Oxygen Radicals Mediate the Cerebral Arteriolar Dilation from Arachidonate and Bradykinin in Cats

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SUMMARY. Topical application of sodium arachidonate (50–200 μg/ml) or bradykinin (0.1–10 μg/ml) on the brain surface of anesthetized cats caused dose-dependent cerebral arteriolar dilation. This dilation was blocked by 67–100% in the presence of superoxide dismutase and catalase. These enzymes did not affect the changes in arteriolar diameter caused by alterations in arterial blood Pco₂, or the arteriolar dilation from topical acetylcholine. Enzymes inactivated by heat had no effect on the vasodilation from arachidonate or bradykinin. Superoxide dismutase alone or catalase alone reduced the dilation during application of 200 μg/ml of arachidonate for 15 minutes; they also completely prevented the residual dilation seen 1 hour after washout, as well as the reduction in the vasoconstrictive effects of arterial hypocapnia observed at this time. The results show that superoxide anion radical and hydrogen peroxide, or radicals derived from them, such as the hydroxyl radical, are mediators of the cerebral arteriolar dilation from sodium arachidonate or bradykinin. These radicals are not the endothelium-derived relaxant factor released by acetylcholine. The presence of both superoxide anion radical and hydrogen peroxide is required for the production of the vascular damage seen during prolonged application of high concentrations of sodium arachidonate. (Circ Res 55: 295–303, 1984)

Methods

Experiments were carried out in cats anesthetized with sodium pentobarbital (30 mg/kg, iv). After completion of tracheostomy, each animal was ventilated with a positive pressure respirator and received 5 mg/kg of gallamine triethiodide for skeletal muscle paralysis. The end-expiratory CO₂ of the animal was monitored continuously with a Beckman infrared CO₂ analyzer and was maintained at a constant level of about 30 mm Hg by adjusting the respirator rate and volume. Arterial blood pressure was measured with a Statham transducer connected to a cannula introduced into the aorta via the femoral artery. Arterial blood samples were collected periodically for the determination of PO₂, PCO₂, pH, and hematocrit. Blood gases and pH were measured with Radiometer electrodes; hematocrit was measured by a micromethod.

Pial precapillary vessels were visualized through an acutely implanted cranial window, as described in detail previously (Levasseur et al., 1975). The window was implanted over the parietal cortex to allow visualization of the vessels in the marginal, suprasylvian, and ectosylvian gyri. The cranial window was equipped with three openings. Two openings were used as inlet and outlet for filling the space under the window with various solutions. The third opening was connected to a Statham pressure transducer for monitoring intracranial pressure. The outlet of the window was connected to plastic tubing arranged in a loop, the open end of which was placed at a fixed level to give a constant intracranial pressure of 5 mm Hg throughout the experiment. The space under the window was initially filled with artificial cerebrospinal fluid (CSF) having a composition identical to that of cats (Levasseur et al., 1975). Pial arterioles were visualized with a Leitz Ultropak microscope equipped with a Vickers image-split-
ting device for measuring vessel diameter. Usually, four to six vessels covering a wide range of vessel caliber were studied in each animal.

We used the following materials: bradykinin acetate, acetylcholine chloride, superoxide dismutase (SOD) from bovine liver (3000 U/mg protein), and catalase from bovine liver (2000 U/mg protein) all obtained from Sigma; arachidonic acid obtained from NuChek. A 10 mg/ml sodium arachidionate stock solution was prepared by dissolving three parts of arachidonic acid and one part sodium carbonate (wt/wt) in distilled water. From this sodium arachidionate stock solution, appropriate volumes were added to artificial CSF to give the desired final concentrations. All solutions were prepared in artificial CSF shortly before the experiment and were placed in a water bath at 37°C until use. The solutions were used to fill the space under the cranial window.

The experimental design was as follows: first, the response of cerebral arterioles to arterial hypocapnia was determined. Only animals whose vessels had normal reactivity were used. After restoration of the Pco₂ to normal, and return of vessel caliber to the control level, dose-response curves to arachidonate, in doses of 50–200 μg/ml, or to bradykinin, in doses of 0.1–10 μg/ml, were obtained in the absence of other agents, as well as in the presence of SOD (60 U/ml) plus catalase (40 U/ml), and in the presence of these same enzymes after they had been inactivated by heat. The order of testing was as follows: in the case of arachidonate, we alternated the testing of the control responses and of the responses in the presence of inactive enzymes and tested the response to the active enzymes last. The reason for this was we suspected that, after application of active enzymes, wash-out might be incomplete. In the case of bradykinin, in one group of animals, we tested first control responses and then responses in the presence of active SOD and catalase. In another series, we alternated the control responses and responses in the presence of inactivated enzymes followed by testing of responses in the presence of active enzymes. This was done to exclude the possibility that tachyphylaxis to bradykinin might influence the results and complicate interpretation. Measurements of vessel caliber were made 2–4 minutes after application of each solution. This allowed ample time for the establishment of a steady state.

In two other groups of cats, we studied the effect of topically applied acetylcholine and the effect of changes in arterial blood CO₂ on vessel caliber with and without topically applied SOD and catalase. The responses to acetylcholine were studied because the relaxant effect of bradykinin and of arachidonic acid in some cases have been reported to be endothelium dependent (Furchgott, 1983). The responses to CO₂ were studied to verify that the effect of SOD and catalase was relatively specific. Acetylcholine chloride was dissolved in artificial CSF to give concentrations equal to 10⁻⁴ to 10⁻⁷ M, and the resultant solutions were used to fill the space under the cranial window. Measurements of vascular caliber were made between 1 and 3 minutes. Arterial hypocapnia was induced by mechanical hyperventilation. Hypercapnia was induced by ventilation with gases containing 3 and 5% CO₂. Each level of CO₂ was maintained for approximately 10 minutes to assure the establishment of a steady state.

In another series of experiments, we evaluated the effect of SOD and catalase separately and in combination on the cerebral arteriolar dilation induced by high concentration of topical arachidonate (200 μg/ml), both during its application as well as 1 hour following washout. We had found earlier that this dose of arachidonic acid, when applied for 15 minutes, caused residual dilation long after washout, accompanied by morphological abnormalities of the endothelium and vascular smooth muscle, as well as reduced reactivity to the vasoconstrictive effects of arterial hypocapnia (Kontos et al., 1980). Cats were assigned to one of several groups which received by topical application the following agents: (1) arachidonate 200 μg/ml; (2) arachidonate 200 μg/ml, plus SOD 60 U/ml; (3) arachidonate 200 μg/ml, plus catalase 40 U/ml, and (4) arachidonate 200 μg/ml, plus SOD 60 U/ml, plus catalase 40 U/ml. These agents were applied under the cranial window for 15 minutes. Vessel diameters were measured again, and then the space under the window was washed with fresh CSF. Vessel diameters and responsiveness to arterial hypocapnia were examined again 1 hour later.

The morphology of cerebral arterioles was studied after the functional studies were completed in the animals which received arachidonate and in the animals which received arachidonate plus SOD plus catalase, as described in detail before (Dietrich et al., 1980). The animal’s head was perfused at a pressure equal to his own arterial blood pressure, first with 0.9% sodium chloride solution and then with a fixative consisting of 2% glutaraldehyde and 2.5% paraformaldehyde in 0.1 M phosphate buffer. When fixation was completed, the arachnoid membrane beneath the cranial window, together with the pial vessels, was removed according to a technique which permits the identification of the same vessels that had been studied previously from the functional standpoint (Dietrich et al., 1980). The pial arterioles were then processed for electron microscopic examination. Scanning electron microscopy was used to determine quantitatively the number of lesions in the endothelium. This was achieved by counting the number of lesions in five randomly selected microscopic fields, each measuring 2100 μm². The average number of lesions per microscopic field was used as a measure of the density of these lesions.

The statistical significance of the results were evaluated by analysis of variance and, if significant differences were found by this analysis, by t-tests modified for multiple comparisons (Wallenstein et al., 1980).

Results

Figure 1 shows that the combination of SOD and catalase inhibited markedly the vasodilative response to topical application of arachidonate. SOD and catalase inactivated by heat had no significant effect on the response. Figures 2 and 3 show that SOD and catalase inhibited the vasodilative response to topical application of bradykinin. Figure 3 shows that SOD and catalase inactivated by heat had no significant effect on the response. Figure 4 shows that the cerebral arteriolar response to changes in arterial blood Pco₂ was not affected by the combination of SOD and catalase. Figure 5 shows that the vasodilative effect of topical acetyl-
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SMALL VESSELS
- Control
  53 ± 2.9 μm (15)
- Inactivated SOD & Catalase
  52 ± 3.0 μm (15)
- Active SOD & Catalase
  49 ± 4.8 μm (15)

LARGE VESSELS
- Control
  163 ± 8.2 μm (18)
- Inactivated SOD & Catalase
  161 ± 8.0 μm (18)
- Active SOD & Catalase
  165 ± 8.8 μm (18)

FIGURE 1. Effect of arachidonic acid on cerebral arteriolar caliber under control conditions (solid circles), in the presence of heat-inactivated SOD and catalase (open circles), and in the presence of active SOD and catalase (open triangles). Mean values ± SE of initial vessel diameters in μm for each group are shown. Number in parentheses after SE is the number of vessels studied. Data are mean ± SE from five cats. Analysis of variance showed that responses with active SOD plus catalase were significantly lower than in the other two groups.

cholines was not affected by the combination of SOD and catalase.

Tables 1–4 summarize the effects of arachidonate with and without SOD and catalase on cerebral arteriolar caliber during the exposure, and 1 hour after washout, as well as the effect on the response to arterial hypocapnia. Table 5 contains a comparison of the vasodilation during and after application of arachidonate with and without SOD and catalase each by itself and in combination. It is seen that arachidonate induced dilation of small and large arterioles during its application, that this dilation persisted 1 hour after washout, and that it was accompanied by reduction in the vasoconstrictive response to hypocapnia. SOD alone or catalase alone reduced the vasodilation during the application of arachidonate and eliminated the residual dilation after washout, as well as the decrease in responsiveness to hypocapnia. The combination of SOD and catalase was most effective; it eliminated the vasodilation during application and converted the residual dilation to a small vasoconstriction. Scanning

FIGURE 2. Effect of bradykinin on cerebral arteriolar caliber under control conditions (solid circles) and in the presence of active SOD and catalase (open triangles). Note that the bradykinin concentration on the abscissa is on a logarithmic scale. Mean values ± SE of the initial vessel diameters in μm for each group are shown. Number in parentheses after SE is the number of vessels studied. Data are mean ± SE from six cats. Analysis of variance showed that responses with active SOD plus catalase were significantly lower than in the control group.
FIGURE 3. Effect of bradykinin on cerebral arteriolar caliber under control conditions (solid circles), in the presence of heat-inactivated SOD and catalase (open circles), and in the presence of active SOD and catalase (open triangles). Mean values ± se of initial vessel diameters in μm are shown. Number in parentheses after se is the number of vessels studied. Data are mean ± se from two cats. Analysis of variance showed that responses with active SOD plus catalase were significantly lower than in the other two groups.

FIGURE 4. Effect of changes in PaCO₂ on cerebral arteriolar caliber under control conditions (solid circles) and in the presence of active SOD and catalase (open circles). Mean values ± se of initial vessel diameters at control PaCO₂ are shown for each group. Number in parentheses after se is the number of vessels studied. Data are mean ± se from five cats. Analysis of variance showed no differences in the responses between the two groups.

electron microscopy of the luminal surface of arterioles from animals treated with arachidonate disclosed focal endothelial lesions in the form of craters or dome-like protrusions into the lumen of the vessels, identical to those described previously (Dietrich et al., 1980; Kontos et al., 1980, 1981; Wei et al., 1980a, 1981). The density of these lesions in 15 vessels was equal to 18.3 ± 2.3 lesions/2100 μm². The number of lesions in the animals treated with arachidonate plus SOD plus catalase was significantly lower; in 10 vessels, the density of these lesions was 2.6 ± 0.8 lesions/2100 μm².

Discussion

The important finding of the experiments described above is that the combination of SOD and catalase inhibited the cerebral arteriolar dilation induced by topical application of either arachidonate or bradykinin. This result could be explained by one of two mechanisms. First, it is possible that the
combination of SOD and catalase inhibited prostaglandin synthesis. This is unlikely for the following reasons: Both SOD and catalase are large molecules and would not be expected to enter cells rapidly. Thus, a pronounced effect on prostaglandin synthesis would not be anticipated in the short time following application we used in the present experiments. Second, prostaglandin synthesis by bovine microsomal fractions was not influenced by SOD (Marnett et al., 1975). Finally, Ellis and Cockrell (1984) found that the combination of SOD and catalase did not inhibit prostaglandin synthesis from exogenous labeled arachidonate by either intact platelets or fragmented platelets. A more likely explanation for the observed inhibition is that the vasodilation caused by topical application of arachidonic acid or bradykinin is mediated via the generation of superoxide anion radical and hydrogen peroxide. As noted in the introduction, we found that, in response to topical application of high concentrations of arachidonic acid and bradykinin, superoxide anion radical appears in the extracellular space of the brain (Kontos and Wei, 1983). Superoxide anion radical could then give rise to hydrogen peroxide by spontaneous

![Figure 5](http://circres.ahajournals.org/)

**Figure 5.** Effect of acetylcholine on cerebral arteriolar caliber under control conditions (solid circles) and in the presence of active SOD and catalase (open circles). Mean values ± se of initial vessel diameters in μm for each group are shown. Number in parentheses after se is the number of vessels studied. Data are mean ± se from five cats. Analysis of variance showed that responses in the presence of SOD plus catalase were not significantly different from those seen under control conditions.

**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>During</th>
<th>After</th>
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<tbody>
<tr>
<td><strong>Diameters of small arterioles (μm)</strong></td>
<td>59 ± 3.8</td>
<td>50 ± 3.5</td>
<td>87 ± 6.8</td>
</tr>
<tr>
<td><strong>Decrease in diameter % of normocapnic value</strong></td>
<td>15 ± 1.2</td>
<td>8 ± 2.6*</td>
<td></td>
</tr>
<tr>
<td><strong>Diameter of large arterioles (μm)</strong></td>
<td>186 ± 9.6</td>
<td>163 ± 7.7</td>
<td>242 ± 12.6</td>
</tr>
<tr>
<td><strong>Decrease in diameter % of normocapnic value</strong></td>
<td>12 ± 0.8</td>
<td>7 ± 2.7*</td>
<td></td>
</tr>
<tr>
<td><strong>Mean arterial blood pressure (mm Hg)</strong></td>
<td>149 ± 10.0</td>
<td>127 ± 10.6</td>
<td>143 ± 15.8</td>
</tr>
<tr>
<td><strong>PaCO₂ (mm Hg)</strong></td>
<td>31 ± 1.5</td>
<td>16 ± 0.8</td>
<td>30 ± 1.8</td>
</tr>
</tbody>
</table>

Values are mean ± se from 14 small and 14 large arterioles in five cats. N = normocapnia; H = hypocapnia.
* Significantly (P < 0.05) different from corresponding value before application.
### Table 2
Effect of Arachidonic Acid (200 μg/ml) Plus SOD (60 U/ml) on Cerebral Arterioles

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
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<tbody>
<tr>
<td><strong>N</strong></td>
<td><strong>H</strong></td>
<td><strong>N</strong></td>
<td><strong>H</strong></td>
</tr>
<tr>
<td>Diameter of small arterioles (μm)</td>
<td>64 ± 3.4</td>
<td>56 ± 3.1</td>
<td>75 ± 4.5</td>
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<tr>
<td>Decrease in diameter</td>
<td>13 ± 1.1</td>
<td>13 ± 1.2</td>
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<tr>
<td>% of normocapnic value</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Diameter of large arterioles (μm)</td>
<td>163 ± 11.4</td>
<td>147 ± 10.8</td>
<td>175 ± 12.8</td>
</tr>
<tr>
<td>Decrease in diameter</td>
<td>10 ± 0.9</td>
<td>9 ± 1.0</td>
<td></td>
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<tr>
<td>% of normocapnic value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>128 ± 5.6</td>
<td>121 ± 7.0</td>
<td>133 ± 2.9</td>
</tr>
<tr>
<td>Paco2 (mm Hg)</td>
<td>33 ± 0.8</td>
<td>18 ± 1.3</td>
<td>33 ± 0.7</td>
</tr>
</tbody>
</table>

Values are mean ± se from 17 small and 13 large arterioles in five cats. N = normocapnic; H = hypocapnic.

### Table 3
Effect of Arachidonic Acid (200 μg/ml) Plus Catalase (40 U/ml) on Cerebral Arterioles

<table>
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<tr>
<td><strong>N</strong></td>
<td><strong>H</strong></td>
<td><strong>N</strong></td>
<td><strong>H</strong></td>
</tr>
<tr>
<td>Diameter of small arterioles (μm)</td>
<td>63 ± 3.3</td>
<td>55 ± 2.8</td>
<td>79 ± 4.6</td>
</tr>
<tr>
<td>Decrease in diameter</td>
<td>12 ± 0.9</td>
<td>12 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>% of normocapnic value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter of large arterioles (μm)</td>
<td>164 ± 10.0</td>
<td>143 ± 8.5</td>
<td>200 ± 13.1</td>
</tr>
<tr>
<td>Decrease in diameter</td>
<td>12 ± 0.8</td>
<td>9 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>% of normocapnic value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>117 ± 2.8</td>
<td>114 ± 5.1</td>
<td>128 ± 7.2</td>
</tr>
<tr>
<td>Paco2 (mm Hg)</td>
<td>31 ± 1.0</td>
<td>18 ± 0.9</td>
<td>31 ± 1.0</td>
</tr>
</tbody>
</table>

Values are mean ± se from 17 small and 17 large arterioles in five cats. N = normocapnic; H = hypocapnic.

### Table 4
Effect of Arachidonic Acid (200 μg/ml), Plus SOD (60 U/ml), Plus Catalase (40 U/ml) on Cerebral Arterioles

<table>
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<tbody>
<tr>
<td><strong>N</strong></td>
<td><strong>H</strong></td>
<td><strong>N</strong></td>
<td><strong>H</strong></td>
</tr>
<tr>
<td>Diameter of small arterioles (μm)</td>
<td>71 ± 2.1</td>
<td>62 ± 2.1</td>
<td>74 ± 3.3</td>
</tr>
<tr>
<td>Decrease in diameter</td>
<td>12 ± 1.1</td>
<td>11 ± 1.6</td>
<td></td>
</tr>
<tr>
<td>% of normocapnic value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter of large arterioles (μm)</td>
<td>176 ± 11.2</td>
<td>155 ± 9.8</td>
<td>180 ± 11.7</td>
</tr>
<tr>
<td>Decrease in diameter</td>
<td>11 ± 0.9</td>
<td>8 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>% of normocapnic value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>127 ± 3.1</td>
<td>110 ± 4.2</td>
<td>127 ± 3.9</td>
</tr>
<tr>
<td>Paco2 (mm Hg)</td>
<td>31 ± 1.3</td>
<td>20 ± 1.4</td>
<td>31 ± 1.1</td>
</tr>
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</table>

Values are mean ± se from 25 small and 25 large arterioles in six cats. N = normocapnic; H = hypocapnic.
Similarly, arachidonate causes relaxation of vascular smooth muscle of canine and rabbit arteries largely by an endothelium dependent mechanism (DeMey et al., 1982; DeMey and Vanhoutte, 1982; Furchgott, 1983; Singer and Peach, 1983). The endothelium dependence of the response to arachidonate in cerebral arteries or arteries of cats in general has not been tested. The present findings show that oxygen radicals are not the endothelium-derived relaxant factor generated by acetylcholine. If the relaxant effect of arachidonic acid on cerebral arterioles is endothelium dependent, one may infer that more than one endothelium-derived relaxant agent exists. Singer and Peach (1983) found that in the isolated rabbit aorta the relaxant effect of arachidonic acid was blocked by lipoxygenase inhibitors and was potentiated by cyclooxygenase inhibitors. This contrasts with the blockade of the relaxant effect of arachidonate on cerebral arterioles by cyclooxygenase inhibitors. The effect of oxygen radical scavengers on the arachidonate-induced relaxation in isolated vessels has not been tested. The possibility exists that an oxygen radical derived from arachidonic metabolism by lipoxygenase might be involved. These differences emphasize the strong possibility of differences between in vivo and in vitro behavior, species differences, and, possibly, differences between large and small vessels.

In earlier experiments, we found that in response to topical applications of arachidonic acid or PGG2 (Kontos et al., 1980), or in response to severe hypertension (Kontos et al., 1981) or experimental brain injury (Wei et al., 1980a, 1981), cerebral arterioles displayed sustained dilation long after these interventions were terminated. This vasodilation was associated with reduced responsiveness to the vasoconstrictive effects of arterial hypocapnia and with the presence of morphological evidence of damage to vascular smooth muscle and to the endothelium. These results suggest strongly that the sustained vasodilation observed 1 hour after arachidonate washout and the associated changes in responsiveness can be used as an indicator of the presence of vascular wall damage. This is supported by the limited electron microscopic observations reported here. With these considerations in mind, our

<table>
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<th>Table 5</th>
<th>Comparison of Percentile Changes in Arteriolar Caliber Caused by Arachidonic Acid with and without SOD and Catalase</th>
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<tbody>
<tr>
<td></td>
<td>Change in diameter (% of control)</td>
</tr>
<tr>
<td></td>
<td>Small arterioles</td>
</tr>
<tr>
<td></td>
<td>During</td>
</tr>
<tr>
<td>Arachidonic acid</td>
<td>50 ± 10.3</td>
</tr>
<tr>
<td>Arachidonic acid plus catalase</td>
<td>25 ± 5.6*</td>
</tr>
<tr>
<td>Arachidonic acid plus SOD</td>
<td>19 ± 5.2*</td>
</tr>
<tr>
<td>Arachidonic acid plus SOD plus catalase</td>
<td>4 ± 3.1*</td>
</tr>
</tbody>
</table>

Values are mean ± se. * Significantly (P < 0.05) different from corresponding arachidonic acid value, based on analysis of variance and Dunnett's t-test.
results concerning the effects of SOD and catalase separately or in combination on the response to topical application of 200 µg/ml of arachidonic acid support the following conclusions. First, the injury to the vascular wall requires the presence of both superoxide anion radical and hydrogen peroxide for its production. The elimination of one of these species by either SOD or catalase separately inhibited the vascular injury. A second conclusion is that superoxide anion radical and hydrogen peroxide, each, by itself, is capable of producing reversible arteriolar dilation. This is supported by the observation that the vasodilatation during application of arachidonic acid was only partially inhibited by SOD or catalase separately, but was completely eliminated by the two enzymes in combination. The fact that both of these radical species are required for the production of vascular injury suggests strongly that the immediate cause of vascular injury is the hydroxyl radical generated from the interaction of the superoxide anion radical and hydrogen peroxide.

The present experiments suggest that it might be advantageous to examine the possibility that responses which were previously ascribed to increased production of stable prostaglandins, such as the vasodilatative responses to arachidonic acid or bradykinin in other vascular beds, might in actuality be due to the associated production of oxygen radicals. The evidence on which the involvement of stable prostaglandins is suspected depends on inhibition of responses by pretreatment with cyclooxygenase inhibitors and by demonstration of increased production of prostaglandins. Both of these findings are also consistent with the view that the observed responses are mediated by oxygen radicals generated in association with accelerated arachidonate metabolism via the cyclooxygenase pathway. Furthermore, since the inhibition of the responses was seen at low concentrations of arachidonic acid and bradykinin, which ordinarily lead to reversible changes without any residual manifestations of vascular damage, it is possible that these radicals may actually have a role in the mediation of physiological responses. The same view has been expressed by Rosenblum (1983), based on the finding of reversible cerebral arteriolar dilation from oxygen radicals generated via the xanthine oxidase reaction.

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