Pharmacological Comparison of Isolated Monkey and Dog Cerebral Arteries


SUMMARY Pharmacological differences between canine and monkey basilar arteries were studied in vitro. The constrictor response of canine basilar artery to either norepinephrine or an α2-adrenoceptor agonist phenylephrine was partly inhibited by an α2-adrenoceptor antagonist yohimbine but not by an α1-adrenoceptor antagonist prazosin. The contraction elicited by an α2-adrenoceptor agonist clonidine was inhibited by neither prazosin nor yohimbine. These results suggest that the receptors in canine basilar artery which mediate norepinephrine-induced contraction are different from classical α1 or α2-adrenoceptors, although they more closely resemble the α2- rather than the α1-subtype. Using monkey basilar artery, phenylephrine produced the same amplitude of maximum contractile response as norepinephrine, though a much higher concentration of phenylephrine than norepinephrine was needed in order to elicit that maximum response. Clonidine did not elicit contractions. The contraction induced by norepinephrine was markedly suppressed by both prazosin and yohimbine in a noncompetitive fashion. The constrictor response of monkey basilar artery to norepinephrine, therefore, appears to be mediated by α2-like adrenoceptors. Comparison of ED50 values for thromboxane A2 revealed that the monkey basilar artery was more sensitive to thromboxane A2 than that of the canine. Prostaglandin F2α produced a larger maximum contraction in monkey basilar arteries than in canine basilar arteries, although the ED50 values for monkey basilar arteries were larger than those for canine basilar arteries. The ED50 values for serotonin in canine basilar arteries were a little less than those for monkey basilar arteries, although both arteries produced nearly identical maximum contractions.

SPECIES DIFFERENCES in the constrictor responses of cerebral arteries to vasoactive agents are of contemporary interest with regard to the pathophysiology of the cerebral circulation. Hardebo, et al.11 reported that histamine was a strong vasoconstrictor in rabbit cerebral arteries but a prominent vasodilator in human cerebral arteries. Norepinephrine is reported to be a much more potent cerebral artery spasmogen in man than in experimental animals such as rats, rabbits or dogs.12 and a potential vasodilator in pig cerebral arteries.3

Postjunctional α-adrenoceptors have recently been subclassified into α1- and α2-type adrenoceptors, based on relative potencies of selective agonists and antagonists.4-8 Experiments using such selective agonists and antagonists have suggested that the vasoconstrictor responses of feline middle cerebral artery6, 10 and canine basilar artery2-11 to exogenous norepinephrine are predominantly mediated by the α1-adrenoceptor subtype. However, the nature of α2-adrenoceptors in canine cerebral arteries still remains controversial since some discrepancy exists between the experimental results by Sakakibara et al.11 and those by Toda.2 Sakakibara et al.11 have reported that an α2-agonist clonidine elicited a constrictor response similar to that induced by norepinephrine, and that the response to either clonidine or norepinephrine was competitively inhibited by an α2-antagonist yohimbine. On the other hand, Toda2 has demonstrated that clonidine-induced constrictions in canine cerebral arteries were appreciably less than those induced by norepinephrine, and that the antagonism of norepinephrine-induced constrictions by yohimbine was noncompetitive in nature. In addition, Toda2 has recently reported that norepinephrine-induced constrictions are predominantly mediated by α1-adrenoceptors in human and monkey cerebral arteries, suggesting species differences in the nature of cerebral arterial α-adrenoceptors. Those results merit further investigations.

Species differences in the constrictor responses of cerebral arteries to vasoactive agents may have to be considered when designing studies of the pharmacology and pathophysiology of the cerebral circulation. In general, nonhuman primates are considered to be the best experimental animals because of anatomical, physiological and pathological relevance. However, only a limited amount of pharmacological information is available on the vascular reactivity of monkey cerebral arteries in vitro.2, 12-14 The present comparative study was undertaken to evaluate the in vitro constrictor responses of monkey and canine cerebral arteries to several vasoactive agents. For correlative purposes, the nature of α-adrenoceptors in canine mesenteric artery was also studied.

Material and Methods

Adult mongrel dogs and cynomolgus monkeys (macaca fascicularis) of either sex were anesthetized with sodium pentobarbital (30 mg/kg) and sacrificed by exsanguination from the femoral artery. The basilar arteries from both species and the canine mesenteric artery were rapidly removed. The arteries were isolated under magnification and placed immediately in oxygenated, modified Kreb’s bicarbonate solution (in mM): NaCl, 120; KCl, 4.5; MgSO4, 1.0; NaHCO3,
SPECIES VARIATIONS IN VASCULAR REACTIVITY/Sasaki et al

27.0; KH₂PO₄, 1.0; CaCl₂, 2.5; and dextrose, 10.0] at 37°C gassed with 95% O₂ and 5% CO₂. The pH of the solution ranged from 7.40 to 7.50. Each artery was cut into 4 mm long ring segments which were suspended between L-shaped stainless steel holders in organ baths with a 10 ml working volume. Resting tension was adjusted to 1.5 g for monkey and canine basilar arteries and 2.0 g for canine mesenteric arteries. The preparations were allowed to equilibrate at 37°C for 60 minutes before use. Dose-response curves for norepinephrine, phenylephrine, clonidine, serotonin, prostaglandin F₂α and thromboxane A₂ (TXA₂) were obtained by cumulative addition of the agonists. The synthetic TXA₂ (9,11-epithio-11,12-methano-TXA₂) was used as a substitute for natural TXA₂ in this experiment. Contractile force was recorded isometrically using a Grass FT.03 force-displacement transducer. The transducer signal was then amplified and displayed on a Gould 260 multichannel recorder. The contractile response to 40 mM KCl was first obtained on each ring segment, then the preparations were repeatedly washed. The contractions induced by 40 mM KCl were taken as 100%. Contractile activities of norepinephrine, phenylephrine, clonidine, serotonin, prostaglandin F₂α and TXA₂ were expressed as a percentage of the contraction elicited by a standard dose of 40 mM KCl. Mean absolute values of the contractions induced by 40 mM KCl in canine mesenteric and basilar arteries and in monkey basilar arteries were 9.12 ± 0.36 grams (mean ± S.E., N = 42), 6.28 ± 0.23 grams (N = 56) and 3.84 ± 0.25 grams (N = 47), respectively. The dry weights of 4 mm long ring segments of canine mesenteric and basilar and monkey basilar arteries were about 0.78 mg, 0.38 mg and 0.30 mg, respectively. In studies examining the inhibitory effects of prazosin and yohimbine on the contraction induced by norepinephrine, phenylephrine, or clonidine, preparations were exposed to those antagonists for 15 minutes before addition of agonists. The effects of β-adrenoceptors and the effects of neuronal and extraneuronal uptake of catecholamines on the constrictor responses of monkey cerebral arteries to norepinephrine were examined by exposing the preparations for 15 minutes to 10⁻⁶ M propranolol, 10⁻⁵ M cocaine or 10⁻⁵ M normetanephrine, respectively. In preliminary experiments using canine mesenteric arteries, it was confirmed that treatment of the specimens for 15 minutes with 10⁻⁶ M propranolol, 10⁻⁵ M cocaine or 10⁻⁵ M normetanephrine augmented the constrictor responses to 10⁻⁶ M norepinephrine by about 9.4% (n = 6), 322% (n = 9), 70% (n = 8), respectively.

Statistical analysis of the dose response curves was done using split-plot analysis of variance (ANOVA), and a Scheffe test was used for subgroup analysis. Comparison of each constrictor response with a matched control at a specific antagonist concentration and at each specific agonist concentration was made using a paired t-test. When p was smaller than 0.01, values were considered to be significantly different. For graphic presentation, the control values were averaged together. The pA₂ values for antagonists were calculated according to the method of Arunlakshana and Schild.15 Computation of dose-response curves and ED₉₀ values was done using probit analysis with the SAS (Statistical Analysis System) computer program.

Drugs and solutions used in this study were (+)-arterenol hydrochloride (Sigma Chemical Co.), 1-phenylephrine hydrochloride (Sigma Chemical Co.), clonidine hydrochloride (Boehringer Ingelheim Ltd.), yohimbine hydrochloride (Sigma Chemical Co.), prazosin hydrochloride (Pfizer Ltd.), dl-propranolol hydrochloride (Sigma Chemical Co.), cocaine hydrochloride (Mallickrodt Co.) normetanephrine hydrochloride (Sigma Chemical Co.), 5-hydroxytryptamine (Sigma Chemical Co.), prostaglandin F₂α (Sigma Chemical Co.), 9,11-epithio-11,12-methano-thromboxane A₂ (Ono Pharmaceutical Co., Ltd.) and ethyleneglycol-bis (β-aminoethyl ether)-N,N'-tetraacetic acid (Sigma Chemical Co.).

Norepinephrine was dissolved using a 50 mM phosphate buffer solution (pH 7.4) which contained 0.1% ascorbate. Prazosin and yohimbine were dissolved in a diluted thanol solution resulting in a final concentration of ethanol in the 10 ml organ bath of 0.001%. Preliminary experiments demonstrated that, at the concentrations used in the present work, this solvent did not affect the contractile responses to norepinephrine, phenylephrine or clonidine. TXA₂ was dissolved in 1/15 M phosphate buffer (pH 7.4) to make a stock solution (3 × 10⁻³ M) and diluted with distilled water before use. All other drugs were dissolved in saline.

Results

The Non-receptor Mediated Responses of Cerebral Arteries

In either canine or monkey basilar arteries exposed for 20 minutes to Ca²⁺-free medium containing 0.5 mM EGTA and depolarized with 80 mM KCl, the addition of Ca²⁺ (0.5, 1, 5, 10 mM) elicited dose-dependent contractions (fig. 1). These non-receptor mediated responses were quantitatively the same in both arterial beds.

The Constrictor Responses to α-adrenoceptor Agonists

Canine Mesenteric Artery

The dose-response curves to α-adrenoceptor agonists are shown in figure 2 (right). Norepinephrine in concentrations ranging from 10⁻⁷ M to 3 × 10⁻⁵ M caused a dose-dependent increase in tension of mesenteric arterial strips. Phenylephrine evoked responses that were similar to, though slightly less in amplitude than, those obtained with norepinephrine. The ED₉₀ (95% confidence interval) for norepinephrine and phenylephrine were 2.47 (1.89–3.25) × 10⁻⁶ M and 3.56 (2.80–4.51) × 10⁻⁶ M, respectively. In contrast, the vasoconstrictor response induced by clonidine was markedly less than that induced by norepinephrine or phenylephrine.

The effects of α-adrenoceptor antagonists on norepinephrine-induced contraction are illustrated in figure 3 (left). Both prazosin and yohimbine shifted the
FIGURE 1. Contractile responses to Ca++ of monkey and canine basilar arteries exposed previously for 20 minutes to Ca++-free medium containing 0.5 mM EGTA and depolarized with 80 mM KCl. The contractile responses are expressed as a percentage of the contraction elicited by a standard dose of 40 mM KCl. The abscissa represents the molar concentrations of Ca++. Results are expressed as mean + SEM. n = number of specimens taken from different arteries.

dose-response curve of norepinephrine-induced contraction to the right. The maximum response to norepinephrine was not reduced by either prazosin or yohimbine. PA₂ values for prazosin and yohimbine were 7.62 ± 0.03 (mean ± SEM) and 6.82 ± 0.05, respectively. As shown in figure 3 (right), both prazosin and yohimbine also caused a parallel shift to the right of the phenylephrine dose-response curve. The PA₂ value for prazosin (7.71 ± 0.08) was higher than that for yohimbine (7.00 ± 0.02).

Canine Cerebral Artery

Cumulative dose-response relationships for the α-adrenoceptor agonists are shown in figure 2 (left). The constrictor response of canine cerebral artery to either norepinephrine or phenylephrine was small when compared to that of the mesenteric artery. The constrictor response of canine basilar artery to phenylephrine was less than that to norepinephrine, except at the concentration of 10⁻⁴ M phenylephrine. Clonidine at high concentrations (10⁻³ M and 3 × 10⁻³ M) produced stronger contractions than norepinephrine, while the constrictor response to lower concentrations (10⁻⁶ M to 10⁻⁴ M) of clonidine was less than that to norepinephrine.

The effects of α-adrenoceptor antagonists on norepinephrine-induced contraction are illustrated in figure 4. Prazosin at all concentrations tested (10⁻⁷, 10⁻⁶ and 10⁻⁵ M) failed to inhibit the contraction produced by 10⁻⁶ M to 3 × 10⁻³ M norepinephrine. Yohimbine at concentrations of 10⁻⁶ M and 10⁻⁵ M suppressed significantly (ANOVA and Scheffe test, p < 0.001) the constrictor response to high concentrations of norepinephrine (10⁻³ M and 3 × 10⁻³ M). Yohimbine at 10⁻⁷ M failed to alter the response to norepinephrine. As shown in figure 5 (lower), 10⁻⁵ M prazosin produced a slight inhibition of the contraction induced by 10⁻⁵ M and 3 × 10⁻³ M phenylephrine. Prazosin at 10⁻⁶ M failed to inhibit the response to phenylephrine. However, 10⁻⁶ M and 10⁻⁵ M yohimbine inhibited in a dose-dependent manner the constrictor response to phenylephrine at all phenylephrine concentrations tested (ANOVA and Scheffe test, p < 0.001) (figure 5, upper). This inhibition was more marked than that produced by prazosin.

Neither prazosin (10⁻⁶ M and 10⁻⁵ M) nor yohimbine (10⁻⁶ M and 10⁻⁵ M) showed any effect on clonidine-induced contractions in canine basilar artery (n = 8).

Monkey Cerebral Artery

Norepinephrine produced dose-related contractions of monkey basilar artery at appreciably lower concentrations (10⁻⁸ M to 3 × 10⁻⁶ M) than in canine basilar artery. Further increases in the concentration of norepinephrine to 10⁻⁵ M and 3 × 10⁻⁵ M elicited relaxation (fig. 6). Treatment of the preparations with 10⁻⁶ M propranolol did not augment the constrictor responses to norepinephrine (n = 7). Application of phenylephrine in concentrations ranging from 10⁻⁷ M to 3 × 10⁻⁴ M to the basilar artery also caused dose-related contractions. The amplitude of the maximum response to phenylephrine was almost the same as that

FIGURE 2. Dose response curves of norepinephrine, phenylephrine, and clonidine for canine basilar (left) and mesenteric (right) artery. Contractile activities of each agonist are expressed as a percentage of the contraction elicited by a standard dose of 40 mM KCl. Results are expressed as mean + SEM. n = number of specimens taken from different arteries.
to norepinephrine, though a much higher concentration of phenylephrine than norepinephrine was needed in order to elicit that maximum response. The ED$_{50}$ (95% confidence interval) of norepinephrine and phenylephrine were $1.00(0.7-1.6) \times 10^{-7}$ M and $4.71(2.33-9.19) \times 10^{-6}$ M, respectively. In contrast, clonidine at concentrations of $10^{-6}$, $10^{-5}$ and $10^{-4}$ M failed to produce contraction, producing weak relaxation, instead.

The vasoconstrictor response to norepinephrine was markedly suppressed by both prazosin ($10^{-6}$ M) (ANOVA and Scheffe test, $p < 0.001$) and yohimbine ($10^{-6}$ M) (ANOVA and Scheffe test, $p < 0.001$), and there was no statistical difference in the degree of antagonism between the two (fig. 7). The maximum contractile response was also inhibited by either antagonist.

Neither $10^{-5}$ M cocaine or $10^{-5}$ M normetanephrine altered the constrictor responses of monkey basilar arteries to norepinephrine at all norepinephrine concentrations tested ($10^{-8}$ M to $3 \times 10^{-5}$ M) ($n = 4$).

The Constrictor Responses to TXA2, Prostaglandin F$_{2\alpha}$ or Serotonin

The dose-response curves for monkey basilar arteries were significantly different from canine basilar arteries for TXA2 (ANOVA, F = 103.35, $p < 0.0001$), prostaglandin F$_{2\alpha}$ (ANOVA, F = 24.34, $p < 0.0001$), and serotonin (ANOVA, F = 38.30, $p < 0.0001$).

As shown in table 1, the mean value for TXA2 ED$_{50}$ in monkey basilar arteries was significantly less than that for canine basilar arteries while the maximum responses were the same in both arterial beds.

Prostaglandin F$_{2\alpha}$ produced a larger maximum contraction in monkey basilar arteries than in canine basilar arteries, although the mean value for the ED$_{50}$ in monkey basilar arteries was larger than that for canine basilar arteries. The mean value for serotonin ED$_{50}$ in monkey basilar arteries was larger than that for canine basilar arteries while both arteries produced nearly identical maximum contractions.

Discussion

The present study has demonstrated the different reactivities of basilar arteries to norepinephrine, TXA2, prostaglandin F$_{2\alpha}$ or serotonin between monkeys and dogs.

Norepinephrine produced strong dose-related contraction of canine mesenteric artery in concentrations ranging from $10^{-7}$ M to $3 \times 10^{-5}$ M. The relative potency of the $\alpha_1$-adrenoceptor agonist phenylephrine was equivalent to that of norepinephrine, while the $\alpha_2$-adrenoceptor agonist clonidine failed to produce such strong contractions. Antagonism experiments revealed that the constrictor response to either norepinephrine or phenylephrine was competitively inhibited by the $\alpha_1$-adrenoceptor antagonist prazosin. Although the $\alpha_2$-adrenoceptor antagonist yohimbine also inhibited the response to either norepinephrine or phenylephrine,
The effects of prazosin (lower) or yohimbine (upper) on the constrictor response of canine basilar artery to phenylephrine. The data were matched by preparation, and statistical analysis comparing control and treatment responses at each agonist concentration was done using a paired t-test. Results are expressed as mean ± SEM. * = p < 0.01. The abscissa represents the molar concentrations of phenylephrine.

The constrictor response of isolated canine basilar artery to norepinephrine was extremely small when compared to that of mesenteric artery of a similar size. This finding is in agreement with the observations of other investigators. The low sensitivity of canine cerebral artery to norepinephrine has previously been suggested to be independent of increased norepinephrine inactivation by amine uptake and catechol O-methyltransferase or masking by β-adrenergic mechanism, since responsiveness was not augmented by treatment with cocaine, normetanephrine, pyrogallol or propranolol. Were the constrictor responses of canine cerebral artery to norepinephrine mediated through the receptor excitation process, sparse distribution of the receptors in canine cerebral artery would be one possible cause for the relative unresponsiveness.

Recently, the atypical nature of α-adrenoceptors in canine cerebral artery has been suggested by experimental results which indicate that the constrictor response induced by either exogenous norepinephrine or transmural electrical stimulation is resistant to phentolamine and phenoxybenzamine. An atypical nature is further supported by our experiment which revealed that the constrictor response of canine basilar artery to norepinephrine is not inhibited by the α₁-adrenoceptor antagonist prazosin while it was partly suppressed by the α₂-adrenoceptor antagonist yohimbine. These findings indicate that the α-adrenoceptors in canine basilar artery are similar to the α₂-subtype rather than the α₁-subtype. Should canine basilar artery contain predominantly α₂-adrenoceptors, α₁-adrenoceptor agonists would be expected to elicit a similar constrictor response to that induced by norepinephrine, while α₂-adrenoceptor antagonists would inhibit the constrictor response. In this experiment, however, the vasoconstrictor response induced by the α₁-adrenoceptor agonist clonidine was quite different from that induced by norepinephrine, and it was not inhibited by either the α₂-adrenoceptor antagonist yohimbine or the α₁-adrenoceptor antagonist prazosin. Therefore, it is likely that clonidine-induced constriction is not mediated by...
either $\alpha_2$ or $\alpha_1$-adrenoceptors but rather by another mechanism. These findings suggest that the receptors in canine basilar artery which mediate norepinephrine-induced contraction are somewhat different from the $\alpha_2$-subtype, although further studies using more selective $\alpha_2$-adrenoceptor agonists and antagonists will be needed in order to better clarify the nature of $\alpha_2$-adrenoceptor subtype in canine basilar arteries.

Recently, it has been reported that the opioid antagonist naloxone selectively inhibited the constrictor response of canine basilar artery to norepinephrine while it failed to alter the response to phenylephrine or clonidine. These results also confirm the atypical nature of receptors which mediate the constrictor response of canine basilar artery to norepinephrine.

This experiment further revealed that the constrictor response of canine basilar artery to phenylephrine was markedly inhibited by yohimbine while it was somewhat resistant to prazosin. Similar effectiveness of yohimbine on phenylephrine-induced constriction of canine cerebral arteries has been observed by Toda. This unusual observation may indicate that the affinity of agonists and/or antagonists for $\alpha_2$-adrenoceptors differ between canine cerebral and mesenteric artery. This unconventional observation merits further investigation.

The vasoconstrictor response of monkey basilar artery to $\alpha_2$-adrenoceptor agonists was substantial using either norepinephrine or phenylephrine, although a much higher concentration of phenylephrine than norepinephrine was needed in order to elicit the same magnitude of contraction. Clonidine failed to produce contraction, producing weak relaxation instead. Antagonism experiments demonstrated that the constrictor response to norepinephrine was inhibited by either prazosin or yohimbine in a noncompetitive fashion. These findings suggest that the constrictor response of monkey basilar artery to norepinephrine is mediated by $\alpha_1$-like adrenoceptors, although the noncompetitive antagonism by prazosin or yohimbine is quite unlike the response of canine mesenteric artery to those drugs. Our experimental results are almost consistent with the findings by Toda. With respect to the antagonism by yohimbine, however, some discrepancy exists between the results by Toda and those of our experiments. Toda reported that yohimbine did not affect the contractile responses of monkey cerebral arteries. On the other hand, the responses were noncompetitively attenuated by yohimbine in our experiments. The reason for this discrepancy is not apparent to the authors. Further studies will be needed in order to resolve this apparent conflict.

The present results further revealed that cocaine or normetanephrine at a concentration of $10^{-5}$ M, which was sufficient to poteniate the norepinephrine-induced constriction of canine mesenteric artery, did not influence the constrictor responses of monkey basilar arteries to exogenous norepinephrine. Similar observations have been reported in canine cerebral arteries. With respect to the inactivation of catecholamines by neuronal and extraneuronal uptake, therefore, no difference exists between monkey and canine cerebral arteries.

Comparison of the mean value for TXA2 $ED_{50}$ revealed that monkey cerebral artery was more sensitive to TXA2 than that of the canine, although the maximum contractions were not significantly different.

### Table 1: Mean Values of Agonist $ED_{50}$ and Maximum Response in Canine and Monkey Cerebral Arteries

<table>
<thead>
<tr>
<th></th>
<th>Dog</th>
<th>Monkey</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$ED_{50}$ (± SEM)</td>
<td>Mean maximum response (± SEM)</td>
</tr>
<tr>
<td>TXA2</td>
<td>10</td>
<td>1.28 (±0.20) $\times 10^{-9}$ M</td>
</tr>
<tr>
<td>Prostaglandin F2α</td>
<td>11</td>
<td>2.56 (±0.28) $\times 10^{-7}$ M*</td>
</tr>
<tr>
<td>Serotonin</td>
<td>15</td>
<td>0.51 (±0.04) $\times 10^{-7}$ M*</td>
</tr>
</tbody>
</table>

Maximum responses were expressed as a percentage of the contraction elicited by a standard dose of 40 mM KCl. $n$ = number of different arterial preparations on which the agonist was tested. *p < 0.01.
Toda\textsuperscript{14} previously reported similar results showing that the ED\textsubscript{50} for carboxylic TXA2 in monkey cerebral artery was significantly less than that for canine cerebral artery. Von Host, et al\textsuperscript{25} demonstrated that natural TXA2, in concentrations of 0.03 to 0.15 nmol, elicited dose-related contractions of human cerebral arteries. When compared to present results, the effective concentrations of TXA2 in human cerebral arteries appear to be closer to those of the monkey than those of the canine.

The constrictor responses of basilar arteries to prostaglandin F\textsubscript{2alpha} and serotonin were also different between monkeys and dogs. Prostaglandin F\textsubscript{2alpha} produced a large maximum contraction in monkey basilar arteries than in canine basilar arteries, although the mean value for ED\textsubscript{50} in monkey basilar arteries was larger than that for canine basilar arteries. Monkey basilar arteries were a little less sensitive to serotonin than canine basilar arteries.

Such species differences may have to be considered when investigating the pharmacology and pathophysiology of cerebral circulation. Heistad, et al\textsuperscript{26} have suggested that there are species differences in cerebral vascular responses to neural stimuli in vivo. Sympathetic stimulation in primates reduces cerebral blood flow while no significant reduction is observed in dogs or cats. Such differences may relate to the different nature of cerebral arterial \alpha-receptors among species. With respect to the etiology of cerebral vasospasm following subarachnoid hemorrhage, norepinephrine has been thought unlikely to play an important role because of the ineffectiveness of sympathectomy or an \alpha-adrenergic blocking agent, phentolamine, in the treatment of vasospasm.\textsuperscript{21} The low concentration of norepinephrine in cerebrospinal fluid\textsuperscript{22} and the low sensitivity of cerebral arteries to norepinephrine in experimental animals such as dogs\textsuperscript{22,23} or rabbits.\textsuperscript{24} However, such a conclusion might be unjustified since primate cerebral arteries are highly sensitive to norepinephrine.\textsuperscript{1, 2, 20-31, 34} Further studies will be needed in order to clarify the role of norepinephrine in the etiology of cerebral vasospasm. The possible role of TXA2 in the pathogenesis of cerebral vasospasm has been suggested in a canine subarachnoid hemorrhage model.\textsuperscript{25, 33} The fact that the primate cerebral artery is more sensitive than the canine to TXA2,\textsuperscript{14, 34} may further support a possible role for TXA2 in human vasospasm.

In summary, the present study has demonstrated differences in the constrictor responses of cerebral arteries to norepinephrine, TXA2, prostaglandin F\textsubscript{2alpha} and serotonin between monkeys and dogs.

References

A VARIETY OF ISCHEMIC BRAIN MODELS have been developed to study ischemic brain disorders including our own dog models. Each model has its own merits and demerits, and the selection of a suitable model often holds the key to the success of a study. Large animals, such as the dog, are not the model of choice when conducting autoradiographic studies because they need much dose of an expensive radioisotope. Undoubtedly, small animals like the rat serve as a better model in such cases. The use of small rodents in the study of brain ischemia, however, has been often hampered by technical difficulties and inconsistent results. The recent development of a four-vessel occlusion model provided a new scope for the use of rats as a model of global ischemia. The relative ease of the procedure has resulted in wide acceptance of this model. The inconsistent results obtained with this model, however, were debated in a recent issue of this journal.

In this communication, we describe experimental brain ischemia produced in rats by occlusion of the common carotid arteries and the basilar artery; this resulted in consistent and severe impairment of the cerebral blood flow. The procedure for producing this model is described, and the results of EEG and autoradiography obtained by this model are compared to those obtained by the four-vessel occlusion model.

Materials and Method

1. Production of Animal Models

Male Wistar rats, weighing 200–250 gm, were used throughout the experiments. Under light halothane anesthesia, a 3 cm skin incision was made on the anterior neck region and a subsequent operation was performed using a surgical microscope.

After dissecting the sternohyoid and omohyoid muscles, the base of the occipital cranium, where the musculus longus capitus terminates, was exposed. A small bone window (3 × 3 mm) was opened, and through the window, the basilar artery was freed from the adjacent tissue, electrocauterized and severed (transcervico-transcervical approach). The wound was closed and the rats were allowed to awaken.

On the day following occlusion of the basilar artery, the rats were subjected to occlusion of the common carotid arteries after the absence of neurological deficits had been confirmed. Approximately 20–30% of rats revealed neurological deficits following the basilar artery occlusion. The neck wound was reopened under halothane anesthesia, the trachea was intubated, and the rats were immobilized with pancuronium bromide. Controlled respiration was instituted using a Harvard Rodent Respirator (Model 681). The common carotid arteries were then clipped bilaterally (referred to hereafter as the three-vessel occlusion model) (fig. 1).

In some rats, an additional surgical procedure assured the blockade of blood flow to the brain through collateral pathways. A thread was carefully passed around the neck sparing the jugular veins, the vagus nerves and the trachea, and the loop of the thread was approximated with caution so as not to disturb venous blood flow and respiration (referred to as the three-vessel occlusion + neck ligation model).

For comparative studies, a group of ischemic rats...
Pharmacological comparison of isolated monkey and dog cerebral arteries.
T Sasaki, N F Kassell, J C Torner, W Maixner and D M Turner

Stroke. 1985;16:482-489
doi: 10.1161/01.STR.16.3.482

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/16/3/482

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/