Paradoxic Relations between Basilar Artery Reconfiguration and Superior Cervical Ganglia Ischemia After Bilateral Common Carotid Artery Ligation

Mustafa Kilic[1], Betul Kilic[2], Mehmet Dumlu Aydin[3], Ayhan Kanat[4], Ilhan Yilmaz[1], Metehan Eseoglu[5], Betul Gundogdu[6]

BACKGROUND: **The relationship between superior cervical ganglia (SCG) ischemia due to bilateral common carotid artery ligation (BCCAL) and basilar artery (BA) reconfiguration was investigated.**

METHODS: **Twenty-three rabbits were randomly divided into 3 groups: group III rabbits underwent BCCAL (n = 13), group II rabbits were sham-operated controls (n = 5), and group I rabbits did not undergo surgery (n = 5). Degenerated neuron densities (DND) within the SCG were correlated with the BA vasodilatation index (VDI).**

RESULTS: **Mean live and DND in SCG of group I rabbits were 11.235 ± 982/μm^3 and 11 ± 3/μm^3, respectively, with a mean heart rate of 294 ± 21 beats/min. Mean SCG DND and heart rates were 213 ± 42/μm^3 and 242 ± 17 beats/min for the sham group (group II) rabbits and 1743 ± 285/μm^3 and 199 ± 19 beats/min for the study group (group III) rabbits, respectively. The BA VDI values in the sham group (group II) (1.32 ± 0.10) and the study group (group III) (0.976 ± 0.112) significantly differed from those in the control group (group I) (1.65 ± 0.12; $P < 0.005$) versus the sham group (group II) ($P < 0.0001$) versus the BCCAL applied group (group III) and between group II and group III ($P < 0.005$).**

CONCLUSIONS: **A meaningful and paradoxic correlation was detected between the BA VDI values and degenerated neuron density of SCG after BCCAL. Although a low degenerated neuron density within SCG may provoke excessive sympathetic activity and prevent excessive BA dilatation with steno-occlusive carotid artery diseases, a high degenerated neuron density may cause dangerous vasodilatation of BA.**

INTRODUCTION

Cerebral arteries are innervated by several systems contributing to the autonomic control of cerebral blood flow[1,2] and brain vessel diameter. Parasympathetic fibers have vasodilatory effects, and sympathetic fibers are vasospastic on cerebral arteries.[2,3] Vasospastic sympathetic innervation of cerebral vessels originates from the postganglionic fibers of the superior sympathetic ganglion rise with its biggest efferent branch and the carotid nerve that assists the carotid plexus.[4] In the pathogenesis of vasospasms, the sympathetic nervous system plays a critical role,[5] because sympathetic innervation promotes cerebral vasoconstriction in response to sharp increases in arterial pressure.[6] In addition, the sympathetic system has trophic effects on cerebral vascular smooth muscle cells.[7] Bilateral common carotid artery ligation (BCCAL) increases blood pressure, generates retrograde blood flow, causes ischemic degenerative variations in target tissues, and leads to significant histomorphologic and hemodynamic variations in the carotid-vertebrobasilar vasculature.[8] Within 2 to 4 months after BCCAL, aneurysm, neovascularization, and vital collateral circulation can form.[9-11] BCCA occlusion causes carotid artery system loss and cervical sympathetic trunk ischemia. Ischemic degeneration of the superior cervical ganglia (SCG) inhibits the sympathetic nervous system, which decreases the heart rate, causing bradycardia and rhythm disorders.[9,12,13] Additionally, SCG ischemia may cause sympathetic hypoactivitiy in the cerebral

Key words
- Basilar artery vasodilatation
- Common carotid artery ligation
- Degenerated neuron density
- Superior cervical ganglion

Abbreviations and Acronyms
BA: Basilar artery
BCCA: Bilateral common carotid artery
BCCAL: Bilateral common carotid artery ligation
DND: Degenerated neuron densities
SCG: Superior cervical ganglia
VDI: Basilar artery vasodilatation index

From the [1]Department of Neurosurgery, Sisli Hamidiye Etfal Education and Research Hospital, Istanbul; [2]Department of Pediatric Neurology, Kocaeli Derince Education and Research Hospital, Kocaeli; [3]Department of Neurosurgery, Medical Faculty of Ataturk University, Erzurum; [4]Department of Neurosurgery, Medical Faculty of Recep Tayyip Erdogan University, Rize; [5]Department of Neurosurgery, Medipol Hospital, Istanbul; [6]Department of Pathology, Medical Faculty of Ataturk University, Erzurum, Turkey

To whom correspondence should be addressed: Mehmet Dumlu Aydin, M.D. [E-mail: nmda11@hotmail.com]

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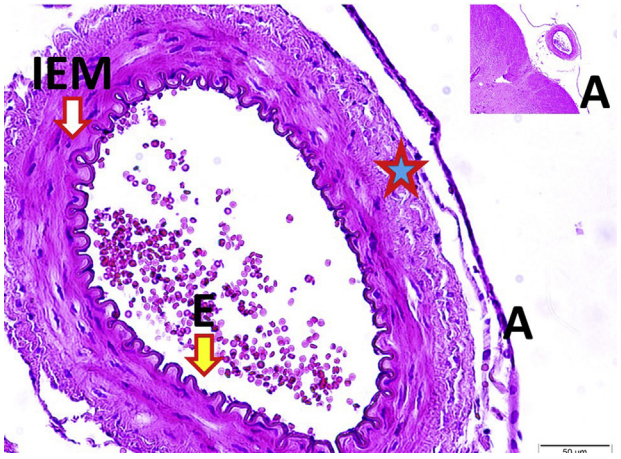

Figure 1. Histologic appearances of basilar artery in sulcus basilaris in pons (light microscopy [LM], hematoxylin and eosin, 4/*A*) and magnified form with arachnoid membrane (*A*), adventitia (*star*), smooth muscles in wall, inner elastic membrane (*IEM*) and endothelium (*E*) in a normal rabbit (LM, hematoxylin and eosin, ×10/Base).

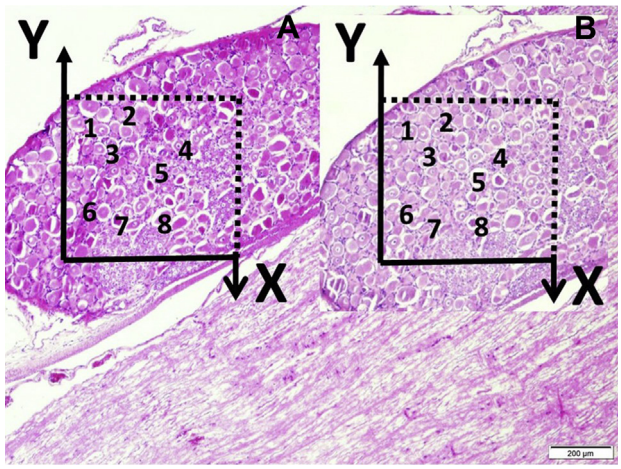

Figure 2. Stereologic cell counting of the superior cervical ganglia in a rabbit. Application of the physical dissector method in which micrographs in the same fields of view (**A**, **B**) were taken from 2 parallel, adjacent thin sections separated by a distance of 5 mm. The upper and right lines in the unbiased counting frames represent the inclusion lines, and the lower and left lines, including the extensions, are exclusion lines. The neuronal nucleoli touching the inclusion lines were excluded, and the nucleoli profiles touching the inclusion lines and located inside the frame were counted as dissector particles unless the profile extended up to the reference section. The number of neurons from the 2 dissectors occurs in a volume given by the product of the counting frame area and the distance between the sections. The numeric density of the neurons was calculated as $NvGN = \Sigma Q - GN/txA$. In this application, (**A**) the nucleoli marked with 2–4, 7, 8 are dissector particles; (**B**) shows them as they disappeared. (**A**) The nucleoli marked with 1, 5, 6 are not dissector particles; (**B**) shows 1, 5, 6 as they disappeared. (light microscopy, hematoxylin and eosin, ×10).

vasculature.[14] Morphometric examination of the basilar arteries (BAs) clearly reveals the critical role of sympathetic nerve innervation in determining BA characteristics after BCCAL.[15] In this study, we investigated whether there is a relationship between SCG ischemia due to BCCAL, heart rate variations after permanent BCCAL, and volumetric changes in BAs.

MATERIALS AND METHODS

Animal Models

Twenty-three adult male albino New Zealand rabbits (mean weight, 3.7 ± 0.4 kg) were used. The animal protocols used were certified by the Atatürk University Medical Faculty Ethics Committee (Erzurum, Turkey), and all guidelines regarding animal care and experiments were followed. The rabbits were randomly divided into 3 groups: group I rabbits did not undergo surgery (control, n = 5), group II rabbits were sham operated (n = 5), and group III rabbits underwent BCCAL (n = 13). The rabbits were initially anesthetized with isoflurane gas applied by face mask, followed by subcutaneous injection of an anesthetic combination (0.2 mL/kg total) containing 30 mg/1.5 mL xylazine, 150 mg/1.5 mL ketamine, and 1 mL distilled water. Prescribed booster doses (0.1 mL/kg) of the anesthetic combination were also injected during the operation. The animals were secured to the operating table in the supine position before a 3-cm midcervical medial incision was made and a common carotid artery sympathetic chain was placed on both sides as described by Yilmaz et al.[14] The common carotid arteries were dissected, and BCCAL was applied to 13 animals in the study group (group III) but not to those in the sham operated group (group II). The animals were followed up for 1 month, and electrocardiographic data were recorded.

Stereologic and Histopathologic Analyses

One month after surgery, all rabbits were killed. The SCGs were bilaterally removed and fixed in 10% formalin for 1 week. They were then sectioned on both sides and horizontally implanted in paraffin bars for histologic examination. The number of SCG neurons was evaluated by the physical dissector method as previously used by some authors.[13,16] Two sections in sequence (dissector pairs) were collected from the reference tissue specimens and set on every slide to estimate the SCG neuron numbers. The sequence of paired references was changed to increase the number of dissector pairs; in this way there was no need to cut new pairs. The mean density of normal (healthy) neurons was calculated according to this formula: $Nv/Gv = \Sigma Q^{-}/\Sigma A \times d$ in SCG (Nv/Gv) per mm^3, where $Q^{-}N$ is the total number of counted neurons in reference sections only, A is the area of the counting frame, and d is the SCG section thickness. To set the dissectors, ΣA was estimated by the formula $\Sigma A = \Sigma Pa$, where a stands for a steady area linked to the set points, and ΣPa is the total of the counting frame set points. Counting frame areas are shown in Figure 1, and the examples were carefully evaluated. In this figure, "A" and "B" refer to continuous sections and were cut 5 mm off; "A" contained a neuronal nucleus, whereas "B" did not. To obtain the total number of neurons in each sample, the Cavalieri volume estimation method was applied, wherein the neuron density was

Table 1. Neuron Density per Cubic Millimeter in Superior Cervical Ganglia and Vasodilatation Index of Basilar Artery

Group	Heart Rate (beats/minute)	Neuron Density in Superior Cervical Ganglia (/μm^3)	Vasodilatation İndex of Basilar Artery (mm^3)
Control group I (n = 5)	294 ± 21	11.235 ± 982	1.65 ± 0.12
Sham group: group II (n = 5)	242 ± 17	213 ± 42	1.32 ± 0.10
Study group: group III (n = 13)	199 ± 19	1743 ± 285	0.976 ± 0.112

P values between control group (group I) and sham group (group II), control group (group I) and study group (group III) were $P < 0.005$ and $P < 0.0001$; respectively. $P < 0.005$ was between control group (group I) sham group (group II); $P < 0.005$ was between sham group (group II) and study group (group III).

multiplied by the volume in every SCG (πm^3). The number of both normal and degenerated neurons in SCG was calculated for each animal. Then, the degenerated neuron densities within the SCG were correlated with the BA vasodilation index (VDI).

Statistical Analysis

The data are presented as mean ± standard deviation unless specified otherwise. The differences in the neuron density and heart rates in SCG were analyzed with SPSS for Windows v.12.0 (SPSS Inc., Chicago, Illinois, USA). The Kruskal-Wallis test and the Mann-Whitney U test were applied to determine statistical differences; differences were considered significant at $P < 0.05$.

RESULTS

Within 1 week after surgery, 2 BCCAL-applied rabbits in group III died. Prior to death, breathing disturbances, loss of consciousness, ischemic attacks, convulsions, and cardiac arrhythmia were observed. The BCCAL-applied (group III) rabbits that survived the 1-month observation period (n = 11) were included in the stereologic and histopathologic analysis.

Histomorphology

In the unbiased counting frames, the inclusion lines are on the upper right and the exclusion lines with extensions are on the lower left. The excluded ones defined the neuronal nucleoli touching the inclusion lines. Nucleoli profiles located inside the counting frame and touching inclusion lines were counted as dissector particles if the profile did not extend up to the associating section. Neurons from the 2 dissectors occur in a volume given by the distance between the sections and product of the counting frame area. The formula $NvGN = \Sigma Q - GN/txA$ gave the numeric density of the neurons. Dissector particles in section A are the nucleoli marked 2–4, 7, and 8 in the application; they disappeared in section B. Nucleoli 1, 5, and 6 are not dissector particles in section A and also disappeared in section B.

Stereology and Histopathology

Figure 2 shows the histopathologic appearance of the basilar artery in pons. The mean heart rate of rabbits in the control group

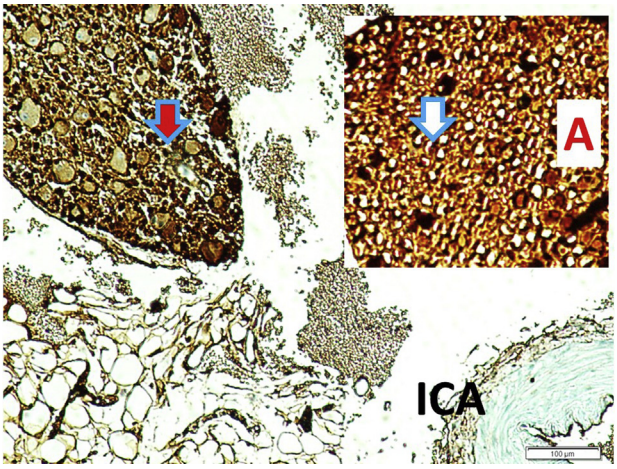

Figure 3. Histopathologic appearance of superior cervical ganglia with apoptotic neurons (*red arrow*) near the internal carotid artery (*ICA*) (light microscopy [LM], terminal deoxynucleotide transferase-mediated deoxy uridine triphosphate nick-end labeling, ×10/Base) and sympathetic nerves with axonolytic fibers of a rabbit that underwent bilateral common carotid artery ligation (*white arrow*). (LM, S-100, ×10/*A*).

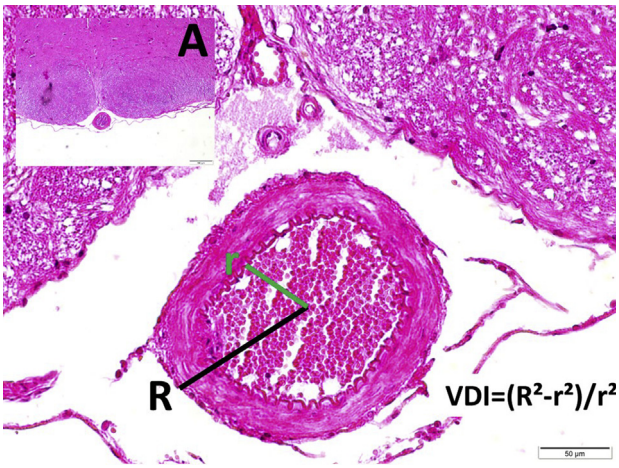

Figure 4. Histopathologic appearance of basilar artery in sulcus basilaris in pons (light microscopy [LM], hematoxylin and eosin, ×4/*A*) and magnified form with vascular index calculation method in a sham-operated rabbit. (LM, hematoxylin and eosin, ×10/Base).

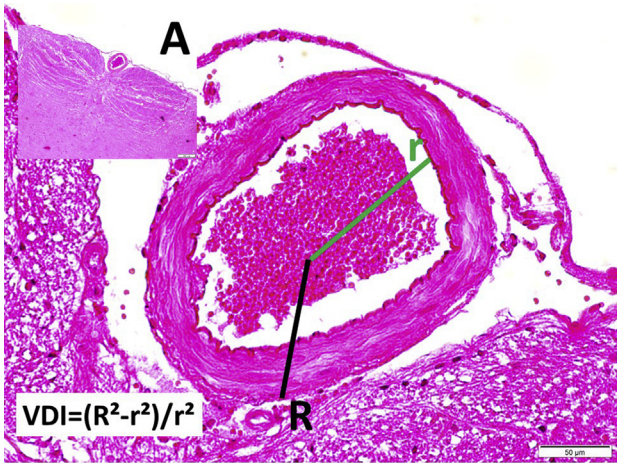

Figure 5. Histopathologic appearance of basilar artery in sulcus basilaris in pons (light microscopy [LM], hematoxylin and eosin, ×4/*A*) and magnified form with thickened arachnoid membrane/adventitia, hyperthyrophied smooth muscles in wall, flattened inner elastic membrane (*IEM*) and endothelium (*E*) in a rabbit that underwent bilateral common carotid artery ligation with less neurodegeneration detected. (LM, hematoxylin and eosin, ×10/Base).

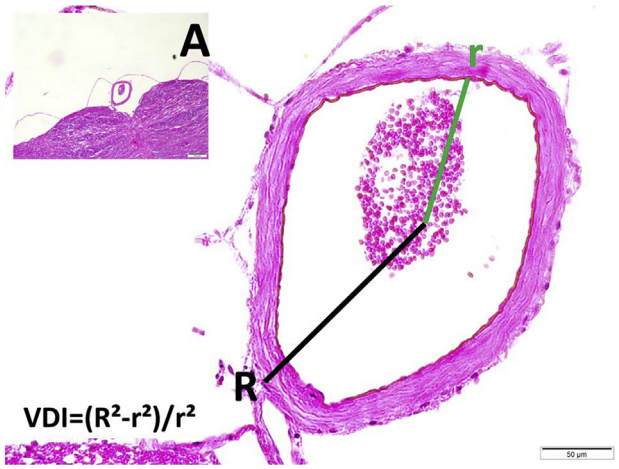

Figure 6. Histopathologic appearance of basilar artery in sulcus basilaris in pons (light microscopy [LM], hematoxylin and eosin, ×4/*A*) and magnified form with thickened arachnoid membrane/adventitia, thinned smooth muscles in thinned wall, significant flattened inner elastic membrane (*IEM*) and endothelium (*E*) with more degenerated neurons in superior cervical ganglia of a study group (LM, hematoxylin and eosin, ×10/Base).

(group I) was 294 ± 21 beats/min, and the mean normal and degenerated neuron densities in the SCG were 11.235 ± 982/mm³ and 11 ± 3/mm³, respectively. The BA VDI value in the control group (group I) rabbits was 1.65 ± 0.12 ($P > 0.5$). The degenerated neuron densities in the SCG and the heart rates were 213 ± 42/mm³ and 242 ± 17 beats/min in rabbits of the sham group (group II) and 1743 ± 285/mm³ and 199 ± 19 beats/min in rabbits with BCCAL (group III), respectively. The BA VDI values in the sham group (group II) (1.32 ± 0.10) and the rabbits with BCCAL (group III) (0.976 ± 0.112) were significantly different from those of rabbits in the control group (group I) versus the sham group (group II) ($P < 0.005$; group I vs. group III, $P < 0.0001$). The BA VDI value was also significantly different between group II and group III rabbits ($P < 0.005$). These results indicated a meaningful and paradoxic relationship between the BA VDI values and the SCG degenerated neuron density. **Table 1** shows the neuron density per square millimeter in the superior cervical ganglia and the VI of the basilar artery. Our findings are seen in **Figures 3–7**.

DISCUSSION

Interpretation and Scientific Implications

BCCAL produces primary redistribution of blood to the brain, with retrograde and increased blood flow in the basilar and vertebral arteries. Important histopathologic and morphologic vertebral, posterior cerebral, posterior communicating, and neck vessel and artery changes occur within 4 months after BCCAL in BA. Intracranial vascular variations mostly regress to their earlier state after 4 months. However, the mechanism(s) that clarify trophic vessel variations in response to changed blood flow remain a topic of discussion. The present results may have some possible correlations with aneurysmal remodeling. Hemodynamic trauma by BCCAL has been demonstrated to activate aneurysmal remodeling when the local hemodynamic forces pass specific ranges at the rabbit basilar terminus.[15] In addition, dangerous hemodynamics probably induce aneurysmal remodeling with missing internal elastic lamina and thinned media aside from the basilar terminus.[15] In the central nervous system, the neuron density of the peripheral nerve ganglions plays a regulatory role for proper nerve function.[3,17] Although tough cerebrovascular innervation pathways are sufficiently critical, the effect of microneuroanatomic architectures of SCG on BA remodeling after BCCAL has not been examined until now. To regulate BA volume, the number of neurons in the SCG likely plays a critical role. In the SCG neurons, vasospastic agents are combined and hindered from nerve endings innervating BAs. According to a previous study, BA vasospasm was highly acute in rabbits with a high neuron density in the cervical sympathetic ganglia.[14] High neuron density of the stellate ganglion can be considered sympathetic overactivity that causes basilar vasospasm and neovascularization,[2] whereas low neuron density of the stellate ganglion can be considered sympathetic hypoactivity that prevents basilar vasospasm and causes vascular wall thinning after bilateral common carotid artery ligation.[14] Interestingly, sympathectomy of the SCG protects the animals against the development of cerebral[18] and BA vasospasm in subarachnoid hemorrhage.[16,19] The proper functioning of the SCG neurons relies on an abundant and continuous supply of oxygen. Continuous oxygen delivery and CO_2 clearance are paramount in the maintenance of normal brain[20] and spinal cord function[21] and, as in this study, ganglion integrity The balance between cell proliferation and cell death is crucial in all tissues, particularly in the nervous system.[22,23] After the SCG was ablated, nerve degeneration began about 28 hours later in the arterial walls. In addition, marked degenerative

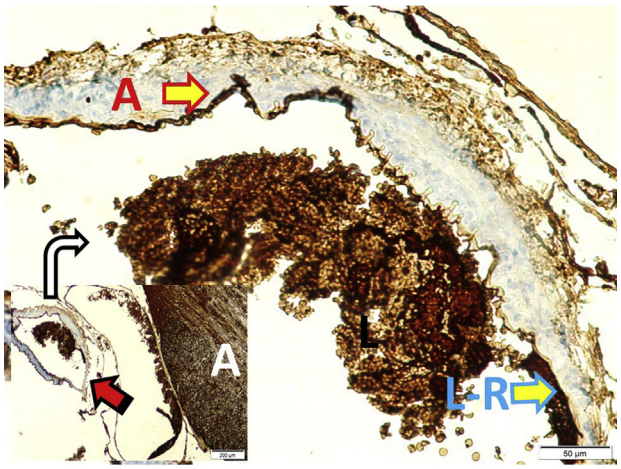

Figure 7. Histopathologic appearance of ruptured inner elastic membrane (*red arrow*) basilar artery in sulcus basilaris in pons (light microscopy [LM], terminal deoxynucleotide transferase-mediated deoxy uridine triphosphate nick-end labeling, ×4/*A*) and magnified form with thickened arachnoid membrane/adventitia, thinned smooth muscles in thinned wall, significant flattened inner elastic membrane (*IEM*), apoptotic endothelium (*yellow arrow*) (*A*), desquamated or losing endothel (*yellow arrow*) (L-R) and ruptured endothel (*R*) is seen (LM, terminal deoxynucleotide transferase-mediated deoxy uridine triphosphate nick-end labeling, ×10/Base).

substances were observed after 40 to 48 hours, and the small cored vesicles of the adrenergic axons died 4 days later. After 3 months, the same action was observed; however, the small cored vesicles were visible again after 6 months. As a result, an important vasodilatation in the BA within 1 month may be seen.[24]

It is critical to pay close attention to the neuronal numbers and densities calculated in each SCG along with the BA volume changes due to BCCAL. Whereas former methods have been partial, the stereologic methods used in the present study provided a more complete evaluation of BA volume and neuron density and numbers in the SCG. Stereology is a useful mathematic system for 3-dimensional determinations, easily defining quantitative aspects like number, size, shape, orientation, and the structure of 2-dimensional measurements.[25] Here, BA volume was the determination chosen to evaluate the severity of BA dilatation after BCCAL, rather than the range of the lumen. By assuming the arteries were cylindrical, BA volume was estimated according to assumptions about the degree of spasm. This method was also unaffected by over-error of estimation of SCG neuron numbers for ganglion or truncation. Hence, the method used to estimate BA volume is as important as that used to estimate the number and density of neurons in each SCG. In rabbits with a high neuron density, the mean BA volume was small, whereas extensive BA dilatation was found in rabbits with a lower neuron density in the SCG. This suggests that more SCG neurons indicate increased synthesis of vasospastic molecules, which hinder nerve terminals concluding at the BAs and constructing them. In spastic cerebral arteries, microvascular aggregation of red blood cells can cause ischemic damage in the brain. In this phase, cerebrovascular hypertension and increased cerebrovascular resistance result in worsened ischemia.[26] Hence, a high neuron density in the SCG may be hazardous for the brain because of its blood flow-reducing effects. Therefore, these entities should be considered potentially hazardous for diseases requiring retrograde blood flow to enhance blood flow to the anterior circulation, such as steno-occlusive carotid artery disease.[16] By contrast, sympathetic nerves interfere with cytoskeletal protein remodeling by phenotypic modulation of vascular pathologic states, such as atherosclerosis. In addition, the sympathetic nervous system may have a beneficial regulatory influence on the histochemical and morphologic changes stemming from atherosclerosis. In a previous study, such results suggested that sympathetic innervation assists in covering vascular tissue from induction of various factors, migration, and stimulation of undifferentiated growth in the vascular wall, which may lead to the changes happening in atherosclerosis.[27]

The neuron density in the cervical sympathetic trunk may play a critical role in the maintenance of cerebral/coronary circulation and in regulating the heart rate within normal limits. A low neuron density of the SCG may cause dangerous heart rhythm complications in steno-occlusive carotid artery disease. Although a low neuron density in the SCG may have a beneficial effect in severely matured steno-occlusive carotid artery disease, it may also be a risk factor because of the declined sympathetic effects that depend on the greater cardiac energy demand of chronic steno-occlusive carotid disorder.

Importance of the Present Report for Neurosurgical Practice

The discipline of cerebrovascular surgery is a young and dynamic field.[28,29] Although cerebrovascular innervation pathways are clearly important, the effect of the microneuroanatomic architectures of the SCG has not been examined on BA remodeling after BCCAL until now. The results of the present study show that a lower SCG neuron number may lead to BA dilatation and a low level of vasodilating factor synthesis after BCCAL. A meaningful and paradoxic correlation was detected between the BA VDI values and the degenerated neuron density of the SCG after BCCAL.Thus, the SCG neuron number also plays a critical role in regulating BA volume. Although a low degenerated neuron density within the SCG may provoke excessive sympathetic activity and prevent excessive BA dilatation with steno-occlusive carotid artery diseases, a high degenerated neuron density may cause dangerous vasodilatation of the BA. The low neuron density in the SCG may be a predisposing factor for basilar dolichoectasia and aneurysm development. Additionally, a high neuron density in the SCG has been shown to have a beneficial effect in preventing dangerous histologic and morphologic changes in the BAs after BCCAL.

Limitations

A limitation of the present study is that we could not demonstrate the degree of neuron damage and its relationship between the loss of protective effect and the level of dangerous enlargement. Why did we use the BCCAL model? There can be concern about the applicability of this model. In this study, dissection of the common carotid arteries in the sham group (group II) itself led to slight to moderate changes in the diameter of the basilar artery, decreased heart rate, and increased neuron density of superior cervical ganglia. Those changes were prominent in BCCAL

animals. The *P* values between the control group (group I) and the sham group (group II) and between the control group (group I) and the study group (group III) were <0.005 and <0.0001, respectively. Sham operation can sometimes be harmful,[30] as in the present study. We observed that only dissection without ligation led to some fibrotic changes in the common carotid arteries in the sham group (group II).

CONCLUSION

BCCAL can cause dangerous histomorphologic changes in the SCG. Ischemic neurodegeneration of the SCG may have beneficial effects by decreasing the amount of sympathetic products therein, which enables greater blood flow to the brain through a more dilatated BA. However, low degenerated neuron density in the SCG may provoke excessive sympathetic activity and prevent excessive BA dilatation during steno-occlusive carotid artery diseases. Whereas a low degenerated neuron density in the SCG may protect against dangerous BA vasodilatation, a high degenerated neuron density relies on dangerous BA vasodilatation after BCCAL. The functional relationship between the heart and the nervous system is an ancient topic.[31] The present study shows that degenerated neurons in the SCG play a critical role in regulating BA reconfiguration, in the preservation of circulation, and in a normal spectrum and heart rate. In steno-occlusive carotid artery disease and acute bradycardia, low neuron density in SCG should be considered a hazardous factor. In addition, neuron degeneration in the SCG may result in dangerous BA vasodilatation. Additional studies are needed.

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