The effects of prostaglandins E₁, A₁, and F₂α on the cerebral circulation of dogs and monkeys

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Alterations in cerebrovascular tone caused by the intracarotid administration of prostaglandin E₁, A₁, and F₂α were evaluated by means of a standard perfusion technique in dogs and monkeys. Only PGF₂α evoked a selective increase in cerebrovascular tone. This effect was observed in both species and resembled the action of serotonin. On the other hand, prostaglandin E₁ selectively reduced cerebrovascular tone in dogs, but had no such specific action in the monkey. Prostaglandin A₁ lacked a specific influence on the cerebral circulation of either species. Since different prostaglandins produced specific and diametrically opposite effects on cerebral circulation, these substances may be useful in experimental studies of vasospasm, and may normally influence cerebrovascular tone.

Key Words: prostaglandin, cerebral circulation, vasospasm, cerebrovascular tone, dogs, monkeys

The prostaglandins (PG's) are a group of biologically active lipid substances isolated from various tissues, including lung, kidney, vesicular gland, thymus, spleen, and brain. These substances are built on the prostanoic acid skeleton whose molecular configuration is visually memorable as a cyclopentane nucleus with two side chains (Fig. 1). Four series of prostaglandins, E, F, A, and B, have been isolated.

Their close molecular kinship, however, contrasts with the wide divergence of their biological effects. The many facets of prostaglandin research have been well reviewed.

In our assessment of pharmacological substances potentially applicable to the problem of cerebral vasospasm, several observations prompted our interest in the possible effects of prostaglandins on cerebral vasculature. Prostaglandin E₁ (PGE₁) and prostaglandin A₁ (PGA₁) directly depress the smooth muscle of resistance type arterioles, causing vasodilatation. Their influence appears unrelated to the catecholamine receptor system. Prostaglandin vasodepression may be related to the regulation of ionic calcium concentration at the cell membrane or intracellularly. A unifying postulate would relate the general effects of these compounds to the adenyl cyclase-cyclic AMP "second messenger" system. PGF₂α exerts a pressor effect on most vascular beds.

These properties of various prostaglandins, although well demonstrated for peripheral vascular beds, have not been previously assessed for the cerebral vessels.

Like many vasoactive compounds, some prostaglandins affect platelet behavior. PGE₁,
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for instance, is a powerful inhibitor of ADP-induced platelet aggregation. Within the central nervous system, prostaglandin is felt to modulate neural transmission. Both PGE$_1$, and PGF$_{2\alpha}$, in fact, are contained in central nervous system tissue in the quantity of 10 mg/gm.

This study evaluates the effects of PGE$_1$, PGA$_1$, and PGF$_{2\alpha}$ on the cerebral vasculature of the monkey and dog.*

Methods

The laboratory animals used in these experiments consisted of six rhesus monkeys, whose cerebral circulation closely resembles that of man, and 11 mongrel dogs, whose peripheral physiological responses to prostaglandins are catalogued in depth in the literature.

The monkeys of both sexes weighed from 3.8 to 6.8 kg. The large mongrels, likewise of both sexes, weighed from 17.5 to 25 kg. All animals were anesthetized with intravenous pentobarbital sodium (25 mg/kg). Endotracheal tubes were inserted, and each animal was allowed to breathe room air.

The experimental perfusion method is schematically represented in Fig. 2. Each animal was heparinized (3 to 6 mg/kg). Thereafter, blood derived from the cannulated iliac artery was led to a siliconized reservoir, the flow modulated by a clamp. The blood was delivered to the carotid system by a Cole Parmer roller pump. The internal carotid artery, unilaterally in the monkey and bilaterally in the dog, was exposed, cannulated, and connected to the output pump. Thereafter, each carotid artery was ligated proximally, and the external carotid was then ligated. The carotid receptors were then denervated. It was demonstrated radio graphically that cerebral blood flow in this dog model was maintained without "steal" by the internal carotid arteries.

The blood flow thus directed into the internal carotid system was adjusted to provide a perfusion pressure equal to that of systemic pressure and was then held constant. Thus, a change in perfusion pressure would inferentially reflect a change in vascular tone within the internal carotid system. The lack of carotid receptor response was easily confirmed by elevating the perfusion pressure and observing the systemic pressure record.

In addition to the perfusion pressure, recordings were made of the systemic arterial pressure (via the right femoral artery), external carotid artery pressure, cerebrospinal fluid (CSF) pressure (via the cannulated cisterna magna), and central venous pressure. It was felt that any change in CSF pressure might reflect a change in vascular volume within a closed space. The EKG and respiratory parameters were likewise recorded. A Statham strain gauge T23BC was used to obtain venous and CSF pressures, and the T23AA for arterial pressures. Blood, pCO$_2$, pO$_2$, and pH were determined before, during, and after each animal study.

The drugs under investigation were introduced into the output flow of the blood pump by means of a Harvard infusion pump. The dosages were varied initially until reproducible responses were obtained. Thereafter, infusion of the drugs was performed at volumes of 0.1 ml/min until all pressure changes observed became stable. Such infusions usually took from 2 to 5 min, after which recovery was observed. The prostaglandins were given two or three times throughout the course of an experiment, and the standardizing drugs were given at the beginning and end of each experiment to see if the vascular responses to these had deteriorated.

Each of the prostaglandins studied (PGE$_1$, PGA$_1$, and PGF$_{2\alpha}$) was dissolved in

* The prostaglandins studied, PGE$_1$, PGA$_1$, and PGF$_{2\alpha}$, were obtained by courtesy of Dr. John E. Pike of the Upjohn Pharmaceutical Company.

PGE

PGF

PGA

PGB

PROSTANOIC ACID

Fig. 1. Diagram of chemical bonds illustrating the prostanoic acid nucleus and the four groups of prostaglandin derived therefrom.
ethanol, and thereafter diluted to desired concentration with physiological saline. Four familiar test drugs (1-norepinephrine barbiturate, serotonin creatinine sulfate, histamine dihydrochloride, and acetylcholine iodide) were used to document the integrity of each animal’s responses before and after prostaglandin infusion as well as for comparative reasons. A crossover design was employed in the administration of the prostaglandins. Dosage details will be presented below. In some experiments all drugs were introduced intravenously in order to compare our systemic findings with those from other studies reported in the literature.

**Results**

Results are summarized in Table 1. The standardizing drugs (Figs. 3–5) used to validate the continued responsiveness of each animal before and after prostaglandin perfusion evoked familiar responses.10 Norepinephrine (Fig. 3) elevated the pressure in all three systems (internal carotid, external carotid, and systemic) as a result of increased systemic pressure. Serotonin has well known pressor effects on cerebral vasculature (Fig. 4). Histamine (Fig. 5) depresses cerebral vascular tone in the monkey without notable effects systemically. Acetylcholine reduces cerebral vascular tone and is apparently broken down by circulating cholinesterase prior to producing effects systemically.

**Prostaglandin E₁**

In the dog, PGE₁ in doses ranging from 0.1 µg/kg/min to 1.0 µg/kg/min (volume 0.1 mm) consistently lowered the perfusion pressure approximately 25% (Table 1 and Fig. 6). Following a noticeable time lag, a drop in systemic pressure (Table 2) occurred, presumably due to a recirculation phenomenon. The selective drop in perfusion pressure indicated reduced cerebral vascular
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**TABLE 1**

*Maximum changes (mm Hg) in mean blood and CSF pressure caused by prostaglandins infused through the carotid system*

<table>
<thead>
<tr>
<th>Drug and Species</th>
<th>No. of Animals</th>
<th>Dose µg/kg/min</th>
<th>Internal Carotid</th>
<th>External Carotid</th>
<th>Femoral</th>
<th>CSF</th>
<th>Venous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dog:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>control</td>
<td>11</td>
<td>—</td>
<td>131.8 ± 11.7</td>
<td>74.4 ± 3.4</td>
<td>126.4 ± 14.0</td>
<td>8.4 ± 2.8</td>
<td>4.7 ± 1.6</td>
</tr>
<tr>
<td>norepinephrine</td>
<td></td>
<td>2-5</td>
<td>+75.3 ± 15.4</td>
<td>+88.1 ± 13.0</td>
<td>+52.6 ± 16.5</td>
<td>+2.7 ± 1.2</td>
<td>+1.5 ± 0.3</td>
</tr>
<tr>
<td>serotonin</td>
<td></td>
<td>1-10</td>
<td>+76.4 ± 14.6</td>
<td>-11.2 ± 9.1</td>
<td>-6.6 ± 4.8</td>
<td>-2.0 ± 0.6</td>
<td>0.0</td>
</tr>
<tr>
<td>PGF₂</td>
<td></td>
<td>1.0</td>
<td>+29.4 ± 10.9</td>
<td>-9.8 ± 8.2</td>
<td>-1.3 ± 0.8</td>
<td>+0.4 ± 0.9</td>
<td>-0.2</td>
</tr>
<tr>
<td>PGA₁</td>
<td></td>
<td>0.1-1.0</td>
<td>-36.9 ± 5.3</td>
<td>-37.6 ± 5.9</td>
<td>-38.4 ± 9.2</td>
<td>+1.1 ± 0.6</td>
<td>+0.1</td>
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<tr>
<td>PGE₁</td>
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<td>0.1-1.0</td>
<td>-37.3 ± 7.1</td>
<td>-25.5 ± 4.4</td>
<td>-27.8 ± 5.8</td>
<td>+0.7</td>
<td>0.0</td>
</tr>
<tr>
<td>acetylcholine</td>
<td></td>
<td>1-2</td>
<td>-23.2 ± 10.4</td>
<td>-6.7 ± 5.2</td>
<td>+1.4 ± 0.8</td>
<td>+0.9</td>
<td>-0.1</td>
</tr>
<tr>
<td><strong>Monkey:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>control</td>
<td>6</td>
<td>—</td>
<td>112.4 ± 6.6</td>
<td>51.5 ± 6.1</td>
<td>110 ± 5.3</td>
<td>9.3 ± 3.0</td>
<td>6.5 ± 2.4</td>
</tr>
<tr>
<td>norepinephrine</td>
<td></td>
<td>2-5</td>
<td>+39.7 ± 8.8</td>
<td>+48.2 ± 6.3</td>
<td>+41.3 ± 5.9</td>
<td>+41.3 ± 5.9</td>
<td>+1.4 ± 1.5</td>
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<tr>
<td>serotonin</td>
<td></td>
<td>5-10</td>
<td>+25 ± 11.4</td>
<td>-10.4 ± 3.8</td>
<td>-5.2 ± 4.6</td>
<td>+1.0</td>
<td>+0.4</td>
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<tr>
<td>PGF₂</td>
<td></td>
<td>10-30</td>
<td>+63.1 ± 15.7</td>
<td>+6.2 ± 4.4</td>
<td>+5.7 ± 3.2</td>
<td>+2.4 ± 1.2</td>
<td>+2.2 ± 0.1</td>
</tr>
<tr>
<td>PGA₁</td>
<td></td>
<td>5-30</td>
<td>-5.8 ± 4.3</td>
<td>-4.1 ± 2.7</td>
<td>-7.5 ± 4.1</td>
<td>+1.4 ± 2.3</td>
<td>+0.1</td>
</tr>
<tr>
<td>PGE₁</td>
<td></td>
<td>5-30</td>
<td>-23.4 ± 7.7</td>
<td>-16.4 ± 6.9</td>
<td>-27.3 ± 8.2</td>
<td>+4.6 ± 3.2</td>
<td>-0.4</td>
</tr>
<tr>
<td>histamine</td>
<td></td>
<td>10-20</td>
<td>-29.8 ± 8.4</td>
<td>-5.2 ± 4.7</td>
<td>-3.3 ± 2.3</td>
<td>+2.0 ± 1.6</td>
<td>0.0</td>
</tr>
</tbody>
</table>

* Pressure recordings are expressed as mean ± S.D. except where low values represent essentially an estimate. Plus signs before mean values indicate a pressor and minus signs a depressor response.

**Fig. 3.** Recording showing that norepinephrine was nonspecific in its effect on cerebrovascular tone when perfused into the internal carotid artery. Note that all of the arterial pressures rose simultaneously, indicating that norepinephrine had passed through the cerebral vasculature before eliciting a response. Arrows signify duration of drug infusion.

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tone rather than systemic pressure variation. In the dosage ranges employed, the magnitude of response paralleled the dose size. The reduction of perfusion pressure caused by acetylcholine was somewhat less than that evoked by PGE1.

In the monkey (Fig. 7), however, PGE1 showed no selective properties. A simultaneous fall of the perfusion pressure accompanied a systemic pressure fall following the intracarotid infusion of PGE1 in doses of 5 to 30 μg/kg/min. Here species variation, common in responses to prostaglandins, may have been an important factor.

Since histamine infusion reduced the perfusion pressure almost 30% without signifi-
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Fig. 6. Recording showing a selective depressor response of the internal carotid pressure caused by prostaglandin E₁. In many dogs a delayed systemic response was also evident (Tables 1 and 2), but distinguishable from the simultaneous drop in all arterial pressures seen with prostaglandin A₁.

Significant systemic response, the unilateral perfusion technique probably does not impair the accuracy of the monkey model.

Prostaglandin A₁

Because of the simultaneous occurrence of vasodepression of similar magnitude in all systems, the animals' responses to intracarotid PGA₁ appeared related to systemic pressure change (Fig. 8, Tables 1 and 2). Thus, PGA₁ demonstrated no selective effects on the cerebrovasculature in either species.

**TABLE 2**

*Differences in the time (sec) of onset of action between perfused internal carotid pressure and other pressures in the monkey (m) and dog (d) produced by intracarotid perfusion of prostaglandins (same as in Table 1)*

<table>
<thead>
<tr>
<th>Drug†</th>
<th>Animal✝</th>
<th>Internal Carotid Pressure (sec)</th>
<th>Minus External Carotid (sec)</th>
<th>Minus Femoral (sec)</th>
<th>Minus CSF (sec)</th>
<th>Minus Venous (sec)</th>
<th>Average Duration of Action‡ (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE</td>
<td>M</td>
<td>33</td>
<td>0.8</td>
<td>5.9</td>
<td>9.1</td>
<td>47</td>
<td>260</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>14</td>
<td>5.5</td>
<td>35</td>
<td>22</td>
<td>62</td>
<td>273</td>
</tr>
<tr>
<td>PGFa</td>
<td>M</td>
<td>71</td>
<td>0.4</td>
<td>24</td>
<td>8.2</td>
<td>—</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>32</td>
<td>7.6</td>
<td>8.2</td>
<td>42</td>
<td>—</td>
<td>381</td>
</tr>
<tr>
<td>PGA₁</td>
<td>M</td>
<td>43</td>
<td>0.2</td>
<td>2.6</td>
<td>4.0</td>
<td>118</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>33</td>
<td>7.4</td>
<td>8.1</td>
<td>31</td>
<td>—</td>
<td>353</td>
</tr>
<tr>
<td>PGE₁</td>
<td>M</td>
<td>36</td>
<td>5.1</td>
<td>5.8</td>
<td>4.0</td>
<td>42</td>
<td>304</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>14</td>
<td>7.8</td>
<td>51</td>
<td>43</td>
<td>—</td>
<td>407</td>
</tr>
</tbody>
</table>

*NE = 1-norepinephrine barbitrate; PG = prostaglandin.
† M = monkey; D = dog.
‡ End of response minus end of injection period.
§ Too few responses.

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Fig. 7. Recording showing the lack of a specific depressor effect of prostaglandin E₁ in the monkey on the vessels perfused. Tracings indicated this drug passed through the cerebral vessels, causing a drop in femoral pressure which, secondarily, reduced the perfusion and external carotid pressures.

Fig. 8. Recording showing that prostaglandin A₁ lacked a specific effect on the internal carotid pressure (perfused), lowering all three arterial pressures simultaneously.
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Prostaglandin F$_{2\alpha}$

In the dog, PGF$_{2\alpha}$ (1.0 μg/kg/min) elevated perfusion pressure selectivity without systemic response. The magnitude of elevation was about one-third that of norepinephrine and serotonin in the dosage forms noted. In the monkey, the cerebrovascular tone increase evoked by PGF$_{2\alpha}$ (10 to 30 μg/kg/min) was of greater magnitude than that of norepinephrine or serotonin in the dosages noted. In neither animal was a systemic effect of recirculated PGF$_{2\alpha}$ noted. It is thus concluded that prostaglandin F$_{2\alpha}$ produced increased tone in the cerebrovasculature of the dog and monkey (Fig. 9 and Tables 1 and 2).

Several general findings are notable. In the technically successful experiment all responses returned to the baseline, and tachyphylaxis did not occur to any prostaglandin preparation. The recorded systemic parameters of blood pressure, EKG, and respiration were consistent with those reported elsewhere in the literature for peripheral intravenous and intra-arterial prostaglandin administration. Significant variation in pO$_2$, pCO$_2$, and pH did not occur throughout the experiments.

Discussion

This study assesses the cerebral vascular responses in dogs and monkeys to prostaglandins E$_1$, A$_1$, and F$_{2\alpha}$ by means of a standard perfusion technique. Several observations indicate that the well-known rete mirabile of dogs does not invalidate a comparison of our experimental findings in this species with those in the monkey. Contrast studies through the perfusion apparatus indicate that minimal external carotid system steal occurs under these experimental conditions. Moreover, serotonin when infused through the carotid system evokes a pressor effect within the perfusion (internal carotid) system and a concomitant depressor effect in the external carotid recording (Table 1). Also, acetylcholine causes a localized depressor response in the internal carotid system, further showing pharmacologically that the perfusion technique used effectively limits the action of drugs to intracranial vessels. Together, such findings indicate that any difference in response to the prostaglandins observed between the dog and monkey is more likely related to pharmacological than to anatomical differences.

In the dog, PGE$_1$ infused intracarotidly preferentially depresses cerebrovascular tone. The magnitude of depression appears dose-related and independent of the expected systemic responses. In contrast, PGE$_1$, even in higher doses, has no apprecia-

![Diagram](Fig. 9. Recording showing clearly the specific pressor effect of prostaglandin F$_{2\alpha}$ on the vessels perfused by the internal carotid artery.)
ble effect on the monkey’s cerebrovasculature, whereas the expected systemic depression occurs. Such species variation in response to the prostaglandins has been well documented.6

PGA1, also a peripheral vasodepressor agent, produced no selective effects on the perfused cerebral vasculature of either species.

The properties of PGF2α differ strikingly from those of PGE1 and PGA1. PGF2α, a known constrictor agent in dogs, evokes a marked pressor response in the cerebral vasculature of both dogs and monkeys. This pressor effect parallels that of serotonin and lacks concomitant change in systemic pressures.

These observations support the opinion of most workers that vasoactive prostaglandins exert their effects directly upon vascular smooth muscle rather than by a central reflexogenic mechanism.12 Moreover, a preliminary report from this laboratory demonstrates that the effect of PGF2α is not mediated through receptors for serotonin or norepinephrine.15

That PGE1 and PGF2α may directly influence the cerebrovasculature is of special interest, since the central nervous system is abundantly endowed with both compounds which “leak” into the cerebrospinal fluid.6 It is thus possible that these compounds may influence physiological and pathological cerebrovascular phenomena. Both, for example, may be important in cerebrovascular autoregulation. Under some circumstances, PGF2α may play a significant role in protracted vasoconstriction, and PGE1 in its eventual lysis.

References

Stockholm, Almqvist and Wiksell, 1966, pp 123–132

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