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Trigeminovascular fibers increase blood flow in cortical gray matter by axon reflex-like mechanisms during acute severe hypertension or seizures

(cerebrovascular circulation/axon reflex/hypertension/seizures/trigeminal nerve)

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ABSTRACT **Cerebral blood flow was measured and compared in 10 symmetrical brain regions following unilateral trigeminal ganglionectomy ($n = 13$), sham operation ($n = 6$), or trigeminal root section (rhizotomy) ($n = 8$) in cats. Multiple determinations were obtained in anesthetized and paralyzed animals using radiolabeled microspheres during (*i*) normocapnia–normotension, (*ii*) hypercapnia (5% CO_2/95% room air), (*iii*) angiotensin-induced acute severe hypertension (190 > mean arterial blood pressure < 210 mmHg), or (*iv*) bicuculline-induced seizures. Flow was symmetrical in all brain regions at rest and during increases induced by hypercapnia in the three groups. During severe hypertension or seizures, marked elevations developed bilaterally (≈93% and ≈130%, respectively). In ganglionectomized animals, increases due to hypertension or seizures were attenuated by 28–32% on the denervated side within cortical gray matter regions corresponding to the anterior, middle, and posterior cerebral arteries. Flow was symmetrical within all brain regions in sham-operated animals and in the rhizotomy group, despite comparable increases in regional cerebral blood flow induced by angiotensin. Hence, the trigeminal nerve mediates blood flow adaptations during severe hypertension and seizures. Furthermore, since trigeminal cell bodies and peripheral axons are destroyed or degenerate following ganglionectomy but not following rhizotomy, local "axon reflex-like" mechanisms mediate these increases in cerebral blood flow.**

The neurogenic control of the cerebral circulation is complex and many aspects are poorly understood. Under resting conditions, the regulation of blood flow is controlled by the partial pressure of carbon dioxide in arterial blood, autoregulation, metabolic and neurophysiological brain activity, and neurovascular influences (cf. ref. 1). Among the neurovascular influences, the role of sympathetic activity has been most extensively studied (2–5). Sympathetic nerves influence blood flow minimally under basal conditions, as evidenced by measurements during electrical stimulation (2, 3) or following chronic ablation (3) of the superior cervical ganglia. However, during severe hypertension or seizures (4), sympathetic nerves attenuate the expected increases in flow and, by so doing, protect against the consequences of severe acute and chronic increases in perfusion pressure. Less consistent flow patterns follow lesioning or stimulating parasympathetic fibers (5, 6).

A third major pathway was recently defined innervating cerebral blood vessels (7). Perivascular sensory axons projecting from the trigeminal ganglia were demonstrated by retrograde (7–9) and orthograde (10) axonal transport techniques as well as by Wallerian degeneration techniques (11) or by surgical lesioning combined with immunohistochemistry (12, 13) or radioimmunoassay (14, 15). Fibers primarily from the ophthalmic division (7, 8) join sympathetic and parasympathetic fibers within the cavernous plexus (11) from which they distribute to the ipsilateral internal carotid artery and the circle of Willis. Trigeminovascular fibers are mainly unmyelinated (16), reside within the adventitial layer, transmit nociceptive information (17, 18), and contain substance P (12), neurokinin A (19), calcitonin gene-related peptide (13), and cholecystokinin 8 (20).

In this report, we examined the possibility that sensory axons participate in the regulation of cerebral blood flow based on knowledge that (*i*) substance P (21, 22), neurokinin A (23), and calcitonin gene-related peptide (13) are cerebrovasodilating molecules; (*ii*) peptides are released from pial vessels *in vitro* by depolarizing stimuli (24); and (*iii*) release mediates vasodilation and/or increases in blood flow following electrical stimulation of sensory nerves in other tissues (25–27). Blood flow was examined during perturbations previously shown to involve nonneurogenic (hypercapnia) and neurogenic mechanisms (at least in part). We conclude that increases in brain blood flow during severe hypertension are not totally passive to the perfusion pressure. Furthermore, increases in flow associated with generalized seizures or hypertension are mediated in part by the trigeminal nerve via local "axon reflex-like" mechanisms involving neuropeptide release from perivascular nerve endings.

MATERIALS AND METHODS

Sham and Lesioning Procedures. Male and female adult mongrel cats (3.0–4.5 kg) were anesthetized with ketamine hydrochloride (30 mg/kg, i.m.) and sodium pentobarbital (10–15 mg/kg, i.p.) and mechanically respirated with halothane anesthesia (0.5–2.0%) as needed. Animals were subjected to unilateral trigeminalectomy as described (15). In this procedure, trigeminal ganglia cell bodies are destroyed and perivascular fibers degenerate accordingly. Sham-operated animals were subjected to craniectomy, exposure of the trigeminal ganglia, as well as an equivalent amount of brain retraction as required for the ganglionectomy.

The trigeminal root (that section between the ganglion and the brainstem) was approached by a left suboccipital craniectomy, which extended laterally and superiorly without damaging the sigmoid or transverse sinuses. The dura was cut along the lateral edge of the craniectomy, and the cerebellum

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Abbreviations: ACA, MCA, and PCA, anterior, middle, and posterior cerebral arteries, respectively.

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was gently retracted medially. A partial cerebellectomy (removal of <20% of a single hemisphere) was necessary in most instances to optimize root exposure for the rhizotomy. The root was transected with microscissors. In this procedure, trigeminal ganglia cell bodies are preserved. The completeness of the ganglionectomy or rhizotomy was confirmed by (*i*) the existence of anesthesia to pin prick and touch in the trigeminal dermatome, and (*ii*) visual inspection of the lesioned site at postmortem examination.

Cerebral Blood Flow. Measurements were made 8–25 days after sham operation, trigeminal ganglionectomy, or rhizotomy. Cerebral blood flow was measured with isotopically labeled microspheres (^{113}Sn, ^{103}Ru, ^{95}Nb, or ^{46}Sc) (28) having a diameter of 16.5 ± 0.2 μm. Animals were anesthetized with sodium pentobarbital (30 mg/kg, i.p.; supplemented with 6.5 mg/hr, i.v.), intubated, paralyzed with gallamine triethiodide (8–12 mg·kg^{-1}·hr^{-1}) and respirated mechanically. The end expiratory CO_2 was monitored with an ET HL 200 CO_2 monitor (Instrumentation Laboratory, Lexington, MA) and temperature was maintained at 37°C–38°C with a heating blanket. Arterial blood pressure was monitored by a transducer (Gould Inc., Oxnard, CA) and a Grass model 7D polygraph. Catheters placed in the vena cava, aortic arch, axillary artery, and left atrium were used for administering drugs, obtaining reference blood samples, monitoring blood pressure, and injecting microspheres, respectively. Microspheres (3.3–8.2 × 10^5; 20–50 μCi; 1 Ci = 37 GBq; in 4 ml of heparinized saline) were vigorously agitated for 5 min immediately prior to injection over a 10-sec period followed by a saline flush. Reference blood samples were collected via a Holter pump starting 10 sec before microsphere injection and continuing for 2 min. Animals were sacrificed with sodium pentobarbital overdose.

The brain was fixed in formalin for 2 days. Tissues were dissected into symmetrical regions. Gray matter from (*i*) anterior cerebral artery (ACA) territory was taken from the parasagittal surface of the frontal lobe, (*ii*) middle cerebral artery (MCA) territory was taken from the frontotemporal region at the level of optic chiasm, and (*iii*) posterior cerebral artery (PCA) territory was taken as a wedge from the occipital pole. White matter was removed from adjacent areas. Samples were weighed and assayed for radioactivity with a Compugamma 1282 γ counter (LKB). Individual isotopes were quantitated by utilizing the appropriate energy window settings (^{113}Sn, 350–400; ^{103}Ru, 450–550; ^{95}Nb, 650–800; ^{46}Sc, 830–1200 keV). Cerebral blood flow (ml per 100 g per min) was calculated as follows: Cb × 100 × RBF/Cr (Cb, counts·g^{-1}·min^{-1} of brain samples; Cr, total cpm in reference blood samples; RBF, arterial withdrawal rate).

Experimental Procedures. *Hypercapnia.* Cerebral blood flow measurements were made 10–15 min after the onset of breathing 5% CO_2 in air.

Hypertension. Cerebral blood flow measurements were made ≈15 min after blood pressure was maintained at ≈200 mmHg by intravenous infusion of angiotensin II (0.8–2.0 μg·kg^{-1}·min^{-1}).

Seizures. A bolus injection of (+)-bicuculline [1 mg·kg^{-1}·ml^{-1} in 0.9% saline/acetone (4:1, vol/vol)] was used to induce generalized seizures. Anesthesia was induced by ketamine (30 mg/kg) and halothane (1–2%) and maintained with urethane (60 mg/kg) in animals paralyzed by gallamine. Electroencephalogram activity was recorded on a Grass model 7D polygraph. Mean arterial blood pressure was maintained below 150 mmHg by controlled hemorrhage.

Blood flow measurements were obtained in the following sequence: hypercapnia, normocapnia–normotension, followed by either severe hypertension or seizures. In some animals, a fourth measurement of blood flow was obtained under resting conditions.

Paired Student's *t* test was used to calculate statistical significance of differences in blood flow among the regions analyzed as well as for differences in blood pressure, P_{CO_2}. Probability values of <0.01 were considered statistically significant.

Materials. Angiotensin II, bicuculline, and urethane were purchased from Sigma; ketamine hydrochloride was obtained from Parke–Davis; sodium pentobarbital was from Anthony Products (Arcadia, CA); halothane was from Halocarbon Products (Hackensack, NJ); gallamine triethiodide was from Lederle Parenterals (Carolina, PR); and microspheres were from New England Nuclear.

RESULTS

Basal Conditions. Mean values for cerebral blood flow ranged from 27 to 58 ml per 100 g per min in 10 brain regions for all three groups of operated animals (Tables 1–4). Regional blood flow was not significantly different between the

Table 1. Blood flow (ml per 100 g per min) in cats following sham trigeminal ganglionectomy (left)

	Basal condition (n = 6)		Hypercapnia (n = 6)		Hypertension (n = 3)		Seizures (n = 3)	
	R	L	R	L	R	L	R	L
Tissue								
Cortical gray matter								
ACA	53 ± 3	52 ± 3	78 ± 10	75 ± 9	142 ± 9	143 ± 9	192 ± 16	186 ± 15
MCA	55 ± 4	54 ± 3	80 ± 10	77 ± 10	147 ± 10	145 ± 10	191 ± 15	189 ± 13
PCA	55 ± 4	53 ± 3	78 ± 8	76 ± 9	147 ± 7	145 ± 6	186 ± 15	186 ± 16
White matter	32 ± 2	34 ± 3	44 ± 4	42 ± 3	38 ± 2	37 ± 2	65 ± 5	66 ± 4
Caudate	59 ± 3	59 ± 4	69 ± 6	70 ± 6	76 ± 5	73 ± 6	181 ± 15	182 ± 15
Thalamus	51 ± 4	53 ± 3	66 ± 7	65 ± 6	78 ± 4	79 ± 4	186 ± 19	184 ± 16
Midbrain	47 ± 4	48 ± 3	56 ± 6	57 ± 4	80 ± 4	80 ± 5	141 ± 13	141 ± 10
Pons	49 ± 4	47 ± 3	55 ± 6	56 ± 7	61 ± 4	61 ± 2	83 ± 7	84 ± 5
Medulla	49 ± 3	47 ± 4	55 ± 7	56 ± 7	72 ± 4	73 ± 5	60 ± 3	62 ± 6
Cerebellum	51 ± 3	52 ± 3	66 ± 6	63 ± 6	102 ± 6	99 ± 5	87 ± 7	86 ± 7
MABP, mmHg	124 ± 2		135 ± 5		197 ± 8		116 ± 5	
Arterial								
P_{CO_2}, mmHg	31 ± 0.7		47 ± 1		29 ± 0.6		33 ± 2	
P_{O_2}, mmHg	116 ± 4		94 ± 7		124 ± 10		123 ± 7	
pH	7.38 ± 0.02		7.24 ± 0.02		7.39 ± 0.02		7.33 ± 0.02	

Values are means ± SEM. MABP, mean arterial blood pressure. R, right side; L, left side.

Table 2. Blood flow (ml per 100 g per min) in cats (n=6) following left trigeminal ganglionectomy

	Basal condition		Hypercapnia		Hypertension	
	R	L	R	L	R	L
Tissue						
Cortical gray matter						
ACA	48 ± 2	47 ± 3	86 ± 6	83 ± 6	145 ± 9	116 ± 7*
MCA	50 ± 3	48 ± 3	88 ± 6	84 ± 6	157 ± 10	122 ± 8*
PCA	48 ± 3	49 ± 2	85 ± 6	84 ± 6	142 ± 9	114 ± 8*
White matter	32 ± 2	32 ± 2	46 ± 3	43 ± 3	37 ± 2	36 ± 2
Caudate	54 ± 4	57 ± 3	72 ± 7	76 ± 4	75 ± 5	72 ± 5
Thalamus	51 ± 4	46 ± 3	66 ± 5	65 ± 3	76 ± 4	80 ± 4
Midbrain	45 ± 4	46 ± 3	56 ± 5	58 ± 3	78 ± 4	75 ± 4
Pons	46 ± 3	47 ± 2	60 ± 4	59 ± 5	60 ± 3	62 ± 3
Medulla	49 ± 3	46 ± 3	57 ± 4	55 ± 4	70 ± 5	68 ± 4
Cerebellum	50 ± 3	47 ± 3	63 ± 4	62 ± 5	98 ± 6	95 ± 5
MABP, mmHg	132 ± 5		144 ± 7		200 ± 3.5	
Arterial						
P_{CO_2}, mmHg	30 ± 0.5		48 ± 1		29 ± 0.6	
P_{O_2}, mmHg	105 ± 7		87 ± 4		112 ± 5	
pH	7.38 ± 0.02		7.24 ± 0.01		7.38 ± 0.02	

Values are means ± SEM. For abbreviations see Table 1.
*$P < 0.01$ as compared to nonlesioned side.

sham-operated and the two lesioned groups or between symmetrical regions within each group. Highest values were measured in caudate and cerebellum and were approximately equivalent in the gray matter territories of the ACA, MCA, and PCA; lowest flow was recorded in all regions of white matter. Since flow in white matter territory supplied by ACA, MCA, and PCA did not differ significantly from one another, only the results from the MCA are shown in Tables 1–4.

Hypercapnia. Arterial partial pressure of carbon dioxide increased from 28–32 to 46–51 mmHg in each of the three groups (Tables 1–3). Symmetrical elevations in flow were present in all brain regions. Highest values were measured in cortical gray matter, caudate, and cerebellum. When expressed as a percentage of flow in the basal condition, the largest increases (51%) were measured in cortical gray area supplied by the anterior cerebral artery.

In ganglionectomized animals, blood flow was greatest in cortical gray matter and responses were symmetrical in each of the animals examined (Table 2).

Among the root lesioned animals, hypercapnia-induced increases were measured in all brain areas and differences between symmetrical brain regions did not reach statistical significance (data not shown).

Acute Severe Hypertension. Angiotensin raised blood pressure from 115–135 to 190–210 mmHg in all three groups of animals. In three ganglionectomized animals, blood pressure was <180 mmHg, and brain blood flow did not increase above basal levels (data neither shown nor included in statistical analysis). When hypertension reached the anticipated range, flow increased significantly in all brain regions (Tables 1, 2, and 4). In sham-operated animals, increases in blood flow were symmetrical. The largest elevations were measured in cortical gray matter; lowest values were measured in white matter (Table 1).

In ganglionectomized animals, increases in flow on the intact side were not statistically different from sham-operated animals (Tables 1 and 2). Symmetrical increases were measured within cortical white matter, caudate nucleus, thala-

Table 3. Blood flow (ml per 100 g per min) in cats (n = 7) following left trigeminal ganglionectomy

	Basal condition		Hypercapnia		Seizures	
	R	L	R	L	R	L
Tissue						
Cortical gray matter						
ACA	52 ± 3	52 ± 3	90 ± 7	89 ± 7	182 ± 11	145 ± 9*
MCA	54 ± 4	53 ± 4	93 ± 8	92 ± 7	186 ± 12	150 ± 9*
PCA	57 ± 4	58 ± 4	91 ± 8	92 ± 9	179 ± 11	143 ± 10*
White matter	33 ± 2	31 ± 2	45 ± 2	42 ± 2	64 ± 3	62 ± 3
Caudate	57 ± 3	55 ± 3	73 ± 5	72 ± 5	166 ± 14	159 ± 13
Thalamus	50 ± 3	53 ± 3	67 ± 5	67 ± 5	149 ± 11	155 ± 12
Midbrain	45 ± 3	48 ± 3	60 ± 4	57 ± 5	124 ± 9	131 ± 10
Pons	46 ± 3	44 ± 3	54 ± 4	52 ± 4	74 ± 5	70 ± 5
Medulla	43 ± 2	44 ± 3	54 ± 6	54 ± 5	52 ± 3	54 ± 4
Cerebellum	52 ± 3	51 ± 4	68 ± 5	66 ± 5	83 ± 5	80 ± 4
MABP, mmHg	122 ± 3		138 ± 4		126 ± 7	
Arterial						
P_{CO_2}, mmHg	30 ± 1		47 ± 1		32 ± 0.8	
P_{O_2}, mmHg	121 ± 8		98 ± 5		127 ± 5	
pH	7.33 ± 0.08		7.25 ± 0.07		7.38 ± 0.01	

Values are means ± SEM. For abbreviations see Table 1.
*$P < 0.01$ as compared to nonlesioned side.

Table 4. Blood flow (ml per 100 g per min) in cats following left trigeminal rhizotomy

	Basal condition (n = 8)		Hypertension (n = 6)		Seizures (n = 5)	
	R	L	R	L	R	L
Tissue						
Cortical gray matter						
ACA	52 ± 5	52 ± 5	146 ± 14	150 ± 12	180 ± 12	176 ± 14
MCA	54 ± 5	57 ± 6	150 ± 16	156 ± 15	184 ± 19	186 ± 14
PCA	54 ± 5	51 ± 6	150 ± 10	152 ± 11	169 ± 17	168 ± 22
White matter	27 ± 2	27 ± 2	44 ± 6	42 ± 6	59 ± 7	59 ± 6
Caudate	56 ± 4	48 ± 5	95 ± 10	99 ± 10	140 ± 18	136 ± 23
Thalamus	48 ± 4	45 ± 4	102 ± 14	96 ± 4	145 ± 18	148 ± 20
Midbrain	44 ± 5	43 ± 5	83 ± 13	83 ± 9	128 ± 18	127 ± 18
Pons	34 ± 4	33 ± 3	59 ± 6	59 ± 6	82 ± 10	85 ± 7
Medulla	30 ± 5	30 ± 5	48 ± 6	52 ± 9	59 ± 9	66 ± 9
Cerebellum	40 ± 4	38 ± 4	77 ± 11	81 ± 13	88 ± 10	87 ± 7
MABP, mmHg	117 ± 2		201 ± 2		127 ± 5	
Arterial						
Pco_2, mmHg	32 ± 1		32 ± 1		33 ± 1	
Po_2, mmHg	111 ± 7		125 ± 9		118 ± 4	
pH	7.33 ± 0.04		7.38 ± 0.02		7.36 ± 0.06	

Values are means ± SEM. For abbreviations see Table 1.

mus, midbrain, pons, medulla, and cerebellum (Table 2). The flow was not statistically different from flow in those same regions in the sham-operated group. Within cortical gray matter on the denervated side, flow was significantly lower ($P < 0.01$) within the territories of the ACA (29% ± 5%), MCA (31% ± 5%), and PCA (28% ± 4%). Each of the six operated animals exhibited reduced values on the operated side, with the greatest individual decrease (45%) measured within the PCA territory. Despite these attenuations, blood flow was still significantly increased above those values obtained during basal conditions. Ten to 15 min after blood pressure returned to normal levels, flow was symmetrical and equivalent to basal values in all brain regions (data not shown). Results were not different statistically between animals sacrificed 8 or 25 days after trigeminal ganglionectomy.

In the rhizotomy group, hypertension-induced increases in blood flow were symmetrical in each animal and were similar in magnitude to the sham-operated group and to the innervated side in the ganglionectomized group (Table 4).

Seizures. Seizures raised blood flow symmetrically within all brain regions of sham-operated animals (Table 1). Greatest increases were measured in cortical gray matter; lowest increments were measured in white matter. Within midbrain and all regions of forebrain, increases in flow exceeded those measured in hypertensive animals.

In ganglionectomized animals, flow on the intact side was similar to flow in sham-operated animals (Table 3). Blood flow differences of <5% were measured within symmetrical regions of caudate, thalamus, midbrain, pons, medulla, and cerebellum. However, within cortical gray matter, increases in blood flow were attenuated on the deafferented side. Within the anterior cerebral artery territory, increases were 72% of the contralateral side. Within the middle and posterior cerebral artery regions, increases were 74% and 70% of the intact side, respectively.

Blood flow data from the root lesioned animals demonstrated symmetrical increases within all examined brain regions. The magnitude of these increases was similar to those of the ganglionectomized group (Table 4).

DISCUSSION

The present studies were undertaken to investigate the relationship between the trigeminovascular system and cerebral blood flow. In this report, we demonstrate that ipsilateral increases in cortical gray matter blood flow induced by hypertension or seizures are attenuated 20–30% following trigeminalectomy but not rhizotomy. Attenuated flow was found within the gray matter regions supplied by the three major forebrain arteries innervated by the trigeminal nerve. This was true despite the fact that flow within the ACA and MCA derives from the carotid circulation, whereas flow within the PCA derives mostly from the vertebrobasilar circulation (29). Furthermore, attenuation of flow was observed only within regions adjacent to pial arteries receiving innervation from the trigeminal nerve. Deep gray matter nuclei (thalamus, caudate) supplied by the PCA and MCA possess a minimal trigeminal innervation and did not manifest significant differences in blood flow between the two sides. Furthermore, the symmetrical flow responses in sham-operated animals suggest that the observed differences were not secondary to brain or blood vessel injury. Taken together our findings indicate that regional cerebral blood flow asymmetries following trigeminalectomy are specific to the trigeminal pattern of vascular innervation.

Based on the observed differences following trigeminalectomy or rhizotomy, we also conclude that vasodilation is locally mediated by peripheral axon reflex-like mechanisms and is not dependent on central neurotransmission. To our knowledge, axonal reflex-like control of cerebral blood flow has not been reported previously. We presume that increases in blood flow are mediated by vasoactive neuropeptides, released from peripheral sensory axons, as demonstrated in other organs and noted in the Introduction. Indeed, substance P release from perivascular axons innervating the circle of Willis was reported following the addition of potassium or capsaicin by calcium-dependent mechanisms (24). The concept of increased flow induced by peripheral sensory axons has been known since 1874 (30) and provides the basis for the so-called axon reflex (31). The possibility that increases in flow are mediated by antidromic mechanisms must be considered as well, because trigeminovascular fibers exhibit extensive axonal branching (10). In fact, a single ganglion cell may send axonal projections to innervate more than one major vessel within the great circle. Based on the above, it would be important to determine the extent to which local axonal control of blood flow is shared by other neural

systems innervating the cerebrovasculature (e.g., sympathetic, parasympathetic, and intrinsic sources).

Of relevance, the trigeminal nerve increases blood flow within the external carotid circulation as well (32). Increased flow during electrical trigeminal stimulation was dependent on intact brainstem connections to the greater superficial petrosal nerve (32). Hence, the trigeminal nerve can modify cephalic blood flow by at least two mechanisms.

The stimulus for trigeminal nerve activation remains to be elucidated during severe hypertension and seizures. Unmyelinated C fibers are depolarized by bradykinin (33) or potassium, and their threshold can be modulated by prostaglandins (34), serotonin (35), and histamine (35). Bradykinin, a known pain mediator, is synthesized by the blood vessel wall during severe hypertension induced by experimental brain injury (36) as are oxygen-derived free radicals (37), a well-known mediator of tissue injury (38). Severe hypertension causes disruption of vascular endothelium in cerebral vessels and increases vascular permeability (39). Because the majority of perivascular afferents are C fibers, and because C fibers become depolarized by tissue injury, a mediator role for bradykinin and oxygen radicals in the trigeminal response merits further study. During seizures, high levels of extracellular potassium (40) may provide the coupling mechanism by which trigeminovascular fibers become activated (24). Of related interest, the occurrence of headaches during severe hypertension or seizures also implies activation of the trigeminovascular system (41) and may develop as the result of mechanisms described above.

Our data indicate that flow-related increases in acute severe hypertension are not totally passive to the perfusion pressure but are partially neurogenically mediated. Trigeminal activation could contribute to the pathophysiological consequences associated with severe hypertension, such as the development of hemorrhage and edema. Indeed, hypertension-induced leakage of iodinated albumin was greater in brain regions possessing an intact trigeminovascular system (42). Hence, strategies to block activation of these nerves should be considered as a potential therapeutic intervention to limit blood flow and vascular permeability. Conversely, activation of this nerve might promote the passage of molecules from the circulation to brain in tissues lacking a blood–brain barrier or when the blood–brain barrier is disrupted.

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