Craniofacial Parasympathetic Ganglia

Part two:

This literature review is designed to assist in the understanding of the autonomic nervous system; for example, for new attention to the etiology, process and management of Craniofacial Neuralgia, Migraine Headaches, Chronic cerebrovascular insufficiency (CCSVI), Tourette syndrome, other movement disorders, Adie syndrome, and possibly more. We have reviewed literature for the basic anatomy of the autonomic nervous system including parasympathetic ganglia in craniofacial variations and contributions. Anatomical variability within the autonomic nervous system has long been accepted. Anatomical variability of surrounding bone and vascular tissue is not included in our study. We were able to search and demonstrate some important research results to promote knowledge and competence in the understanding of the craniofacial autonomic nervous system. Special attention is given to molecular biology research, in order to be able to find the answer to meticulous neurological process that directly relate to the autonomic nervous system.

Three parasympathetic ganglia are located in hardly accessible areas of the head – inside the orbit, infratemporal fossa, and in the pterygopalatine fossa. There is still a long way to go to completely understand the physiology of each and every parasympathetic ganglia, their micro-physiology, biological processes, and neuronal bundle groups within the system.

Having broad knowledge of anatomy is essential for practicing neurology. Certain anatomical structures call for detailed studies due to their anatomical and functional importance. Nevertheless, some structures are difficult to visualize and identify due to their small volume and complicated access. Such is the case of the parasympathetic ganglia located in the craniofacial part of the autonomic nervous system, which include: the ciliary ganglion (located deeply in the orbit, laterally to the optic nerve), the pterygopalatine ganglion (located in the pterygopalatine fossa), the submandibular ganglion (located laterally to the hypoglossus muscle, below the lingual nerve), and the otic ganglion (located medially to the mandibular nerve, right beneath the oval foramen). [1]

A ganglion is a mass of nervous tissues found in some peripheral nerves. Ganglia are located on the roots of spinal nerves and on the sensitive roots of the trigeminal, facial, glossopharyngeal, Vagus, and vestibulocochlear nerves. Ganglia also appear in association with the autonomic nervous system. Each ganglion is covered by a smooth and dense capsule of fibrous connective tissue, with cells similar to associated flattened fibrocytes, which extends to the nerves' perineurium, sending numerous extensions to the ganglion's interior. Ganglia vary considerably in size, shape and location. [2]

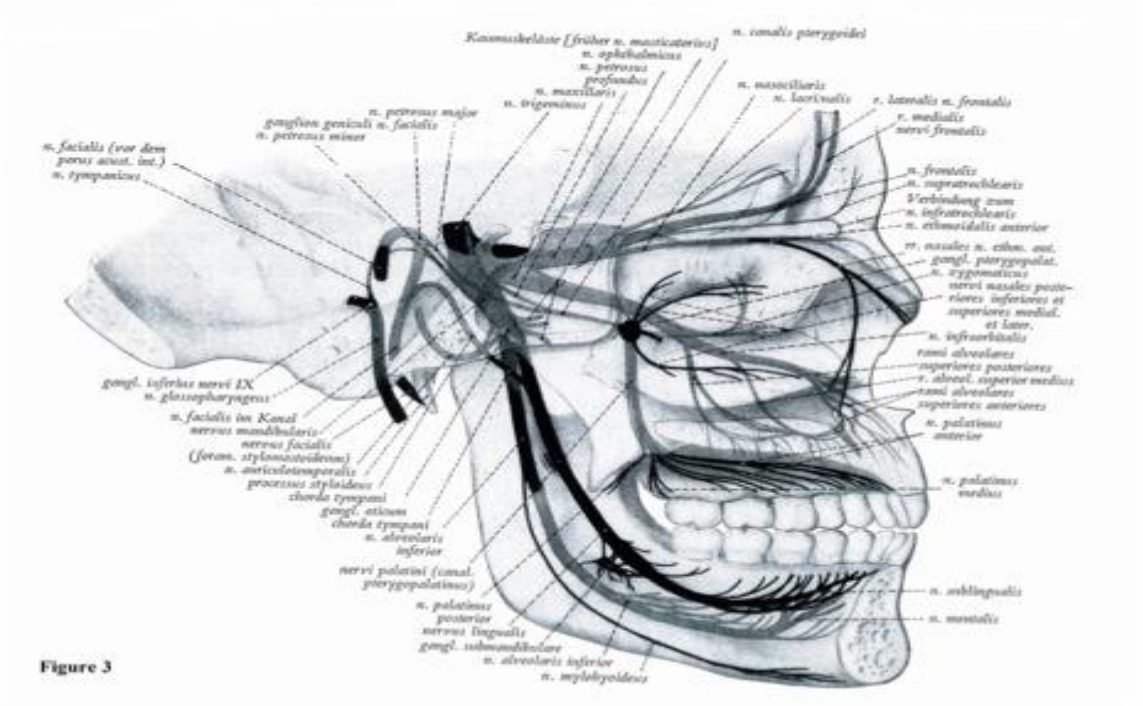


Figure 1: Trigeminal Nerve Division & Relationship to the Parasympathetic Ganglia

I - CILIARY GANGLION:

The ciliary ganglion is a parasympathetic ganglion located in the posterior orbit. It measures 2-3 mm in diameter and contains approximately 2,500 (range 1000 - 6800) neurons. It lies in fat-filled connective tissue in the posterior orbit, just anterior to the superior orbital fissure *(kuntz, 1954).* A small accessory ciliary ganglion sits in the long ciliary nerve arising from the ophthalmic nerve *(Grimes and von Sallman, 1960*). [3] Preganglionic axons from the Edinger-Westphal nucleus travel along the oculomotor nerve and form synapses with these cells. Some preganglionic fibers probably also reach the ciliary ganglion via the long ciliary branch of the trigeminal nerve. *(Zhang et all,1994).* The postganglionic axons run in the short ciliary nerves and innervate two eye muscles: [3]

- The sphincter pupillae constricts the pupil, a movement known as Miosis. The opposite, Mydriasis, is the dilation of the pupil.
- The ciliary muscle contracts, releasing tension on the Zonular Fibers, making the lens more convex, also known as accommodation. [4]

However, anatomical and histological variations exist, which may be accompanied by variations in the number of neurons, too. The ciliary ganglion is an intraorbital neural structure approximately 3 mm in size, situated near the orbital apex, posterolateral to the

globe in loose areolar tissue between the optic nerve and lateral rectus muscle. The mean distance between the ganglion and the optic nerve is 2.9 mm (range: 2.70 – 3.10 mm) and the mean distance between the lateral rectus muscle and the ganglion is 10.4 mm (range: 9.20 – 11.20 mm). Six to 10 short ciliary nerves arise from the ganglion and run forward in a curving manner with the ciliary arteries above and below the optic nerve. [5]

The Ciliary ganglion is in close contact with the ophthalmic nerve, but separated from the muscle by some loose fat, and it is close to the ophthalmic artery. [6]

Variations exists even in anatomic studies from different centers and specialties: "After the dissection, we could see that in 28 human heads the ciliary ganglion was located deeply in the eye socket, in its posterior third, laterally to the optic nerve, and it was functionally attached to the oculomotor nerve. In the remaining 12 human heads, we observed that the ganglion occupies a posteroinferior, intermediate or anterosuperior position in respect to the common tendinous ring and optic nerve. Regarding morphology, the ciliary ganglion had a small, oval, and flattened shape, measuring approximately 1 x 1 mm." 1 Moreover, in terms of location, our study agrees with the results found by *Tsybul'kin*[6] *(2003),* who observed that the ganglion occupies a posteroinferior, intermediate or anterosuperior position in respect to the common tendinous ring (Zinn's ligament) and optic nerve. This author also found that a posteroinferior position of the ganglion was typical to brachycephals, while the anterosuperior position was found in dolichocephals.

"From a morphological point of view, the ciliary ganglion is small and flat, about the size of a pinhead.[2] This ganglion may also be oval shaped,[5] quadrilateral shaped,[6] of irregular form, egg-shaped, or rectangular.7 In addition, measuring 1 mm by 2 mm[2] or 3 mm by 3 mm,[8] it can be as big as a corn seed[7] or be positioned with its largest diameter parallel to the optic nerve's axis". [1]

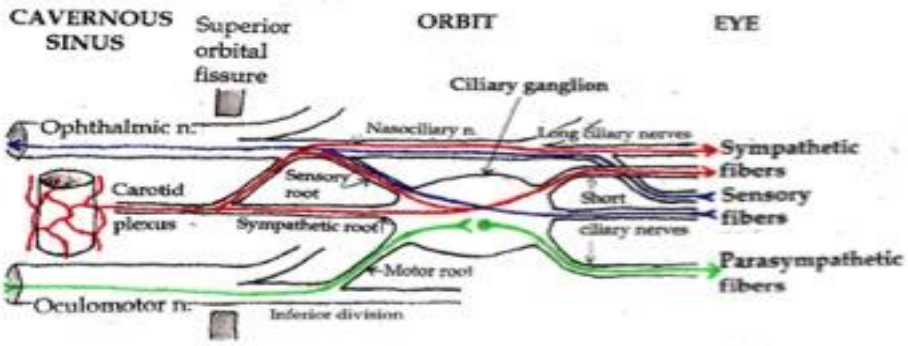
Disorders related to ciliary ganglion include Adie Syndrome, sometimes known as Holmes-Adie Syndrome or Adie's Tonic Pupil. Pathophysiology of pupillary symptoms of Holmes-Adie Syndrome are thought to be the result of a viral or bacterial infection that causes inflammation and damage to neurons in the ciliary ganglion, an area of the brain that provides parasympathetic control of eye constriction. Additionally, patients with Holmes-Adie Syndrome can also experience problems with autonomic control of the body. This second set of symptoms is caused by damage to the dorsal root ganglia of the spinal cord. [7]

Another associated neurological disorders related to ciliary ganglion disorder and its physiologic pathway is known as light-near dissociation. The pupil does not react to light, but it does react to accommodation. This is called "light-near dissociation".

In Adie syndrome, damage involving the ciliary ganglion manifests light-near dissociation and a tonically dilated pupil (usually unilateral).

The sensory sympathetic fibers pass through the ganglion without interruption, while the parasympathetic fibers synapse within the ganglion. The blood supply of the ciliary ganglion is from posterior ciliary, muscular, ophthalmic, and central retinal arteries. 6

The diagram below demonstrates the functional pathway of autonomous fibers passing different nerve branches and through the ciliary ganglion for relay.



Pathways in the ciliary Ganglion. Green = parasympathetic; Red = sympathetic; Blue = sensory.8 *

While the number of ganglion cells in the non-diseased ciliary ganglion has not been established, the cell body counts of the ciliary ganglion in diseased patient in postmortem studies by Perez and Keyser demonstrated that: “the mean cell body counts of 16 pairs of ganglia were 2473+/- 1289 for the Rt. Side, 2316+/- 1036 for the Lt. side, and 2394+/- 1153 cell bodies when 32 ganglia were averaged. The minimum count was 1088 (specimen 5) and the maximum count was 6835 (specimen 3)”. 6

In 1968, Harriman and Garland reported on a man aged 49 years, at the time of his death, who had a right tonic pupil. At necropsy, the right ciliary ganglion…contained very few normal ganglion cells”. 9

So far, macroanatomic-histologic studies presented by a decade of past studies reveal pathologic changes in the ganglion neuronal number loss, as well as physiologic loss. While molecular biology and molecular genetic research nowadays provide more resources for the key changes in the etiology of the neuronal changes, the answer to key changes needs to be determined.

II - PTERYGOPALATINE/SPHENOPALATINE (PPG/SPG) GANGLION:

The pterygopalatine ganglion, also known as sphenopalatine ganglion, lies deep within the pterygoid fossa, rostral to the anterior opening of the pterygoid canal and inferior to maxillary nerve *(Kuntz 1945; Mitchell 1953a).* It is the main parasympathetic ganglion of the upper jaw and related structures. The ganglion is about 3mm long, containing about 56 500 closely packed ovoid nerve cell bodies, 20m X 30m in diameter, with thick branching dendrites often bearing knob shaped endings *(Slavish 1932; Pearson and Pytel, 1978b: Wilson, 1984).* Some neurons have long, multi-branched dendrites that contribute to dense dendritic glomeruli *(Slavish, 1932).* Preganglionic axons reach the pterygopalatine ganglion from the facial nerve, via the greater superficial petrosal nerve and the nerve of the pterygoid canal (Vividian nerve). Small groups of nerve cell bodies occur in the distal portion of the nerve of the pterygoid canal, proximal to its junction with the pterygopalatine ganglion *(Nomura and Matsuura, 1972).* Ocular rami carry postganglionic vasodilator fibers projecting to blood vessels of the eye *(Ruskell, 1970, 1970b and1985).* 3

Most neurons in the human pterygopalatine ganglion are cholinergic; however, other studies revealed stains demonstrating VIP, peptide, histidine, methionine (PHM), helospectin, and pituitary adenylate cyclase-activating peptide (PACAP), NOS. 3

Other investigators show that a specific set of vasodilator neurons innervates the cerebral arteries *(Chorobski and penfield, 1932; Suzuki et al., 1984; Edvinson et al., 1987).* 3

The pterygopalatine ganglion is important for intraocular pressure balance and cerebral vasodilatation associated with vascular originated headaches. It is located deeply in the pterygopalatine fossa, close to the sphenopalatine foramen and in front of the pterygoid canal. The pterygopalatine ganglion was located in the pterygopalatine fossa and was functionally attached to the facial nerve. This ganglion had the largest size when compared to the other ganglia and it had a flattened form. 10 Concerning morphology, there are several descriptions of the pterygopalatine ganglion. According to some researchers, the pterygopalatine ganglion is slightly flat,[1,2] with a triangular and flat form[2] and is the biggest peripheral ganglion of the cranial parasympathetic system. However, for others, this ganglion is polymorphic, and can be rhomboidal, pear-shaped, semi-lunar, triangular, or fusiform, with volumes similar to that of a lentil (5 mm to 7 mm length).[7] In our study, the pterygopalatine ganglion had a flat form and presented the largest size (3 to 5 mm); hence, our results concur with the description made by *Warwick, Williams[1] (1979).* 10

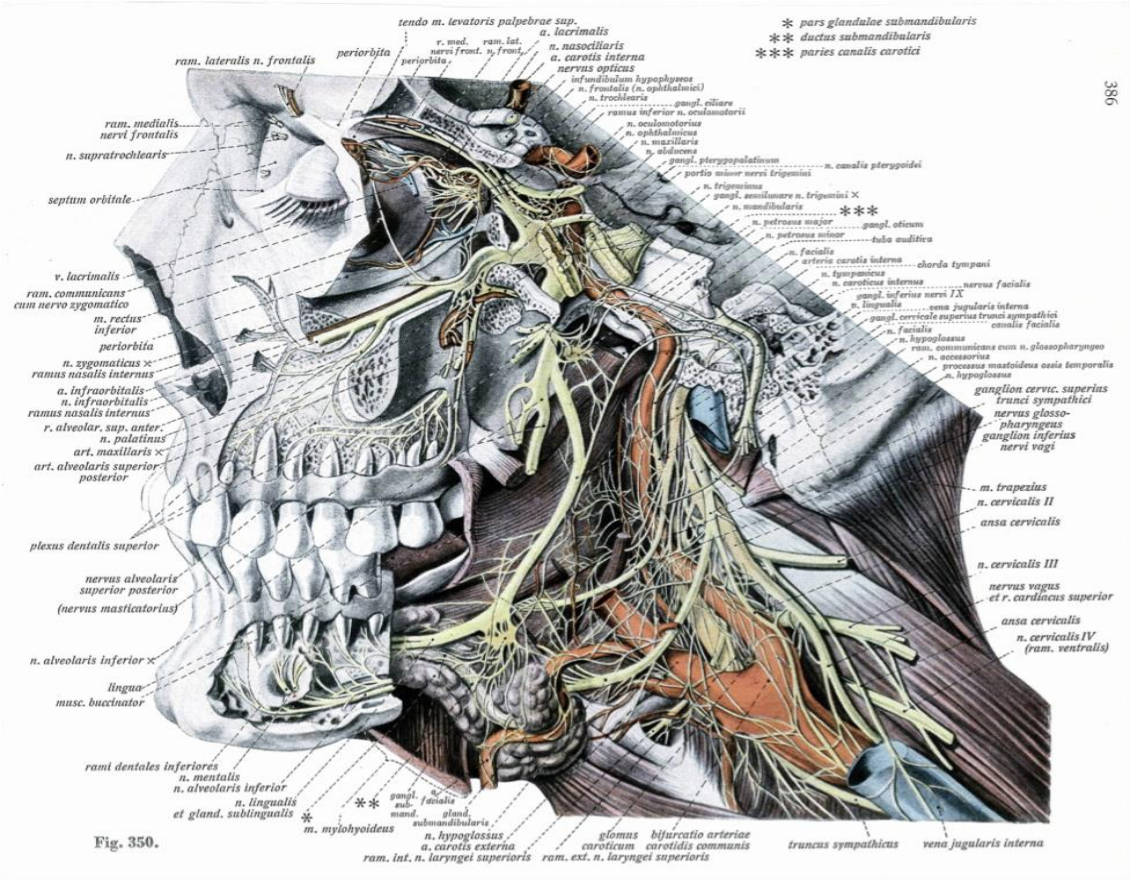


Fig. 350.

Figure 2: The basic anatomy of the craniofacial autonomic nervous system, including parasympathetic ganglia in craniofacial variations and contributions. 11 *

The effect of SPG stimulation on rCBF was also measured using fluorescent angiography *(Fig. 2A).* During SPG stimulation, intensity curves for the selected arteriole and venule showed a larger incline in signal intensity and a higher maximum, indicating increased blood flow *(Fig. 2B).* When the stimulation intensity was raised from 1 to 3 mA, the arterial diameter reached its maximum; a further increase in stimulation intensity led to a decrease in the vascular diameter *(Fig. 2C).* The arterial-venous peak-to-peak interval, an indirect measure of blood flow, generally decreased when the stimulation intensity was increased, suggesting that stimulation-induced vasodilatation is indeed associated with enhanced blood flow within the affected vasculature (Fig. 2B). In these experiments, stimulus-induced vasodilation and elevation of blood flow were not associated with a significant increase in BBB permeability measured using fluorescent angiography [20] (data not shown and see below). 12

While previous studies in monkeys demonstrated that SPG stimulation induces dilatation of constricted large vessels (internal carotid, anterior cerebral and middle cerebral arteries), in a sub-arachnoid hemorrhage model 13, our study shows that similar dilation occurs in small surface arterioles (but not venules) of the healthy brain. Recently, a similar

protocol has been shown to increase perfusion in MRI scans of rats following MCAO occlusion, suggesting that the vasodilation we observed in superficial vessels reflects a general response of both superficial and deep vessels to stimulation of the parasympathetic fibers of the greater superficial petrosal nerves. 14

Intensive research demonstrated the important role of PPG in the cerebral and neural blood flow. Although brain cell viability depends largely on cerebral circulation, mechanisms of blood flow control, such as autoregulation, or of the pathogenesis of functionally impaired blood supply to brain regions, are also critical. Impairment of PPG, here, may cause hypoxemia in the cerebral gray matter and gyri and may cause release of unprecedented stimulation of motoric neurons by increasing cell permeability to known interleukins and other inflammatory cytokines. We know already that vascular injury play an essential role in regulating vascular wall structure and function through production of chemokines, cytokines, growth factors, and reactive oxygen species (ROS). 15

Parasympathetic influences on cerebral blood vessels may not only play a role in normal physiological function but also may contribute to pathological states. For example, parasympathetic nerves from the PPG may participate in development of cluster headaches, which may respond to blocking function of those same nerves. 16

We hypothesized that parasympathetics provide a tonic vasodilator influence and tested that hypothesis by measuring cerebral blood flow in anesthetized rats before and after removal of a pterygopalatine ganglion. Cerebral blood vessels are richly innervated both by central pathways *(Reis, 1984;Vaucher & Hamel, 1995)* and by sympathetic and parasympathetic nerves *(Wahl & Schilling, 1993)* and are further influenced by metabolic activity of local CNS neurons *(Dirnagl et al., 1994; Harder et al., 2002).* We have focused on the parasympathetic innervation derived from neurons of the pterygopalatine ganglion (PPG), also referred to as the "sphenopalatine ganglion". We, like others *(Morita-Tsuzuki et al., 1993),* have shown that electrical stimulation of the PPG causes cerebral vasodilatation. 17

Other similar studies in vivo animal subjects show the parallel results in the physiology of the PPG toward cerebral blood circulations. However, we did not find any studies relating any cerebral pathology to PPG dysfunction or abnormality in humans.

"**Denervation of the ganglion** elicited cerebral vasoconstriction indicates that vasodilator nerves from the vasomotor center are tonically active. Stimulation of the greater petrosal nerve, upstream of the pterygopalatine ganglion, also elicited cerebral vasodilatation, which was abolished by treatment with the nitric oxide synthase inhibitor and with hexamethonium, indicate that the nerve is in connection via synapses with the nitrergic nerve innervating cerebral arteries." *(Neuroscience. 2000; 96(2):393-8).* Cerebral

vasodilatation is induced by stimulation of the pterygopalatine ganglion and greater petrosal nerve in anesthetized monkeys. [18]

Studies in rodents, dogs, and monkeys have demonstrated that stimulating neurons within the tendency toward practical therapeutic approach to PPG in human disorders and conditions may increase with detailed physiologic and technical capabilities.

SPG after permanent middle cerebral artery occlusion (MCAO) leads to an ipsilateral increase in regional cerebral blood flow (rCBF) [9]–[13] and, at high stimulation intensities, to BBB breakdown [14]. In a magnetic resonance imaging (MRI) study in rats, *Henninger and Fisher (2007)* [15] reported that a single train (four sets) of SPG stimulation, 15 minutes after MCAO led to elevated rCBF in the peri-ischemic region and to a significantly reduced infarct volume 24 h after treatment. In accordance, a recent study has shown that resection of the SPG leads to an increased infarct volume following MCAO [16].

Stimulation of the Sphenopalatine Ganglion Induces Reperfusion and Blood-Brain Barrier Protection in the Photothrombotic Stroke Model. [19]

The SPG is the source of parasympathetic innervations to the anterior cerebral circulation, which comprises the middle cerebral artery, the anterior cerebral artery, and their tributaries.

Animal studies showing that electrical stimulation of the sphenopalatine ganglion (SPG) exerts beneficial effects in the treatment of stroke have led to the initiation of clinical studies. However, the detailed effect of SPG stimulation on the injured brain is not known.

Conclusive results in animal studies from the same study source showed that: “in the present study, we examined – for the first time – the effect of SPG stimulation on the diameter and blood flow in surface cortical vessels in healthy and ischemic brains. We further tested the effect of repetitive SPG stimulation on cortical electrophysiology within the peri-infarct region in the photothrombosis model. The main findings of this study were: **(1)** SPG stimulation led to intensity- and pulse width- dependent vasodilation and increased rCBF.

(2) SPG-induced vasodilation facilitated partial reperfusion of occluded vessels in the phothrombosis RB model.

(3) the peri-ischemic zone showed increased permeability of the BBB, which was reduced in size for both immediate and delayed stimulation of the SPG;

(4) the necrotic core lesion was smaller following SPG treatment.

(5) fast cortical electrical activity and seizure-like events were prominent from day 3 after photothrombosis and reduced to control levels in SPG treated animals". Stimulation of the Sphenopalatine Ganglion Induces Reperfusion and Blood-Brain Barrier Protection in the Photothrombotic Stroke Model. [19]

The **pterygopalatine ganglion** innervates the cerebral circulation in laboratory mammals *(Keller et al, 1985, Walters et al. 1954*). A similar arrangement is likely in humans, the probable pathways following the ethmoidal arteries and *nerves (Mitchell, 1954; Hara and Weir, 1988).* [3]

Immunohistochemistry revealed enhanced expression of TNF-α, TNF-R1 and TNF-R2 in the walls of cerebral arteries at 48 hours after occlusion of middle cerebral artery (MCAO) and subarachnoidal hemorrhage (SAH), compared with control. Several studies have recognized that inflammation is a key element in the pathophysiology and outcome after stroke. Cytokines are polypeptides, generally associated with inflammation, immune activation, and cell differentiation. TNF-α is a 17 Kd polypeptide cytokine that may affect growth, differentiation, cell proliferation, immunomodulation, survival, and function of cells including those of the immune system, microglia, astrocytes and SMCs. [20]

These cellular responses are mediated through two distinct TNF-α receptors: TNF-R1 is expressed on all cell types, whereas TNF-R2 is expressed only on cells of the immune system and on endothelial cells. [21]

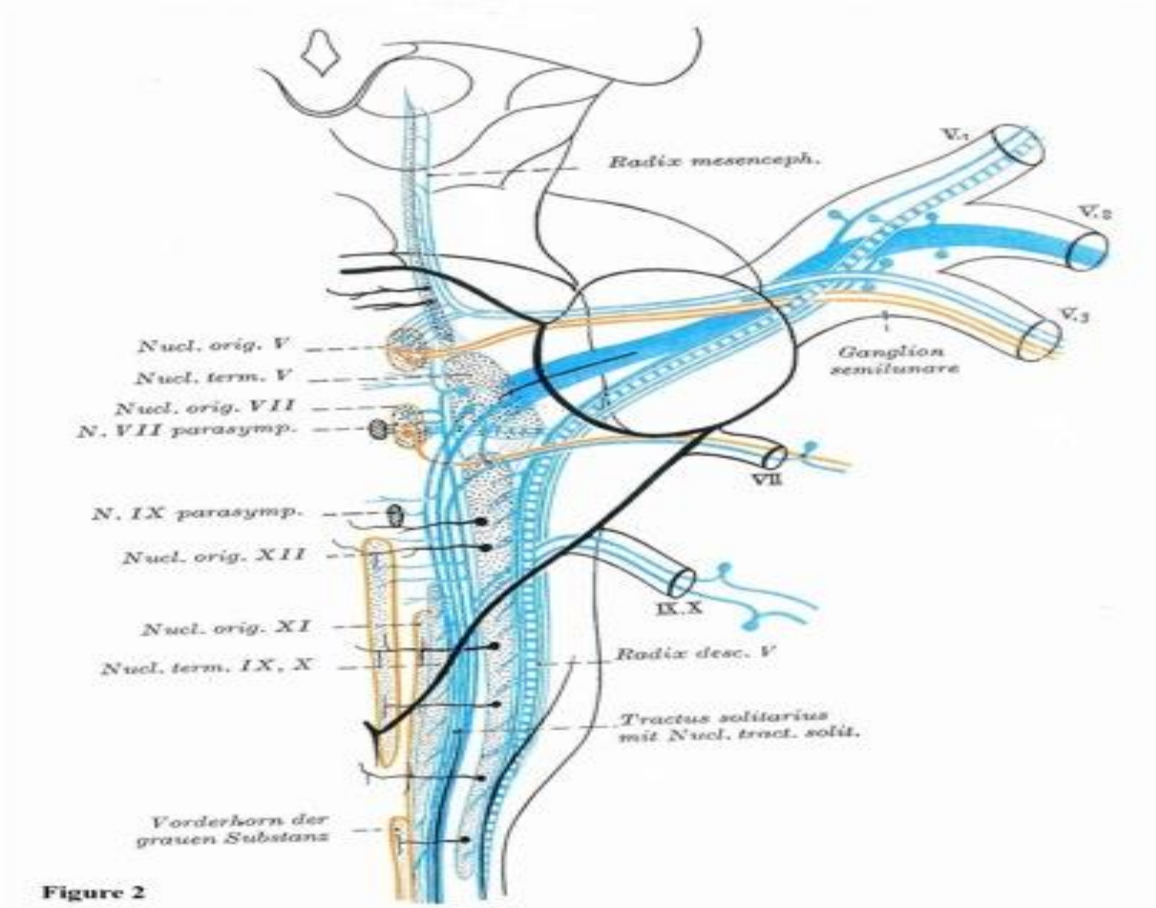


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Figure 3: The main sensory nucleus receives its afferents (as the sensory root) from the semilunar ganglion through the lateral part of the pons ventral surface.

TNF-α, TNF-R1 and TNF-R2 mRNA levels have been shown to increase in the brain after both permanent and transient MCAO in the rat and mouse (10, 36, 37), and in neuro-retinal arteries following ischemia in the pig and mouse. In closed head injury, the mRNA and functional activity (cytotoxicity) of TNF-α are increased, and increased TNF-α protein levels have been noted by Western Blot in the brain after stroke. 23 Thus, there is a correlation between TNF-α and brain damage.

Studies have shown that TNF-α can increase the permeability of the blood-brain barrier (BBB) via activation of the ERK1/2 pathway and increase the expression of TNF-R1 and TNF-R2. Treatment with U0126 inactivates this signaling pathway and decreases the expression of the TNF receptors. Understanding the molecular biologic events involved in brain ischemia and their induction through either arterial or venous blockage, may help clarify several autonomic disease related conditions. It is even possible that trigeminal neuralgia, CCSVI, multiple sclerosis (MS), Tourette syndrome, Sluder's neuralgia, and

Ramsey Hunt syndrome share similar patterns of mechanism, each involving slightly variable trigger forms, neuronal levels, and/or parasympathetic ganglionic involvement.

Binding of TNF-α to its cell surface receptors results in activation of mitogen activated protein kinase (MAPK), which may lead to activation of two transcription factors, Activation protein-1(AP-1) and NF-KB, which regulate expression of numerous components of the immune system. These components include pro-inflammatory cytokines, chemokines, adhesion molecules, and inducible enzymes such as nitric oxide synthase and cyclogenase-2. Dysregulation of this signaling may result in inflammatory and autoimmune diseases. NF-kB proteins are predominantly located in the cytoplasm and associated with members of the inhibitory IkB family such as IkB- α, IkB-β, IkB- ε. IkB proteins are believed to sequester NF-kB in the cytoplasm by masking its nuclear localization sequences. Thus, activation of NF-kB depends on degradation and phosphorylation of IkB. [27, 24]

III - SUBMANIDULAR GANGLION:

The submandibular ganglion is located lateral and superior to the hypoglossus muscle, lateral to the submandibular gland, deep to the lingual nerve, and is functionally attached to the facial nerve by the chorda tympani nerve. It appears small and fusiform.

According to the literature, the submandibular ganglion is located in the upper part of the hypoglossus muscle.[1] It is an autonomous nervous structure with reduced dimensions and a characteristic that can vary from triangular, egg-shaped, or plexiform. Its size can be compared to that of a lentil or a corn seed; therefore, its dissection is extremely difficult.[7] Our anatomic pieces showed that the submandibular ganglion is a small, fusiform structure (2 to 3 mm), which is in accordance with the description made by *Warwick, Williams[1] (1979)*. While investigating the lingual nerve's relationship to the submandibular ganglion in 32 adult bodies, it was observed that in 46.9% of the cases, the lingual nerve and the submandibular ganglion were fused, and in 53.1% they were free.[10] Our comparative analysis allowed us to observe a variation in the lingual nerve's association point to the submandibular ganglion, yet the fusion of these two anatomic structures was not observed.

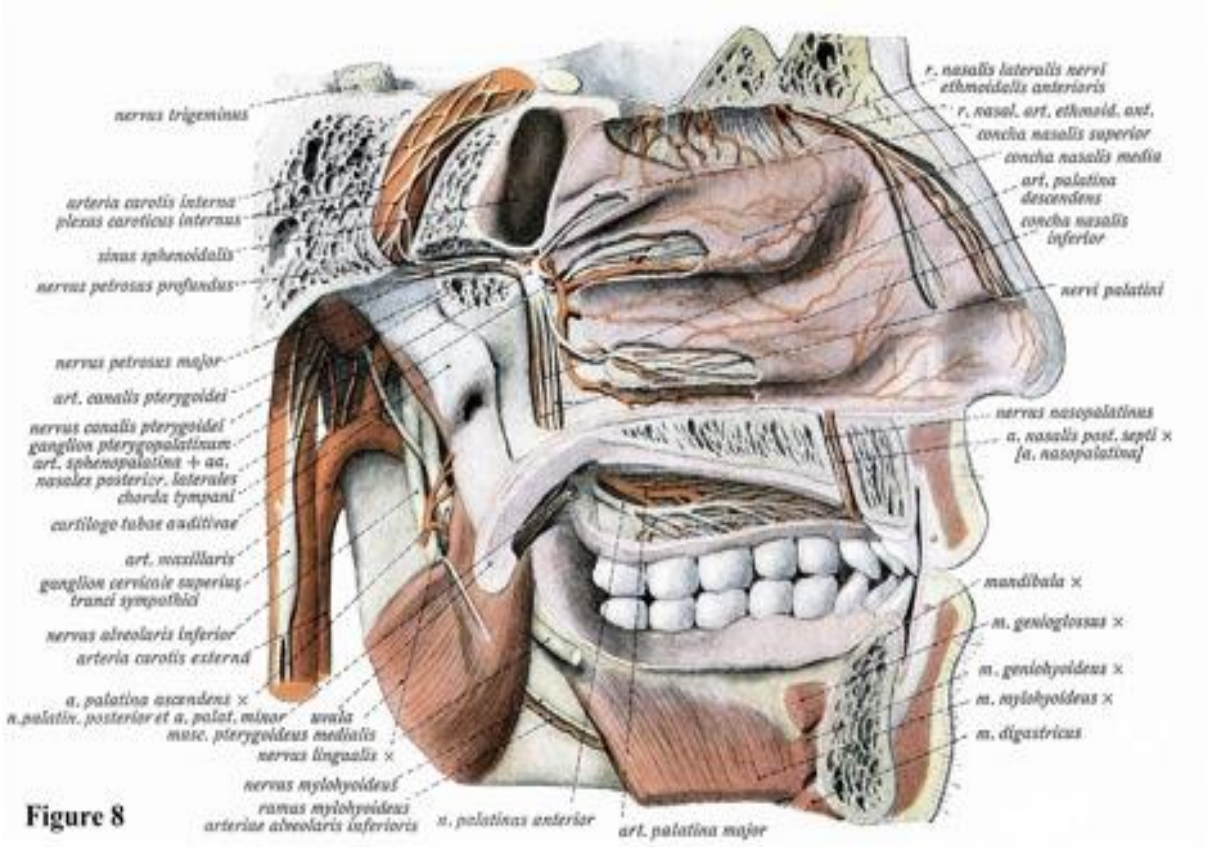

Figure 8

Figure 4: The Maxillary Nerve Branches, Supplies, and Pterygopalatine ganglion. The posterior superior alveolar nerves are usually 2 in number. They supply the mucosa of the posterior cheek and gingiva. *

Blood flow in oral tissues, including the tongue, salivary glands, gingiva, dental pulp, and lip, play an important role in modulating the complex oral functions involved in food intake. Oral tissue circulation is regulated by nitric oxide (NO) synthesized by neuronal NO synthase, which is mainly present in parasympathetic vasodilator neurons also produced by endothelial NO synthase.

There is evidence supporting the hypothesis that the superior salivary nucleus delivers central information through the geniculate ganglion and greater petrosal nerve to the pterygopalatine ganglion, which sends off impulses through nitrergic nerves to oral tissues.28 Neurogenic and endothelial nitric oxide regulates blood circulation in lingual and other oral tissues. 29

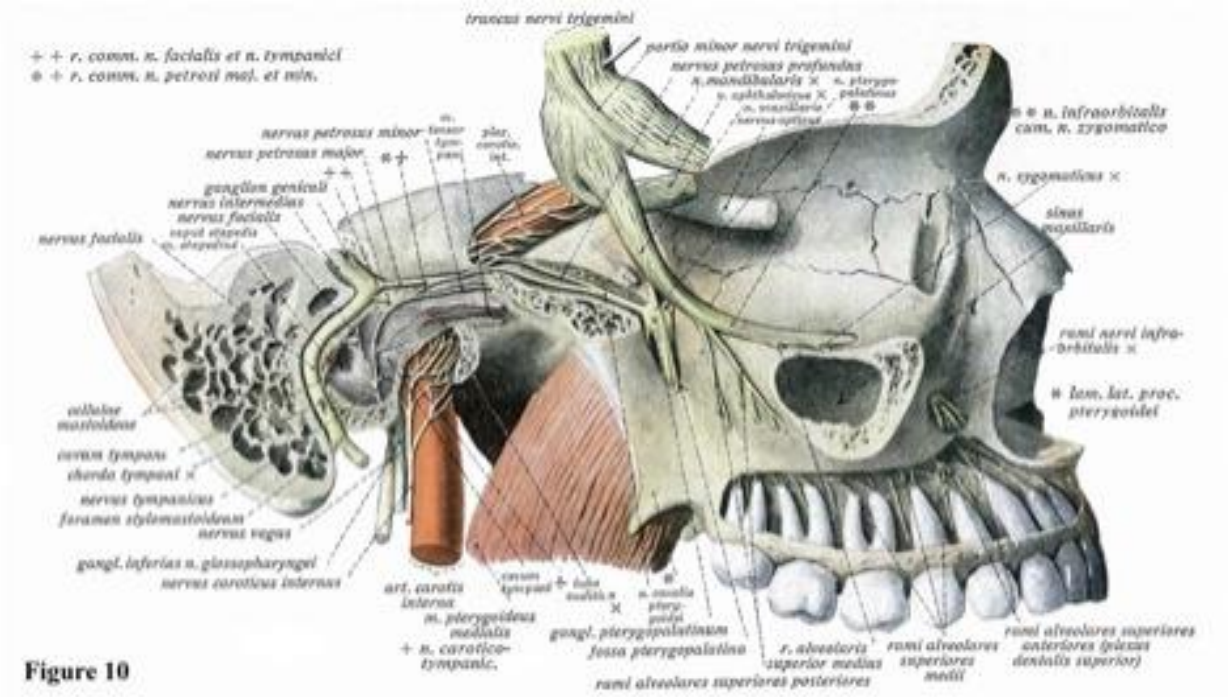

Figure 5: Topographic relationship of the Trigeminal nerve divisions, rami communicantes of facial nerve with tympanic nerve, rami communicantes of major and lesser petrosal nerves. *

IV - OTIC GANGLION:

The Otic ganglion is exceedingly small and may exist only as a group of microganglia, medial to the mandibular nerve, just distal to its exit from the skull *(Kuntz, 1945; Mitchell, 1953a).* The preganglionic pathway is usually said to arise from the glossopharyngeal nerve (IX n) via the tympanic plexus and the lesser petrosal nerve. However, an additional preganglionic pathway runs via the chorda tympani nerve, carrying preganglionic input from the facial nerve *(Reichert and Poth, 1933; Kuntz, 1945; Mitchell, 1953; Diamant and Wiberg, 1965, Kuchiiwa et al, 1998).* Some Otic ganglion neurons project directly to vasculature in the jaws and the cerebral circulation *(Wlaters et al., 1938),* while others may provide weak innervation to sweat glands around the lips *(Wilson, 1935, List and Peet, 1938).* Otic ganglion neurons are morphologically similar to those of the pterygopalatine ganglion *(Slavich, 1032).* Animal studies show that some vasodialtory otic ganglion neurons project to the cerebral vasculature *(Kadota et al., 1996).* 3

The otic ganglion is located directly under the oval foramen.[1-3,5] Regarding location, our results are in accordance with what is stated in the literature. Morphologically, the otic ganglion is small, oval, and slightly flat[1] or has the aspect of a lentil, and its form can have slender variations.[7] However, our observations concur with the previous description made by *Warwick, Williams[1] (1979),* i.e., the otic ganglion seen in our anatomic specimens does not reach the size of a lentil. 1

Analysis of the otic ganglion in humans describes it as an oval structure, measuring 3.5 – 4.5 mm in length, 3 mm in width, and 1.5 mm in depth. It was observed that the otic ganglion was present in 18 infratemporal fossae (10 cadavers), having a structure similar to that of the classical description. It was also observed that there are connections between the ganglia and both the lesser petrosal and Auriculotemporal nerves. In 13 ganglia, a connecting branch to the medial pterygoid muscle was evident and, in 9 other ganglia, a small ramus to the sympathetic plexus of the middle meningeal artery was noted. In most infratemporal fossae, the ganglionic form was seen bilaterally (8 cadavers), although in two instances this form was seen unilaterally, and only a small thickening was found on the contralateral side. This thickening on the medial aspect of the mandibular nerve was seen in two additional infratemporal fossae in two other cadavers. In the other 8 fossae, no specific anatomic structure could be discerned.[11] our observations revealed ganglionic forms bilaterally in all the analyzed anatomic specimens. [30]

Conclusions:

With this study, we conclude that there is no significant variation regarding the location of the studied ganglia. Morphologically, our observations concur with previous classical descriptions of the parasympathetic ganglia, but we observed variations regarding proximity of the otic ganglion to the mandibular nerve. We also observed that there were variations regarding the number and volume of fiber bundles connected to the submandibular, otic, and pterygopalatine ganglia. [30]

From a clinical standpoint, a Vienna/USA Orthodontist was able to demonstrate interesting findings with relief of Tourette syndrome and other movement disorders. He was able to show that there is a connection between Tourette's syndrome and temporomandibular joint dysfunction *(Stack).* Decreased joint space in the temporomandibular joints creates middle ear symptoms and overstimulation of Auriculotemporal nerve, which leads to movement disorders. There is an almost immediate calming effect on the patients experiencing Dr. Stack's treatment protocol, which lasts longer and longer as times goes on (Stack). [31]

These single center experience shows the possibility of mechanical stimulation of the SPG, as witnessed in TS, and directly affecting the pre-central gyrus and specifically areas of Broca 4 and 8 of precentral gyrus that are supplied by the middle cerebral artery. However, the laboratory research on mammals does not provide evidence of movement provocation by approach to SPG, possibly because the animals are sedated and anesthetized. On the other hand, the investigators may not be aware of those clinical symptoms related to SPG. Therefore, coordination of the neuro-molecular biological investigations between scientist and clinician may help us better understanding these associations, and perhaps with less speculation.

In summary, recent molecular and cell biology studies and findings suggest that the adventitia maintains multiple types of progenitor cells that appear to act in concert to coordinate the healing response to vascular injury. We speculate that disorders such as **"Chronic Cerebrovascular Insufficiency (CCSVI**)", and **"Trigeminal Neuralgia"** are acquired events in the process of life and may be directly associated with the autonomic nervous system and tunica adventitia of Vaso Vasorum as well as Vaso Nervorum. Importantly, the nature of these disorders is vasoconstrictive, not vasodilative. Still, many questions remain to be answered before the picture becomes clearer and more unique. We may further speculate that the parasympathetic craniofacial ganglia play a major role in movement disorders such as Tourette's syndrome.

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