 and PGI2 cause a dose-dependent decrease in BP in the three strains of rats. The actual decrease in BP to PGE2 and PGI2 was significantly greater in the SHRs at all doses administered. However, these data must be interpreted with caution because the initial BP of the SHRs was also greatly elevated above those of the controls.

A plot correlating the resting BP with the actual decrease in BP to 10.0 nmoles PGI2/100 gbw is shown for the combined groups of W, SHR and WKY rats (fig. 1). There is a highly significant correlation between these parameters, indicating that the vasodepressor response is directly related to the initial level of the BP. A similar and significant correlation also exists between initial BP and the hypotensive response to doses of PGI2 or PGE2 that we employed in the three strains of rats when they were evaluated separately or together. We interpret these results to mean that the enhanced vasodepressor responses are not necessarily a result of an inherent specific increase in sensitivity of the SHR to prostaglandins but rather a consequence of the elevated BP per se. This latter supposition was lent further credence by the experiments in which the hypotensive responses to i.a. injections of NaNP at 0.1, 1.0 and 10.0 nmoles/100 gbw were measured in the three groups of rats.

The actual drop in BP to all but the lowest dose of NaNP was significantly greater in the SHRs; however, the percent change in BP did not vary among
### TABLE 1. Decrease in Blood Pressure after Intrarrenal Injection of Prostaglandins (PGE₂ and PGI₂)

<table>
<thead>
<tr>
<th>Rat</th>
<th>0.01 (nmole/gbw)</th>
<th>0.1 (nmole/gbw)</th>
<th>1.0 (nmole/gbw)</th>
<th>10.0 (nmole/gbw)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PGE₂</td>
<td>PGI₂</td>
<td>PGE₂</td>
<td>PGI₂</td>
</tr>
<tr>
<td>WKY</td>
<td>MAP</td>
<td>ΔMAP</td>
<td>%ΔMAP</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>114 ± 4</td>
<td>9 ± 1</td>
<td>8 ± 1</td>
<td>(9)</td>
</tr>
<tr>
<td>SHR</td>
<td>MAP</td>
<td>ΔMAP</td>
<td>%ΔMAP</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>143 ± 2†</td>
<td>146 ± 4†</td>
<td>138 ± 2†</td>
<td>(11)</td>
</tr>
<tr>
<td>Wistar</td>
<td>MAP</td>
<td>ΔMAP</td>
<td>%ΔMAP</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>107 ± 3</td>
<td>10 ± 1</td>
<td>10 ± 1</td>
<td>(13)</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± 1 SE; MAP = mean arterial blood pressure (mm Hg); ΔMAP = change in blood pressure (mm Hg); %ΔMAP = percent change in blood pressure; (n) = number of animals.

*Wistar Kyoto (WKY) rats differ from Wistar rats (p < 0.05).
†Spontaneously hypertensive rats (SHR) differ from WKY controls (p < 0.05).
§SHRs differ from Wistar controls (p < 0.05).

the three strains except at a dose of 1.0 nmole/100 gbw, a dose to which W rats responded with a greater depressor response than either SHR or WKY rats (table 2). Additionally, a plot correlating the initial BP with the actual drop in BP to 10.0 nmoles NaNP/100 gbw in the three groups of animals combined indicates a highly significant correlation between these two parameters (fig. 2). Similar correlations exist in each of the three groups when evaluated separately.

When the percent change in mean arterial blood pressure (%ΔMAP) to the injection of PGE₂ was calculated we found that, while the hypotensive responses did not differ between SHR and W rats, the %ΔMAP was significantly greater in both SHR and W as compared to WKY rats at all doses of PGE₂ except at a concentration of 0.01 nmole/100 gbw (table 1). The percent change in MAP to the administration of PGI₂ did not differ significantly between SHR and normotensive control rats except at 0.1 nmole/100 gbw, the only dose to which SHRs were more responsive than WKY rats. However, PGI₂ elicited a greater %ΔMAP in W as compared to WKY rats at all doses.
TABLE 2. Decrease in Blood Pressure after Intraarterial Injection of Sodium Nitroprusside (Na NP)

<table>
<thead>
<tr>
<th>Rat</th>
<th>BP</th>
<th>0.1</th>
<th>1.0</th>
<th>10.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>WKY</td>
<td>MAP</td>
<td>108 ± 3</td>
<td>107 ± 3</td>
<td>110 ± 3</td>
</tr>
<tr>
<td></td>
<td>ΔMAP</td>
<td>7 ± 1</td>
<td>36 ± 1*</td>
<td>67 ± 3</td>
</tr>
<tr>
<td></td>
<td>%ΔMAP</td>
<td>7 ± 1</td>
<td>34 ± 1*</td>
<td>62 ± 2</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>(9)</td>
<td>(9)</td>
<td>(9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SHR</th>
<th>MAP</th>
<th>154 ± 5†</th>
<th>153 ± 5†</th>
<th>157 ± 5†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ΔMAP</td>
<td>7 ± 1</td>
<td>47 ± 2†</td>
<td>96 ± 4†</td>
</tr>
<tr>
<td></td>
<td>%ΔMAP</td>
<td>5 ± 1</td>
<td>32 ± 2†</td>
<td>61 ± 1</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>(11)</td>
<td>(11)</td>
<td>(12)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wistar</th>
<th>MAP</th>
<th>103 ± 4</th>
<th>104 ± 3</th>
<th>104 ± 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ΔMAP</td>
<td>7 ± 1</td>
<td>41 ± 1</td>
<td>65 ± 2</td>
</tr>
<tr>
<td></td>
<td>%ΔMAP</td>
<td>7 ± 1</td>
<td>40 ± 1</td>
<td>63 ± 2</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>(10)</td>
<td>(10)</td>
<td>(10)</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± 1 se; MAP = mean arterial blood pressure (mm Hg); ΔMAP = change in blood pressure (mm Hg); %ΔMAP = percent change in blood pressure; (n) = number of animals.

- Wistar Kyoto (WKY) rats differ from Wistar rats (p < 0.05).
- Spontaneously hypertensive rats (SHR) differ from WKY rats (p < 0.05).
- SHRs differ from Wistar rats (p < 0.05).

except 0.01 nmole/100 gbw. The data also indicate that PGF sub 2 is about 10 times more potent than PGE 2 as a vasodilator in the three strains of rats at doses exceeding 0.01 nmole/100 gbw (table 1) since approximately 10 times more PGE 2 than PGF 2 is required to give an equivalent drop in BP. In addition, PGF 2 induced a longer lasting BP reduction than equal doses of PGE 2 (fig. 3). The stable metabolite of PGF 2, 6-oxo-PGF 10 , did not lower BP in any of the animals at doses up to 20 nmole/100 gbw.

The i.a. injection of AA induced regularly a biphasic response in BP in all strains of rats consisting of an initial transient fall followed by a secondary, more sustained hypotensive response (fig. 4). Only the transient event was elicited by the i.a. administration of linolenic or oleic acids.

The depressor response induced by di-homo-γ-linolenic acid was in no way different from that following injections of nonspecific fatty acids, indicating that this fatty acid did not serve as an adequate substrate for blood vessel cyclooxygenase in the rat.

Indomethacin did not abolish or alter the initial fall in MAP to AA but did completely inhibit the secondary hypotensive response (fig. 4) without appreciably influencing the basal MAP in any of the strains of rats. It follows that the secondary long-lasting reduction in BP is mediated by PGs whereas the initial short-lasting hypotensive response is characteristic of the injection of all fatty acids in each of the three groups examined.

Blood pressure responses to i.a. injections of 10, 100, 300, 500, and 1000 nmole AA/100 gbw are summarized in table 3. The actual BP reduction following equivalent doses of AA did not vary significantly between the WKY and W rats at either 10 or 100 nmole AA/100 gbw, whereas at higher doses the W rats were significantly more responsive to AA.

In contrast SHRs exhibited a significantly smaller response than either W or WKY rats to the lowest dose of AA and also a smaller response than W rats to 100 nmole AA/100 gbw.

When percent reduction in BP (perhaps a more accurate measure of the responsiveness to a vasodepressor agent than actual drop in BP) was con-
TABLE 3. Decrease in Blood Pressure after Intraarterial Injection of Arachidonic Acid (AA)

<table>
<thead>
<tr>
<th>Rat</th>
<th>BP</th>
<th>10</th>
<th>100</th>
<th>300</th>
<th>500</th>
<th>1000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAP</td>
<td>n mole AA/100 gbw</td>
<td>MAP</td>
<td>AMAP</td>
<td>MAP</td>
<td>AMAP</td>
</tr>
<tr>
<td>WKY</td>
<td>MAP</td>
<td>120 ± 3*</td>
<td>118 ± 3*</td>
<td>121 ± 4</td>
<td>121 ± 4</td>
<td>131 ± 3</td>
</tr>
<tr>
<td></td>
<td>ΔMAP</td>
<td>6 ± 2</td>
<td>22 ± 3</td>
<td>29 ± 2*</td>
<td>38 ± 6*</td>
<td>42 ± 4*</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>(17)</td>
<td>(19)</td>
<td>(12)</td>
<td>(6)</td>
<td>(20)</td>
</tr>
<tr>
<td>SHR</td>
<td>MAP</td>
<td>165 ± 5††</td>
<td>156 ± 4††</td>
<td>160 ± 6†</td>
<td>165 ± 6†</td>
<td>174 ± 4††</td>
</tr>
<tr>
<td></td>
<td>ΔMAP</td>
<td>1 ± 1††</td>
<td>16 ± 2†</td>
<td>34 ± 3†</td>
<td>46 ± 3</td>
<td>47 ± 4</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>(16)</td>
<td>(18)</td>
<td>(13)</td>
<td>(14)</td>
<td>(20)</td>
</tr>
<tr>
<td>Wistar</td>
<td>MAP</td>
<td>106 ± 3</td>
<td>107 ± 3</td>
<td>113 ± 3</td>
<td>119 ± 4</td>
<td>124 ± 4</td>
</tr>
<tr>
<td></td>
<td>ΔMAP</td>
<td>6 ± 2</td>
<td>23 ± 2</td>
<td>45 ± 2</td>
<td>51 ± 3</td>
<td>55 ± 4</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>(15)</td>
<td>(17)</td>
<td>(17)</td>
<td>(12)</td>
<td>(15)</td>
</tr>
</tbody>
</table>

Results are expressed as mean =•± 1 SE; MAP = mean arterial blood pressure (mm Hg); ΔMAP = change in blood pressure (mm Hg); (n) = number of animals.

*Wistar Kyoto (WKY) rats differ from Wistar rats (p < 0.05).
†Spontaneously hypertensive rats (SHR) differ from Wistar Kyoto (WKY) rats (p < 0.05).
‡SHRs differ from Wistar rats (p < 0.05).

sidered, SHRs had a higher threshold to AA and were significantly less responsive than either W or WKY rats at the two lower doses of AA administered (fig. 5). Furthermore, W rats reacted with greater hypotensive responses to doses of 300 nmoles AA/100 gbw and higher than did SHR or WKY rats.

Discussion

The role of PGs in the etiology and pathogenesis of hypertension is not clear. There exists, however, sufficient evidence to indicate that PGs can contribute to the regulation of circulatory homeostasis. Prostaglandin E₄ has been implicated as the endogenous vasodepressor metabolite of AA; however, more recent data suggest that PGI₄ might be the major prostaglandin synthesized by vascular tissue. In light of the observation that PGE₄ and PGI₄ are potent vasodilators and are synthesized by blood vessels from endogenous substrate, one might propose that a decreased responsiveness to PGs or perhaps an altered capacity to synthesize vasodilator PGs may contribute to the development of hypertension.

Whenever hypotensive responses to PGs are examined on the basis of percent changes in BP, the present data indicate that there are no significant differences between SHR and W rats to injections of either PGE₄ or PGI₄ or between SHR and WKY rats to PGI₄. In contrast, hypotensive responses to PGE₄ were generally greater in SHR as compared to WKY rats. Since PGE₄ reduces norepinephrine release from sympathetic nerve endings, it has been suggested that by virtue of diminishing the effects of increased sympathetic activity characteristic of the SHR, it may evoke a greater depressor response in the hypertensive animal than in normotensive controls. This hypothesis is lent further credence by our data since we found essentially no differences between SHRs and either group of normotensive control rats in the hypotensive responses to PGI₄, a substance that has been reported to be many times less potent than PGE₄ in inhibiting sympathetic neurotransmitter releases. Furthermore, recent studies have demonstrated that the reduction in BP to the i.v. administration of PGE₄ may be mediated in part by a reflex initiated by vagal afferents and that SHRs seem especially sensitive to this effect. The observations above could explain the more pronounced hypotensive response of SHR as compared to WKY rats to PGE₄. The fact that both PGE₄ and PGI₄ generally elicited smaller hypotensive responses in WKY than W rats, however, suggests that variances between SHR and WKY rats with regard to the BP-lowering effects of PGs may be not...
only related to basal BP but may also be strain-dependent since such variances exist between the two normotensive controls. Moreover, the increased responsiveness of SHR and W as compared to WKY rats to PGE₂ or PGI₂ seems specific for PGs in that the administration of NaNP resulted in a % Δ MAP that essentially did not vary among the three groups of rats.

Previously others²⁸ have found that no difference exists with regard to the BP-lowering effect of i.a. injections of PGD₂ and PGE₂ between the New Zealand genetically hypertensive strain and normotensive control rats. These results are contrary to recent reports suggesting that both PGI₁²⁸ and PGE₂²⁸ are significantly more active in causing vasodepressor responses in SHR than in normotensive rats. In these experiments not only was the PGE₂-induced absolute drop in BP well correlated with the initial BP, but, also, reducing the BP of the SHRs by means of antihypertensive drug therapy proportionately reduced the hypotensive response to PGE₂ to a level obtained in control rats.²⁸ These data might be interpreted to indicate that there is no inherent increase in sensitivity in SHRs to PGE₂ were it not for the fact that injections of acetylcholine and isoproterenol elicited identical, absolute reductions in BP in untreated SHR and control animals.²⁸ In contrast, a similar study²⁸ has shown that the actual reduction in BP to acetylcholine is greater in SHR and renal hypertensive rats than in normotensive controls whereas the percent change in BP is similar among the three groups. Our data also indicate that a positive correlation exists between initial BP and the actual reduction in BP to constant doses of PGs or NaNP in control groups as well as in SHRs. On the basis of these and all other experimental results described above, it seems reasonable to conclude that SHRs do not have a decreased responsiveness to vasodepressor PGs, an alteration that might have helped to explain the elevation of BP in the New Zealand strain of genetically hypertensive rats.³⁴ M It has also been reported¹ that isolated perfused kidneys of both salt-loaded and renal hypertensive rats release less PGE₂-like activity when stimulated with norepinephrine and AA than kidneys of normal rats. One can only speculate as to whether the changes above and the decrease in the responses to AA in the SHR that we observed are secondary to the hypertension or are primary factors in the initiation or maintenance of the elevated BP. The present data also do not clarify whether differences in uptake or alterations in the conversion of AA are the cause of the changes observed in the SH rat. Notwithstanding the above possibilities, one might hypothesize that, whereas in the normal rat the primary metabolite of AA in small resistance vessels is PGI₂, in the SHR a decrease, however subtle, in the ratio of released PGI₂ to PGE₂ occurs to account for the reduced response to AA.

In conclusion, it seems most likely that PGs are intimately involved in the regulation and/or maintenance of BP in the SHR. Whether the reduced

Arachidonic acid is readily converted to PGs by rat aortic strips in vitro³¹ and in vivo.⁴ While it is still uncertain which of the vasodepressor PGs produced is the principal one, it appears that both PGE₂⁴ and PGI₂²⁸,³⁰ are readily synthesized in vitro by rat vascular tissues. Whichever PG is released, the present data demonstrate that the hypotensive responses elicited by the administration of threshold or low doses of AA in vivo are significantly smaller in SHRs than in either group of normotensive control animals.

On the other hand, the hypotensive response to higher doses of AA (300 nmoles and above) did not differ between SHR and WKY rats but was significantly lower than those in W rats. That the greater hypotensive response of W rats to the higher doses of AA is not simply due to an increased responsiveness to synthesized PGE₂ or PGI₂ is evidenced by the observation that there are no significant differences between SHR and W rats to the injection of either of these PGs. However, blood vessels of W rats may have a greater maximum capacity to synthesize vasodepressor PGs from AA than either SHR or WKY rats. That the hypotension is due to PG synthesis is convincingly shown by the fact that indomethacin completely inhibited the response (fig. 4) and that neither oleic acid nor linolenic acid caused a sustained depression in BP. Furthermore, administration of di-homo-γ-linolenic acid did not result in systemic hypotension even when injected at the largest dose in any of the three strains of rat, suggesting that AA is the preferred substrate for PG synthesis in these animals.

Prostaglandins might be implicated in the genesis of hypertension in a variety of ways. Recent studies have shown that SHR arterial tissue releases more PGE₂⁴,⁵ and PGI₂²⁸ than vascular tissue obtained from normotensive rats. Other studies have indicated that a change in the activity of PG-degrading enzymes might be an important factor in the development of high BP in the New Zealand strain of genetically hypertensive rats.³⁴ M It has also been reported³⁰ that isolated perfused kidneys of both salt-loaded and renal hypertensive rats release less PGE₂-like activity when stimulated with norepinephrine and AA than kidneys of normal rats. One can only speculate as to whether the changes above and the decrease in the responses to AA in the SHR that we observed are secondary to the hypertension or are primary factors in the initiation or maintenance of the elevated BP. The present data also do not clarify whether differences in uptake or alterations in the conversion of AA are the cause of the changes observed in the SH rat. Notwithstanding the above possibilities, one might hypothesize that, whereas in the normal rat the primary metabolite of AA in small resistance vessels is PGI₂, in the SHR a decrease, however subtle, in the ratio of released PGI₂ to PGE₂ occurs to account for the reduced response to AA.

In conclusion, it seems most likely that PGs are intimately involved in the regulation and/or maintenance of BP in the SHR. Whether the reduced
capacity to utilize exogenously administered AA is a reflection of an inherent change in the blood vessels of the hypertensive animal and whether this change is of pathophysiologic significance is open to question and will have to await further study.

Acknowledgments

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