Contributions From the Upper Cervical Dorsal Roots and Trigeminal Ganglia to the Feline Circle of Willis

Kiyoshi Saito, MD, and Michael A. Moskowitz, MD

To further define the sensory projections to the circle of Willis, we measured concentrations of immunoreactive substance P in pial arteries of cats following either bilateral removal of the C1-3 dorsal root ganglia (six cats) or bilateral removal of the trigeminal ganglia (three cats). Removal of the dorsal root ganglia decreased concentrations of the tachykinin substance P in the vertebral artery and the basilar artery and its branches by 72% and 50–66%, respectively. Bilateral removal of the trigeminal ganglia decreased substance P concentrations in all forebrain vessels including the rostral basilar artery, although only concentrations in the anterior cerebral artery were significantly lower than those in unilaterally lesioned cats (p<0.01). Hence, the vertebrobasilar artery and its tributaries are invested by substance P-containing fibers originating from the upper cervical dorsal root ganglia, and the anterior cerebral artery is innervated by both trigeminal ganglia. If a similar anatomy exists in humans, our data provide an explanation for the occipital localization of headaches arising from the vertebrobasilar arteries and for bilateral headaches following stimulation of the anterior cerebral artery. (Stroke 1989;20:524–526)

The pattern of headaches that develops following mechanical or electrical stimulation of the large cerebral arteries comprising the circle of Willis or due to diseases involving these vessels were elucidated in humans by the studies of Ray and Wolff,1 McNaughton,2 Penfield,3 Fay,4 and Fisher.5 To determine the origin of fibers that mediate this pain, sensory projections to the circle of Willis have been traced histochemically6 or determined by measuring the effects of trigeminal lesions on the concentration of immunoreactive peptides found in pial arteries7 or by measuring lesion-induced changes in the density of immunoreactive perivascular axons.8 Previous data indicate that unilateral lesions decrease concentrations of substance P (SP) in the rostral circle by only 30–50% 2–3 weeks after lesioning and do not alter SP concentration within the vertebrobasilar system, except in the superior cerebellar artery (SCA).7 The source of the remaining SP has not been determined. Hence, our study was undertaken to determine the extent to which major pial arteries within the circle of Willis receive SP-containing projections from the upper cervical dorsal root ganglia (DRGs) or from both trigeminal ganglia (TGs).

Materials and Methods

Cats weighing 2.5–4.0 kg were anesthetized with halothane and placed in the prone position. An incision in the midline was made extending from the external occipital protuberance to the spinous process of C4. The muscles were separated, and the laminae of C3 were exposed. The C3 DRG was located within the foramen of the C3 lamina, lying just caudal to the vertebral artery (VA) and was dissected after unroofing the foramen, taking special care to preserve the integrity of the adjacent VA. The C2 DRG was located within the foramen of the C2 lamina, lying just caudal to the vertebral artery (VA) and was dissected after unroofing the foramen, taking special care to preserve the integrity of the adjacent VA. The C1 DRG was dissected out of the intervertebral foramen, was dissected and removed. The C1 DRG was excised following a small laminectomy in the caudal portion of the C1 lamina. Postoperatively, the cats demonstrated a loss of position sense and muscle strength in the neck but were otherwise healthy. The TG was removed using a subtemporal extradural approach as described previously9 except that the cats were anesthetized with halothane; both TGs were removed on the same day. Special care was taken to protect the temporal lobe from damage by retraction. After surgery, the cats lost facial

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sensation and strength in the muscles of mastication and required feeding by orogastric tube.

The cats were killed 10 days after surgery with an overdose of pentobarbital. The cerebral arteries were removed and prepared for SP radioimmunoassay and protein determination as described previously.\(^7\) SP radioimmunoassay (antisera F\(_2\)) was carried out as previously reported\(^8\) except that the buffer for the assay contained 0.2% bovine serum albumin and that the tracer was added 4–6 hours after the addition of the antibody. This procedure increased the assay sensitivity (10% displacement) to 0.5 fmol/tube. SP concentrations were expressed as femtomole per milligram of protein.

Data from eight intact (normal) cats and from six cats following unilateral removal of the TG were taken from our previous studies.\(^7\) Cat-to-cat variations in the concentrations of the SP necessitated that each cat be used as its own control following either bilateral removal of the upper cervical DRG or bilateral removal of the TG. To determine the effects of the former, mean SP concentration in vessels within the rostral portion of the circle of Willis (anterior cerebral artery [ACA], middle cerebral artery [MCA], internal carotid artery [ICA], and posterior communicating artery [PCoM]) served as the reference for SP concentrations within vessels of the posterior fossa. Since axonal tracing from rostral vessels failed to identify transported marker in the upper cervical DRG (B.B. Walters and M.A. Moskowitz, unpublished data), we believe that this assumption is justified. Similarly, in previous experiments we determined that SP concentrations did not decrease in the VA or the anterior inferior cerebellar artery (AICA) following removal of the TG.\(^7\) Hence, in our present studies, mean SP concentration in these vessels served as the reference for SP concentrations in the rostral vessels to determine the effects of bilateral removal of the TG.

Results

SP concentrations as percent of that in the reference vessels decreased in the SCA, the caudal half of the basilar artery (BA), the AICA, and the VA (ranging from 28% to 54%) but did not change in the posterior cerebral artery (PCA) following removal of the upper cervical DRG (Table 1). The greatest decrease was found in the VA. The magnitude of these decreases was similar to that detected within the rostral circle of Willis following unilateral removal of the TG. A similar innervation has been described in the great circle of gerbils,\(^10\) guinea pigs,\(^11\) and rats\(^12\) and has been inferred in humans from mechanical stimulation studies.\(^1\) Although one report failed to identify labeled cells in the DRG after horseradish peroxidase was applied to the BA,\(^13\) our data indicate that pial arteries within the feline posterior fossa receive axonal projections from the DRG.

SP concentrations in the AICA and VA did not differ significantly between normal and TG-lesioned cats (data not shown). When expressed as percent of that in the reference vessels, SP concentrations in all pial arteries from the intact side of unilaterally lesioned cats closely approximated 100% (ranging from 92% to 116%; Table 2), thereby suggesting the lack of a rostro-caudal SP concentration gradient within the circle of Willis. On the lesioned side, SP concentration decreased in all vessels (ranging from 39% to 69%); the most pronounced reduction was in the MCA. After bilateral removal of the TG, SP concentration in the rostral half of the BA also decreased (to 42%).

Discussion

Our results agree with previous reports\(^8\),\(^10\)--\(^12\),\(^14\) suggesting that the TGs send axonal projections to the ACA, MCA, PCA, ICA, PCoM, SCA, and rostral BA and indicate that the ACA and rostral BA receive projections from both TGs. Since the superior sagittal sinus also receives bilateral TG innervation,\(^14\) together these findings suggest that midline vascular structures are innervated by sensory fibers projecting bilaterally.

This anatomy, if present in humans, establishes an anatomic basis to explain some clinical aspects

<table>
<thead>
<tr>
<th>Artery</th>
<th>Normal (n=8)</th>
<th>Lesioned</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior cerebral</td>
<td>126±24%</td>
<td>112±31%</td>
<td>3</td>
</tr>
<tr>
<td>Superior cerebellar</td>
<td>97±12%</td>
<td>54±8%*</td>
<td>3</td>
</tr>
<tr>
<td>Basilar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rostral half</td>
<td>112±23%</td>
<td>58±20%*</td>
<td>2</td>
</tr>
<tr>
<td>Caudal half</td>
<td>93±15%</td>
<td>34±6%*</td>
<td>2</td>
</tr>
<tr>
<td>Anterior inferior cerebellar</td>
<td>143±25%</td>
<td>46±11%*</td>
<td>3</td>
</tr>
<tr>
<td>Vertebral</td>
<td>80±14%</td>
<td>28±12%*</td>
<td>3</td>
</tr>
</tbody>
</table>

Data are mean±SEM % of mean value in reference vessels. *p<0.05 different from reference vessels by Student’s paired \(t\) test.

Table 2. Substance P Depletion in Feline Pial Arteries Following Unilateral or Bilateral Trigeminal Ganglionectomy

<table>
<thead>
<tr>
<th>Artery</th>
<th>Unilateral lesions (n=6)</th>
<th>Bilateral lesions</th>
<th>Value</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intact side</td>
<td>Lesioned side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cerebral</td>
<td>98±12%</td>
<td>56±8%</td>
<td>22±3%*</td>
<td>3</td>
</tr>
<tr>
<td>Middle cerebral</td>
<td>101±18%</td>
<td>39±12%</td>
<td>23±4%</td>
<td>3</td>
</tr>
<tr>
<td>Posterior cerebral</td>
<td>113±14%</td>
<td>56±8%</td>
<td>44±5%</td>
<td>3</td>
</tr>
<tr>
<td>Internal carotid</td>
<td>92±9%</td>
<td>49±16%</td>
<td>30±4%</td>
<td>3</td>
</tr>
<tr>
<td>Posterior communicating</td>
<td>116±20%</td>
<td>59±12%</td>
<td>35±7%</td>
<td>3</td>
</tr>
<tr>
<td>Superior cerebellar</td>
<td>109±13%</td>
<td>69±18%</td>
<td>49±5%</td>
<td>3</td>
</tr>
<tr>
<td>Basilar</td>
<td>85±16%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rostral half</td>
<td>42±8%</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Caudal half</td>
<td>100±20%</td>
<td></td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

Data are mean±SEM % of mean value in reference vessels. *p<0.01 different from lesioned side by Student’s unpaired \(t\) test.
of headache. For example, our data are compatible with observations that electrical stimulation of the vertebrobasilar arteries in humans causes pain referred to the occiput and neck (C2,3 dermatome).1 Stimulation of more rostral vessels causes pain referred to the forehead (first trigeminal dermatome). The referral of pain from the cerebral vessels to the trigeminal or upper cervical dermatome relates to the convergence of both visceral (vascular) and somatic (cutaneous) afferents onto single neurons within the trigeminal nucleus caudalis.15 Along similar lines, our data provide an explanation for the occurrence of bilateral head pain noted upon mechanical stretching of the SCA in humans.4 Furthermore, based on its dual innervation, one might anticipate a both frontal and occipital location for headaches arising from the SCA. To our knowledge, the pattern of headache associated with lesions of the SCA have not been described.

The source of the SP remaining in pial arteries following surgical deafferentation is unknown. Projections from sympathetic ganglia seem unlikely since forehead (first trigeminal) dermatome). The referral of pain to the occiput and neck (C2,3 dermatome). Further, based on its dual innervation, one might anticipate a both frontal and occipital location for headaches arising from the SCA. To our knowledge, the pattern of headache associated with lesions of the SCA have not been described.

The source of the SP remaining in pial arteries following surgical deafferentation is unknown. Projections from sympathetic ganglia seem unlikely since superior cervical ganglionectomy did not change SP concentrations in the vessels of the circle of Willis.7 SP may be contained within parasympathetic fibers or within intrinsic sources from the brain.16 One recent report demonstrated the presence of SP within endothelial cells,17 and our laboratory has recently obtained data by radioimmunoassay and high-performance liquid chromatography documenting the presence of tachykinin within endothelial cells from the circle of Willis in humans (M.D. Linnik and M.A. Moskowitz, unpublished data). Additional studies will be necessary to clarify this point.

Sensory fibers including those that contain SP not only transmit nociceptive information but also actively dilate cerebral blood vessels18,19 and increase cerebral blood flow20 during severe hypertension and seizures. Following unilateral removal of the TG, the blood flow increases induced by severe hypertension or seizures were 25% lower on the lesioned than on the unlesioned side when measured using radioabeled microspheres.21 Recent data suggest that these increases in blood flow are mediated by local axonal mechanisms and do not involve central transmission. Dual (sensory, motor) function of perivascular afferents suggest a complex role for tachykinin and other neuropeptide-containing sensory fibers in the physiology of the cerebrovasculature.

References

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