Effects of Cocaine on Pial Arterioles in Cats

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Mark L. Hudak, MD, and Richard J. Trastman, PhD

We used the closed cranial window technique to observe the responses of pial arterioles to topical application of cocaine in 29 anesthetized cats. Alterations in arteriolar diameter were dependent on the concentration of cocaine applied. Cocaine dissolved in artificial cerebrospinal fluid at concentrations of $10^{-8}$ or $10^{-7}$ M was without effect. Concentrations of $10^{-6}$ and $10^{-5}$ M produced dilation (4.9±1.5% [mean±SEM] and 5.9±2.0%, respectively) in large arterioles (>100 μm) but no significant change in the diameter of small arterioles (<100 μm). A concentration of $10^{-4}$ M dilated both large and small arterioles (20.3±3.1% and 12.0±7.1%, respectively). Pretreatment with 1 mg/kg i.v. propranolol blocked the increase in pial arteriolar diameter after application of $10^{-4}$ M cocaine and produced significant vasoconstriction in small arterioles (−8.3±3.1%). Cocaine produces vasodilation of cat cerebral arterioles. This effect appears to be mediated, at least in part, by mechanisms that depend on stimulation of β-adrenergic receptors. (Stroke 1990;21:1710-1714)

Hemorrhagic and ischemic stroke in the setting of chronic cocaine abuse are frequently attributed to the drug’s sympathomimetic properties. By a variety of mechanisms, perhaps most prominently by its ability to interfere with reuptake of norepinephrine by sympathetic nerve endings, cocaine causes vasoconstriction. Thus, systemic administration of cocaine is followed by a sharp increase in peripheral vascular resistance and acute hypertension. Authors have speculated that the acute hypertension contributes to intracranial hemorrhage and that local vasoconstriction contributes to cerebral ischemia.

These hypotheses are attractive, but more data are needed. Although cocaine clearly leads to peripheral vasoconstriction and preliminary data suggest that the same may be true of cerebral vessels, it has long been known that the responses of cerebral and peripheral vessels are not necessarily the same. The present study was designed to examine the hypothesis that cocaine causes concentration-dependent changes in the caliber of large and small cerebral vessels in vivo by examination of the effects of topical cocaine on the diameter of pial arterioles in anesthetized cats.

Materials and Methods

We studied 29 cats of either sex weighing 3.2–4.3 kg. The cats were initially anesthetized with 30 mg/kg i.p. sodium pentobarbital. Catheters were placed into a femoral vein to administer drugs and fluid and into a femoral artery to measure arterial blood pressure and to sample arterial blood for blood gas tensions, pH, and glucose concentration. The trachea was cannulated, and the cats were paralyzed with 0.1 mg/kg pancuronium bromide and mechanically ventilated using a Harvard ventilator (South Natick, Mass.). Ventilatory rate and tidal volume were adjusted to maintain Paco2 at 30–40 mm Hg, and supplemental oxygen was used to maintain PaO2 above 100 mm Hg. Anesthesia was maintained with continuous intravenous infusion of 0.05–0.1 mg/kg/min sodium pentobarbital. Rectal temperature was maintained at 37–38.5°C with a servo-controlled heating pad.

A closed cranial window was employed to visualize the pial microcirculation. After retraction of the scalp, we performed a craniotomy immediately caudal to the coronal suture. The dura was reflected over the bony rim. Bleeding from the cut edges of the dura was controlled by crushing dural vessels with microforceps. An 18-mm-diameter window consisting of a metal ring fitted with a glass coverslip was centered over the craniotomy and secured with bone wax and dental acrylic. After the space beneath the window was filled with artificial cerebrospinal fluid (CSF), polyethylene catheters filled with artificial CSF were
tractions were not studied. Furthermore, the effect of
and brain edema. Therefore, this and higher concen-
duced irreversible vasodilation, microhemorrhages,
shown that cocaine concentrations of 10^-3 M pro-
was injected, and after 30 minutes the measurements
The measurements were repeated; a second solution
vessel diameters were measured again. The window
was blinded to the com-
leted with artificial CSF that had been warmed
and bubbled with air and 5% CO2 at 38° C.
Approximately 30 minutes after the establishment
of the cranial window, two baseline measurements of
microvascular diameter were made with an optical
image splitter (Vickers, England) attached to a dis-
sectioning microscope (Wild, Heerbrugg, Switzerland).
We measured the diameters of 3-12 arterioles in
each cat. Constant perfusion of artificial CSF equil-
ibrated with the above gas mixture was started at
0.2-0.3 ml/min, and the measurements were re-
peated. Freshly prepared cocaine solution or vehicle
(artificial CSF) was then infused into the window. After 30 minutes the
final measurements were made.
Mean arterial blood pressure was recorded with each
measurement of each vessel. The pH, Pco2, and Po2 of
blood and the artificial CSF were measured with each
series of vascular measurements. Glucose concentra-
tion was estimated with Dextrostix (Ames, Elkhart,
Ind.).
Arterioles were divided into large (>100 μm) or
small (<100 μm) subgroups on the basis of initial
diameter measurements. Statistical analysis was
done using t tests to test the changes in diameter and physiologic measurements. Values are pre-
ated as mean±SEM.

Results
Table 1 shows pial arteriolar diameters before and
after the application of cocaine or artificial CSF.
Average responses were first calculated for the 3-12
arterioles evaluated in each cat. Responses in Table 1
represent the mean of those averages. Degrees of
freedom for statistical calculations were thus deter-
mined by the number of cats rather than by the
number of arterioles. Large and small arterioles were
evaluated separately.
Significant changes in diameter were evident at
cocaine concentrations of ≥10^-4 M. The data are
displayed as percentage changes in Figure 1. No significant alterations in caliber were seen with arti-

<table>
<thead>
<tr>
<th>Solution</th>
<th>Cats (n)</th>
<th>Large</th>
<th>Change (%)</th>
<th>Small</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Diameter (μm)</td>
<td></td>
<td>Diameter (μm)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Before</td>
<td>During</td>
<td></td>
<td>Before</td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10^-4 M</td>
<td>6</td>
<td>156±6</td>
<td>187±5*</td>
<td>20.3±3.1†</td>
<td>20</td>
</tr>
<tr>
<td>10^-3 M</td>
<td>7</td>
<td>154±8</td>
<td>163±10*</td>
<td>5.9±2.0†</td>
<td>19</td>
</tr>
<tr>
<td>10^-2 M</td>
<td>7</td>
<td>146±4</td>
<td>153±5*</td>
<td>4.9±1.5†</td>
<td>21</td>
</tr>
<tr>
<td>10^-1 M</td>
<td>6</td>
<td>154±12</td>
<td>153±11</td>
<td>-1.0±1.0</td>
<td>20</td>
</tr>
<tr>
<td>10^-2 M</td>
<td>6</td>
<td>155±16</td>
<td>159±16</td>
<td>0.9±0.8</td>
<td>28</td>
</tr>
<tr>
<td>Artificial cerebrospinal fluid</td>
<td>11</td>
<td>151±9</td>
<td>152±9</td>
<td>0.1±0.8</td>
<td>45</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
* p<0.05 different from before by t test.
† p<0.05 different from 0 by t test.
ficial CSF alone or with cocaine concentrations of $10^{-8}$ or $10^{-7}$ M. Large arterioles dilated at $10^{-6}$ and $10^{-5}$ M and both large and small arterioles dilated at $10^{-4}$ M cocaine (Figure 1).

These alterations could not be attributed to changes in mean arterial blood pressure, pH, or arterial blood gases (Table 2). We considered the possibility that baseline mean arterial blood pressure might in some way determine the magnitude of the cocaine effect. However, standard regression analysis showed no significant correlation between pial arteriolar responses to cocaine and baseline values of mean arterial blood pressure.

Propranolol was used to explore the involvement of $\beta$-adrenergic mechanisms in vasodilation. Intravenous propranolol (1 mg/kg) caused a significant decrease in heart rate but no significant change in arteriolar diameter. The dilator responses of both large and small arterioles to $10^{-4}$ M cocaine were blocked in cats pretreated with propranolol. Indeed, dilation in small arterioles was replaced by significant vasoconstriction (Table 3, Figure 1).

**Discussion**

Our experiments show that topically applied cocaine dilates pial arterioles in cats. Although we found no effect of concentrations below $10^{-6}$ M, large arterioles dilated at $10^{-6}$ and $10^{-5}$ M and all arterioles dilated at $10^{-4}$ M cocaine. Pretreatment with intravenous propranolol eliminated, and in small vessels reversed, the significant dilation induced by $10^{-4}$ M cocaine.

Changes in vascular caliber could not be attributed to alterations in mean arterial blood pressure or to changes in arterial pH, $\text{Paco}_2$, or $\text{PaO}_2$. Furthermore, we administered the solutions (artificial CSF with and without cocaine) in a blinded, semirandom fashion to minimize the possibility that the increasing response to higher concentrations of cocaine could be attributed to time, previous exposure to the drug.

**TABLE 2. Physiologic Measurements in Cats Before and During Perfusion With Indicated Solutions**

<table>
<thead>
<tr>
<th>Solution</th>
<th>Cats (n)</th>
<th>Mean arterial blood pressure (mm Hg)</th>
<th>$\text{pH}$</th>
<th>$\text{Paco}_2$ (mm Hg)</th>
<th>$\text{PaO}_2$ (mm Hg)</th>
<th>Glucose (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$10^{-4}$ M</td>
<td>6</td>
<td>Before</td>
<td>97±13</td>
<td>7.44±0.01</td>
<td>31.2±0.6</td>
<td>159.5±14.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During</td>
<td>100±13</td>
<td>7.41±0.00</td>
<td>32.9±1.4</td>
<td>153.3±15.0</td>
</tr>
<tr>
<td>$10^{-5}$ M</td>
<td>7</td>
<td>Before</td>
<td>116±11</td>
<td>7.43±0.01</td>
<td>32.4±1.3</td>
<td>140.7±13.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During</td>
<td>114±10</td>
<td>7.43±0.01</td>
<td>32.9±1.0</td>
<td>134.7±10.3</td>
</tr>
<tr>
<td>$10^{-4}$ M</td>
<td>7</td>
<td>Before</td>
<td>117±8</td>
<td>7.42±0.02</td>
<td>31.9±2.1</td>
<td>157.0±13.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During</td>
<td>118±9</td>
<td>7.43±0.02</td>
<td>30.7±1.6</td>
<td>150.9±10.9</td>
</tr>
<tr>
<td>$10^{-7}$ M</td>
<td>6</td>
<td>Before</td>
<td>106±11</td>
<td>7.45±0.02</td>
<td>33.9±0.8</td>
<td>138.5±8.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During</td>
<td>107±12</td>
<td>7.45±0.02</td>
<td>33.7±0.4</td>
<td>146.5±7.8</td>
</tr>
<tr>
<td>$10^{-4}$ M</td>
<td>6</td>
<td>Before</td>
<td>106±12</td>
<td>7.40±0.00</td>
<td>35.4±0.5</td>
<td>145.1±5.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During</td>
<td>109±13</td>
<td>7.38±0.01</td>
<td>36.2±1.1</td>
<td>143.8±4.9</td>
</tr>
<tr>
<td>Artificial cerebrospinal fluid</td>
<td>11</td>
<td>Before</td>
<td>99±9</td>
<td>7.41±0.00</td>
<td>32.8±1.1</td>
<td>140.6±7.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During</td>
<td>97±7</td>
<td>7.42±0.01</td>
<td>34.0±1.2</td>
<td>139.3±5.8</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
Whether such vasoconstriction would be roughly twice those in plasma, whereas concentrations of catecholamines should have been estimated from plasma levels. Plasma cocaine concentrations in humans after intravenous doses of 0.5 mg/kg or after smoking coca paste are approximately $10^{-5}$ M. Data in experimental animals and humans suggest that CSF concentrations would be roughly twice those in plasma, whereas concentrations in brain exceed those in plasma by almost an order of magnitude. These data suggest that the highest concentration employed in our study ($10^{-4}$ M) would be approximately in the range anticipated for cocaine intoxication.

The circumstances of our study differ from the human situation in two major ways. First, the species is different. Data from other laboratories suggest that topical cocaine constricts cerebral vessels. The reason for the discrepancy between those data and our results is not clear, but pial vessel constriction was reported in rats. It is thus possible that responses vary among species. Second, the drug was administered topically rather than intravenously. Topical application evaluates the direct effect on cerebral resistance vessels in situ and avoids the confounding effect of cocaine-induced hypertension. Systemic hypertension would ordinarily be expected to be accompanied by autoregulatory vasoconstriction in pial vessels. Whether such vasoconstriction would be impaired in the presence of cocaine awaits further study.

The effects of cocaine are complex, and it would have been difficult to predict the results of our experiments in advance. On one hand, topical cocaine might lead to vasoconstriction. This drug is a potent sympathomimetic that acts in a variety of ways, depending on the species and the particular vessel, to enhance the effect of catecholamines. In certain situations cocaine also appears to promote catecholamine release. Since norepinephrine causes cat pial vessels to constrict, topical cocaine would be expected to result in vasoconstriction.

On the other hand, cocaine in anesthetic concentrations would be expected to be a vasodilator. This effect appears at somewhat higher concentrations than those associated with catecholamine effects. Although depression of neural transmission begins at cocaine concentrations as low as $10^{-5}$ M, the reduction in vascular responsivity to norepinephrine does not appear until concentrations reach $10^{-4}$ M. Against the hypothesis that vasodilation in our experiments was due to an anesthetic effect is the finding that dilation disappeared after pretreatment with propranolol. The mechanism by which propranolol acted is uncertain. It seems unlikely that the drug blocked beta receptors on the vessel itself. Vasodilatory beta receptors are present in cat cerebral arteries, but alpha vasoconstrictor effects predominated. Thus, the net effect of vasoactive concentrations of catecholamines should have been vasoconstriction.

It is possible that propranolol blocked a cocaine-induced, $\beta$-adrenergic-mediated increase in cerebral metabolism. Porrino et al. showed that glucose metabolism in the somatosensory cortex of conscious rats increases by 14% after 5 mg/kg i.v. cocaine. The mechanism of the increase has not been defined, but it is likely to be due to increased intrasynaptic monoamine concentrations. Increased central catecholamine levels in other settings are associated with increased cerebral metabolism and blood flow. Such effects should be blocked by propranolol. Propranolol lowers the cerebral metabolic rate in normal subjects and inhibits the increase in

### Table 3. Effects of $10^{-4}$ M Cocaine on Pial Arteriolar Diameter and Physiologic Measurements in Cats Pretreated With Intravenous Propranolol

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>After propranolol</th>
<th>Before cocaine</th>
<th>During cocaine</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cats (n)</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>...</td>
</tr>
<tr>
<td>Arterioles (n)</td>
<td>52</td>
<td>52</td>
<td>44</td>
<td>44</td>
<td>...</td>
</tr>
<tr>
<td>Diameter (µm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large arterioles</td>
<td>168±16</td>
<td>167±15</td>
<td>180±21</td>
<td>176±21</td>
<td>-2.1±3.9</td>
</tr>
<tr>
<td>Small arterioles</td>
<td>83±2</td>
<td>81±2</td>
<td>80±2</td>
<td>74±3</td>
<td>-8.3±3.1f</td>
</tr>
<tr>
<td>Physiologic measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>119±5</td>
<td>116±8</td>
<td>112±8</td>
<td>111±8</td>
<td>...</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>176±16</td>
<td>114±8‡</td>
<td>116±7‡</td>
<td>117±6‡</td>
<td>...</td>
</tr>
<tr>
<td>pH₄</td>
<td>7.42±0.02</td>
<td>7.43±0.02</td>
<td>7.40±0.01</td>
<td>7.42±0.02</td>
<td>...</td>
</tr>
<tr>
<td>Paco₂ (mm Hg)</td>
<td>36.2±1.8</td>
<td>35.7±1.5</td>
<td>36.9±1.3</td>
<td>36.9±1.8</td>
<td>...</td>
</tr>
<tr>
<td>Pao₂ (mm Hg)</td>
<td>163.3±15.9</td>
<td>158.2±12.7</td>
<td>154.8±14.5</td>
<td>148.2±14.5</td>
<td>...</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>10.8±0.8</td>
<td>10.9±0.6</td>
<td>10.7±0.4</td>
<td>10.7±0.8</td>
<td>...</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *p<0.05 different from before cocaine by t test. ‡p<0.05 different from 0 by t test. ‰p<0.05 different from control by t test.
cerebral metabolism during immobilization stress.\textsuperscript{30} The mechanism is thought to be blockade of the central catecholamine effect.

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References


\textbf{Key Words}: cocaine  microcirculation  vasoconstriction  cats
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