Pathways of Parasympathetic and Sensory Cerebrovascular Nerves in Monkeys

Jan Erik Hardebo, MD; Mohammed Arbab, MD; Norihiro Suzuki, MD; and Niels Aage Svendgaard, MD

Using immunohistochemistry, we studied the origins and pathways of parasympathetic and sensory nerve fibers to the pial arteries in four squirrel monkeys. Following its application to the surface of the middle cerebral artery, the retrograde axonal tracer True Blue accumulated in parasympathetic neurons of the sphenopalatine ganglion and the internal carotid ganglion. The latter is strategically located where the internal carotid artery enters the cranium. Fibers from the sphenopalatine ganglion reach the internal carotid artery in the cavernous sinus region after running as rami orbitales. Before reaching the internal carotid artery, the fibers bypass aberrant sphenopalatine ganglia, with the most distant, the cavernous ganglion, being located in the cavernous sinus region. True Blue also accumulated in sensory neurons of the ophthalmic and maxillary divisions of the trigeminal ganglion and in sensory neurons of the internal carotid ganglion. Fibers from the ophthalmic division of the trigeminal ganglion reach the internal carotid artery as a branch through the cavernous sinus, bypassing the cavernous ganglion. Fibers from the maxillary division also bypass the cavernous ganglion after reaching it via a recurrent branch of the orbitociliary nerve. Thus, the cavernous ganglion forms a confluence zone for parasympathetic and sensory fibers in the region. In addition, parasympathetic and sensory fibers leave the confluence zone to follow the abducent and trochlear nerves backward to the basilar artery and tentorium cerebelli, respectively. Clinical implications are discussed. (Stroke 1991;22:331–342)

Blood vessels of the brain surface, and to some extent those of its parenchymal branches, are supplied with sympathetic, parasympathetic, and sensory nerve fibers, spreading like a network in the adventitia. It has been long known that all sympathetic fibers (except those in the caudal basilar artery in some species) originate in the superior cervical ganglion. An origin for parasympathetic fibers in the sphenopalatine and otic ganglia has been demonstrated in rats and cats by the retrograde axonal tracer technique, by nerve section, and by histochemical mapping of the putative transmitters acetylcholine (cholinesterase, choline acetyltransferase [ChAT]) and vasoactive intestinal polypeptide (VIP). By this latter technique (histochemical staining of the putative transmitters substance P and calcitonin gene-related peptide [CGRP]), an origin for supratentorial cerebrovascular fibers in the trigeminal ganglion, primarily its ophthalmic division, has been demonstrated in rats, cats, and monkeys. Parasymathetic and sensory fibers in the basilar artery have their cell bodies in the vagal and upper cervical dorsal root ganglia and possibly in the sphenopalatine ganglion in rats and cats, and in cynomolgus monkeys an additional supply from the trigeminal ganglion has been demonstrated. In rats, an additional source for cerebrovascular parasympathetic and sensory nerves has been identified, namely the internal carotid ganglion, located along the greater superficial petrosal nerve pathway to the sphenopaltine ganglion, at its junction with the sympathetic internal carotid nerve on the surface of the internal carotid artery. The presence of the internal carotid ganglion has also been described in humans and monkeys. One further possible source for innervation of the cerebrovascular nerves in humans and monkeys is the miniganglia described to be lateral to the internal carotid artery in the matrix between vessels of the cavernous sinus. By using a combined retrograde axonal tracer and immunohistochemical transmitter staining technique, we studied the precise origins and probable pathways of parasympathetic and pain fibers to vessels on the brain surface in monkeys.

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Materials and Methods

We used four squirrel monkeys (Saimiri sciureus) weighing 650–780 g. Anesthesia was initiated by the inhalation of 4% isoflurane (Abbott Laboratories, North Chicago, Ill.) followed by 0.05 mg/kg i.m. atropine. The monkeys were intubated, and anesthesia was maintained with 2% isoflurane in 70% N₂O and 30% O₂. In two animals a left-sided frontotemporal craniotomy was performed under sterile conditions. The dura mater was incised, and the arachnoid just distal to the trifurcation of the middle cerebral artery was opened. A small piece of polyethylene film was inserted between the brain cortex and the three branches of the middle cerebral artery. A small piece of Spongostan (Ferrosan, Copenhagen, Denmark) preabsorbed with 25 μl of the retrograde axonal tracer True Blue²² was then applied on the exposed segments of the middle cerebral artery. The opened arachnoid was made to adhere to the surface of the piece of Spongostan, and another piece of polyethylene film was placed over the application site to prevent contact with the dura of the water-soluble dye. The dura was closed water-tight, the bone flaps were replaced, and the skin was sutured. Pilot experiments in two monkeys revealed that the tracer does not accumulate in cranial ganglia after its application to an area of the brain surface devoid of larger branches of the middle cerebral artery.

Six days after the application of True Blue, the two animals were anesthetized with 14 mg/kg i.m. alfaxalone-alfadolone acetate followed by 10 mg/kg i.v. thiopental. Their chests were opened, and the mon-
FIGURE 2. Coexistence of vasoactive intestinal polypeptide (VIP) and choline acetyltransferase (ChAT) (a and b) and of substance P (SP) and calcitonin gene–related peptide (CGRP) (c and d) in perivascular nerve fibers in small pial arteries of squirrel monkey. Fluorescence immunohistochemistry. Scale bars = 50 μm.

keys were perfused through the left ventricle with saline followed by fixation with an ice-cold mixture of 2% paraformaldehyde and 15% saturated aqueous picric acid solution in 0.1 M phosphate buffer (pH 7.2). The following tissues were dissected out: the superior cervical, ciliary, sphenopalatine, otic, genic-
The specimens were exposed to the peptide antiserum for 24 hours at 4°C in a moist chamber. The site of the antigen–antibody reaction was revealed by the application of fluorescein isothiocyanate (FITC)-labeled pig anti-rabbit or goat anti-mouse immunoglobulin G (IgG) (Dukopatts, Copenhagen, Denmark and Sigma Chemical Co., St. Louis, Mo., respectively) in a 1:20 or 1:80 dilution, respectively. For double-staining we also used tetramethylrhodamine isothiocyanate (TRITC)-labeled goat anti-rabbit IgG (Milab) and FITC-labeled goat anti-guinea pig IgG (Sigma) in 1:320 and 1:160 dilutions, respectively. All antisera contained 0.3% Triton X-100 and 0.25% bovine serum albumin (for the ChAT antiserum Triton X-100 was excluded). Control sections were exposed to antisera that had been preabsorbed with excess antigen (10–100 μg synthetic or natural peptide per milliliter diluted antiserum) and displayed no immunoreactivity.

The slides were examined in an epi-illumination fluorescence microscope fitted with filter settings appropriate for True Blue, FITC, or TRITC fluorescence. The number of True Blue–positive cells in the ganglia were counted on serial sections, avoiding recounting of the same cell on consecutive sections. Every fifth section of the frontal dura was stained with hematoxylin and eosin.

### Results

In the first two monkeys, a network of fiber bundles and individual nerve fibers positive for VIP, ChAT, substance P, and CGRP was seen in even the smallest pial vessels contained in the spread preparations (diameters of approximately 50 μm) (Figure 2). ChAT displayed a weaker fluorescence than the other peptides. All ChAT-positive fibers also contained (or ran in close association with fibers containing) VIP, whereas approximately 60% of the VIP-positive fibers were ChAT-positive. Almost all substance P–positive fibers also contained (or ran in close association with fibers containing) CGRP, whereas about 80% of the CGRP-positive fibers were substance P–positive. In the intracranial segment of the internal carotid artery, fiber bundles of VIP+ChAT− and CGRP+Substance P–positive fibers were seen as were a few delicate varicose fibers positive for VIP, CGRP, and substance P apparently innervating the artery. The pial arterial wall at the site of True Blue application was intensely labeled, and a limited spread of the dye was seen to areas immediately surrounding the artery (i.e., the pial mater and underlying cortex). No dye was seen in the overlying dura mater.

### Table 1. Number of Cells in Various Ipsilateral Cranial Ganglia That Accumulated True Blue After Application to Trifurcation of One Middle Cerebral Artery in Squirrel Monkeys

<table>
<thead>
<tr>
<th>Ganglion</th>
<th>Monkey</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior cervical</td>
<td>1</td>
<td>52</td>
</tr>
<tr>
<td>Ciliary</td>
<td>2</td>
<td>47</td>
</tr>
<tr>
<td>Sphenopalatine</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Aberrant sphenopalatine</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Cavernous</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Otic</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Internal carotid</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>Geniculate</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Trigeminal Ophthalmic division</td>
<td>1</td>
<td>41</td>
</tr>
<tr>
<td>Maxillary division</td>
<td>2</td>
<td>33</td>
</tr>
<tr>
<td>Glossopharyngeal</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Vagal</td>
<td>2</td>
<td>6</td>
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<td></td>
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All dendrites, trigeminal, superior and inferior glossopharyngeal, and vaginal ganglia on both sides; the contents of the cavernous sinus region on the left side; the left internal carotid artery (at its entrance into the cranium through the carotid canal) with the internal carotid ganglion and adjacent segments of the greater superficial petrosal and vidian nerves (Figure 1); the branches of the left orbitociliary nerve with its accompanying rami orbitales (Figure 1) running from the maxillary nerve to the medial infraorbital fissure; the nasociliary nerve and accompanying structures in the ethmoidal foramen on both sides; the basal frontal dura on both sides; the tracer application sites with the underlying brain and the overlying dura mater; and the remaining facial vessels. In the other two animals, perfusion-fixed as above, the abducent and trochlear nerves were dissected out separately along their whole intracranial courses from the brain stem to their exits through the supraorbital fissure.

The tissues were immersed in fixative for 2 hours and thoroughly rinsed for 24 hours in Tyrode's solution containing 10% sucrose at 4°C. The pial vessels were spread out on glass slides. The other preparations were frozen and serially sectioned at 10-μm thicknesses in a cryostat. The cavernous sinus region was sectioned in the frontal plane, and the proximal internal carotid artery was sectioned at right angles to its length axis.

The sections and spread preparations were processed for immunohistochemical demonstration of dopamine β-hydroxylase, ChAT, VIP, substance P, and CGRP with the indirect immunofluorescence method. The dopamine β-hydroxylase antiserum was raised in rabbits (Lot No. 2012, Eugene Tech, Allendale, N.J.) and used in a 1:320 dilution. Monoclonal ChAT antiserum was raised in rats (166, P.M. Salvaterra, Duarte, Calif.) and used in a 1:20 dilution. The VIP antisera were raised in rabbits or guinea pigs (Code No. 7854 or 8701, respectively; Milab, Malmö, Sweden) and used in 1:320 or 1:1,280 dilutions. Rabbit substance P antiserum was supplied by Milab (Code No. 8127) and used in a 1:160 dilution, and monoclonal rat substance P antiserum was supplied by Seralab, Stockholm, Sweden (Code No. NC1/34HL) and used in a 1:160 dilution. Rabbit CGRP antiserum (Code No. 8425, Milab) and guinea pig CGRP antiserum (BGP 470-1, Milab) were used in 1:640 dilutions.

The specimens were exposed to the peptide antiserum for 24 hours at 4°C in a moist chamber. The site of the antigen–antibody reaction was revealed by the application of fluorescein isothiocyanate (FITC)-labeled pig anti-rabbit or goat anti-mouse immunoglobulin G (IgG) (Dukopatts, Copenhagen, Denmark and Sigma Chemical Co., St. Louis, Mo., respectively) in a 1:20 or 1:80 dilution, respectively. For double-staining we also used tetramethylrhodamine isothiocyanate (TRITC)-labeled goat anti-rabbit IgG (Milab) and FITC-labeled goat anti-guinea pig IgG (Sigma) in 1:320 and 1:160 dilutions, respectively. All antisera contained 0.3% Triton X-100 and 0.25% bovine serum albumin (for the ChAT antiserum Triton X-100 was excluded). Control sections were exposed to antisera that had been preabsorbed with excess antigen (10–100 μg synthetic or natural peptide per milliliter diluted antiserum) and displayed no immunoreactivity.

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FIGURE 3. Following its application to ipsilateral middle cerebral artery, True Blue (TB) accumulated in three neurons (arrows) of sphenopalatine ganglion (SPG) (a) that were also positive for vasoactive intestinal polypeptide (VIP) (b). Most neurons in this ganglion are VIP-positive. In rostral division of internal carotid ganglion (ICG), TB was found in two neurons (c) that were VIP-positive (d). Fluorescence immunohistochemistry. Scale bars=50 μm.
FIGURE 4. Following its application to ipsilateral middle cerebral artery, True Blue (TB) was found in neuron (a) of ophthalmic division of trigeminal ganglion (TG) that contained both substance P (SP) (b) and calcitonin gene–related peptide (CGRP) (c). In rostral division of internal carotid ganglion (ICG), TB was found in neurons (d) that were positive for both vasoactive intestinal peptide (VIP) (e) and choline acetyltransferase (ChAT) (f). Scale bars=50 μm.
FIGURE 5. Most neurons in cavernous ganglion were positive for vasoactive intestinal polypeptide (VIP) (a and b). Some were also positive for choline acetyltransferase (ChAT) (arrows) (b and c). Scale bars=50 μm.

True Blue accumulated in neurons of the superior cervical, sphenopalatine, internal carotid, and trigeminal ganglia of both monkeys (Table 1) but not in the ciliary, cavernous, otic, geniculate, glossopharyngeal, or vagal ganglia or the aberrant sphenopalatine ganglia along the rami orbitales. Within the
trigeminal ganglion True Blue accumulated in both the ophthalmic and maxillary divisions. Almost all True Blue–positive cells in the superior cervical ganglion were positive for dopamine β-hydroxylase, and in the sphenopalatine ganglion the same was true for VIP. In this ganglion approximately 60% of all neurons were positive for VIP (Figure 3b). About 30% of the True Blue–VIP–positive cells were also positive for ChAT. In the trigeminal ganglion approximately 60% and 70% of the True Blue–positive cells were also positive for substance and CGRP, respectively (Figures 4b and 4c). The internal carotid ganglion (Figure 1) consisted of a larger group (about 30) of VIP–positive cells (Figure 3d), several of which also contained ChAT (Figures 4e and 4f), located rostral to a group of about 10 cells that were CGRP– and substance P–positive. Double-staining with VIP and CGRP revealed that the larger group of cells did not contain CGRP and that the smaller group of cells did not contain VIP. All True Blue–positive cells in the internal carotid ganglion were either VIP–ChAT–positive (Figures 3c and 3d; Figures 4d, 4e, and 4f) or CGRP–substance P–positive.

Among the ganglia that did not accumulate the tracer, a large percentage of VIP–positive cells were found in the cavernous, otic, glossopharyngeal, and vagal ganglia (Figures 5a and 5b) and the aberrant sphenopalatine ganglia. Several VIP–positive neurons were also ChAT–positive (as demonstrated for the cavernous ganglion in Figures 5b and 5c). Only one cavernous ganglion was found within the cavernous sinus in each monkey (see References 13, 19, and 21). The location and probable connections of the cavernous ganglion are indicated in Figures 1 and 6. None of the approximately 30 cells in this ganglion were CGRP– or substance P–positive (every second section was double-stained for either VIP–ChAT or CGRP–substance P).

Aberrant VIP–ChAT–containing ganglia (negative for CGRP and substance P) and VIP–ChAT–positive fibers were found along the whole course of the rami orbitales. The rami orbitales appeared to mingle with fibers of the orbitociliary nerve branch on their course from the sphenopalatine ganglion toward the medial infraorbital fissure. No neurons were found directly on the surface of the internal carotid artery. Several CGRP–substance P–positive cells were found in the upper glossopthtalineal and vaginal ganglia, and a few such cells were observed in the geniculate ganglion.

In the other two monkeys, fibers positive for both VIP and ChAT or substance P in the abducens nerve and for substance P in the trochlear nerve were seen near the margin of these nerves from about halfway along their intracavernous courses and caudally toward their origins from the brain stem. In the caudal intracavernous part of the abducens nerve a few CGRP–substance P–positive neurons were seen, and in one monkey a single VIP–ChAT–positive neuron was found.

No VIP– or ChAT–positive fibers were seen in the nasociliary nerve or other structures passing through the ethmoidal foramen, except in the adventitia of blood vessels. No VIP–, ChAT–, CGRP–, or substance P–positive fibers bundles could be found in the basal frontal dura from the level of the ethmoidal foramen and caudally. Also, no fiber bundles could be observed in hematoxylin and eosin–stained sections of the basal frontal dura.

Discussion

We confirm in monkeys that perivascular pial sympathetic nerves originate in the superior cervical ganglion and that there is no contribution of nerve branches from the contralateral ganglion at the level of the trifurcation of the middle cerebral artery.

One major finding is that parasympathetic fibers to this part of the pial vasculature originate in the ipsilateral sphenopalatine and internal carotid ganglia. According to the number of True Blue–labeled cells, these two ganglia contribute to innervation to similar extents. The probable pathways are summarized in Figure 7. The pathway from the sphenopalatine ganglion to the pial vessels is not identical to that found in rats, where the fibers take a short course on the medial orbital wall up to the ethmoidal foramen to enter the skull and follow the internal ethmoidal artery back to the anterior part of the circle of Willis. No such fiber connection was found in...
monkeys. Instead, a highly likely course for the fibers from the sphenopalatine ganglion is via rami orbitales, which in monkeys join a recurrent branch of the orbitociliary nerve from the maxillary nerve to reach the cavernous sinus region (via the medial infraorbital fissure) (Figures 1 and 6). Direct documentation of such a pathway may be obtained from studies in which True Blue application is combined with nerve section. In the cavernous sinus region a plexus-like nerve formation has been demonstrated in cynomolgus monkeys, with fiber branches to/from the adjacent internal carotid artery and ophthalmic, trochlear, and abducent nerves (Figure 6). Although we could not satisfactorily demonstrate branches from the plexus to the internal carotid artery, evidence from nerve sections in cynomolgus monkeys have shown that at least some of the branches are parasympathetic in nature.

The internal carotid ganglion is located on the wall of the internal carotid artery, where the greater superficial petrosal nerve is joined by the internal carotid nerve to form the vidian nerve. The internal carotid ganglion is also found in rats and humans. It appears to be strategically located on the lateral wall of the internal carotid artery just at its entrance through the skull base (Figure 1). In all three species the internal carotid ganglion consists of a distal (rostral) parasympathetic subdivision and a proximal sensory subdivision, as characterized by their neuronal contents of VIP+ChAT and CGRP+ substance P, respectively. The fibers travel a very short course in the greater deep petrosal nerve to the arterial adventitia. The fibers seem not only to course as bundles along the intracranial internal carotid artery to reach its pial ramifications, but also to innervate the intracranial segment of the artery with some delicate fibers. In line with this, substantial amounts of VIP are found by radioimmunoassay in the intracranial segment of the human internal carotid artery.

No True Blue-positive cells were found in the VIP+ChAT-positive miniganglia along the rami orbitales and orbitociliary nerve directed to the cavernous sinus nor in the VIP+ChAT-positive ganglion in the trabeculae of the cavernous sinus. This indicates that these ganglia do not innervate structures as far
The possibility remains that the internal carotid artery itself, the circle of Willis, and its proximal branches may be reached by fibers from these ganglia. Other nearby target structures are, however, equally likely as candidates: 1) the walls of venous vessels of the cavernous sinus, 2) the capsule of the glandular tissue of the hypophysis, 3) the basilar artery and its branches, reached by fibers running on the surface of the abducent nerve backward, as supported by our findings of VIP+ChAT-positive fibers on the nerve surface, 4) the tentorium cerebelli, reached by a fiber bundle forming the nervus tentorii, which follows the trochlear nerve backward, and 5) fibers from the plexus joining the adjacent cranial nerves, which may follow them rostrally to orbital structures.

In rats and cats the otic ganglion has been shown to contribute parasympathetic fibers to the cerebrovascular innervation. We observed no such contribution in our two monkeys. The same was valid for the ciliary, geniculate, glossopharyngeal, and vagal ganglia. However, the limited number of animals studied and the single application site for the tracer along the vascular tree implies that negative findings should be interpreted with caution.

The source for sensory innervation of the middle cerebral artery with CGRP+substance P-positive fibers appears to be threefold, as summarized in Figure 8. As judged from the number of True Blue-positive cells, the major contribution comes from the ophthalmic division of the ipsilateral trigeminal ganglion. The pathway for these fibers has been demonstrated in cynomolgus monkeys by the aid of electron microscopy and nerve sections. The fibers bridge to the cavernous plexus from the ophthalmic nerve shortly rostral to the ganglion, and an additional bridge exists between the plexus and the rostral segment of the internal carotid artery just before the artery bends upward in the sinus (Figure 6). A few reports in humans have identified fine branches connecting the internal carotid artery with the medial surface of the ophthalmic nerve shortly rostral to the ganglion, but it was not clarified whether such fibers were sympathetic or sensory origin. Recently, a pathway between the ophthalmic nerve and the plexus has been demonstrated in humans, as well as a probable extension of the pathway to the intracavernous internal carotid artery. Substantial levels of

**FIGURE 8.** Schematic overview of origins and pathways of sensory fibers to right intracranial internal carotid artery and pial arteries in monkeys. ACA, anterior cerebral artery; BA, basilar artery; DPN, deep petrosal nerve; EF, ethmoidal foramen; GSPN, greater superficial petrosal nerve; ICA, internal carotid artery; ICG, internal carotid ganglion; ICN, internal carotid nerve; MCA, middle cerebral artery; NCN, nasociliary nerve; OCN, orbitociliary nerve; PCA, posterior cerebral artery; RO, rami orbitales; SCG, superior cervical ganglion; SPG, sphenopalatine ganglion; TG, trigeminal ganglion; VN, vidian nerve.
CGRP and substance P are found in this segment of the artery in humans.19

No CGRP- or substance P-positive fiber bundles were observed in the basal frontal dura. This and other anatomic data given above speak against a pathway via the nasociliary nerve (from the ophthalmic division of the trigeminal ganglion) through the ethmoidal foramen and basal frontal dura to the circle of Willis, as is found in rats.12

Fibers from the ipsilateral maxillary division of the trigeminal ganglion apparently travel in the orbitociliary nerve branch to run through the cavernous nerve plexus and bridge to the internal carotid artery together with fibers from the ophthalmic division.13 Apparently, some substance P-positive fibers from the ophthalmic and maxillary divisions join the recurrent nerve of the plexus to run along the abducens nerve to innervate the basilar artery and its branches, as also shown by denervation experiments in cynomolgus monkeys.13 The unexpected finding of a few CGRP+ substance P-positive neurons in the abducens nerve may represent aberrant trigeminal neurons along this pathway. Further, in monkeys some substance P-positive fibers from the ophthalmic division leave the plexus to join the tentorial nerve, which follows the trochlear nerve to the rostral origin of the tentorium cerebelli and innervates the tentorium, occipital dura, and falx and their sinuses.26

A third source of sensory fibers to the middle cerebral artery was found in the few CGRP+ substance P-positive cells in a subdivision of the ipsilateral internal carotid ganglion. The fibers reach the internal carotid artery via the greater deep petrosal nerve and run in bundles along the artery to reach the pial vessels or form a terminal network on the artery.

The upper cervical dorsal root ganglia were not studied since it is highly unlikely that they contribute to the sensory innervation of supratentorial vessels.5,12,17

As recently demonstrated, activation of the cerebrovascular parasympathetic and sensory nerves leads to a marked increase in cortical blood flow.31-35 Thus, upon activation these systems may ensure a sufficient blood supply to the brain when it is threatened or when the demand is raised as during ischemia, seizures, and severe hypertension.31-35 If the perivascular parasympathetic nerves terminate close to the pain fiber endings, released VIP may even enhance the activation of the pain fiber transmitter(s).36

Our demonstration of a sensory innervation of the intracranial segment of the internal carotid artery may contribute to the understanding of the pathophysiology of syndromes with retro-orbital pain (cluster headache, ophthalmoplegic migraine, and Tolosa Hunt's syndrome).18,37

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References


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