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Innervation of pineal gland by the nervus conarii: a review of this almost forgotten structure

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Abstract: The nervus conarii provides sympathetic nerve innervation to the pineal gland, which is thought to be the primary type of stimulus to this gland. This underreported nerve has been mostly studied in animals. One function of the nervus conarii may be to activate pinealocytes to produce melatonin. Others have also found substance P and calcitonin gene-related peptide from the nervus conarii ending in the pineal gland. The following paper reviews the extant medical literature on the nervus conarii including its anatomy and potential function.

Key words: Nervus conarii, Pineal gland, Innervation, Anatomy, Review

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Introduction

Anatomy

The pineal gland (epiphysis) is a neuroendocrine organ found between the two cerebral hemispheres of the brain. Zaccagna et al. [1] found it to project caudally to the third ventricle's posterior wall into the quadrigeminal cistern, sitting superior to the splenium of the corpus callosum, inferior to the quadrigeminal plate, and lateral to the pulvinar of the thalamus. The pineal gland is attached to the brain via the pineal stalk which is connected to the habenular and posterior commissures [2]. The pineal gland receives autonomic innervation from the nervi conarii, which originate bilaterally from the superior cervical ganglion (SCG) located at the skull base (Fig. 1, 2). Descending first-order neurons from the hypothalamus reach the intermediolateral (ILM) column of the spinal cord near the C8-T2 parts of the spinal cord. The superior cervical ganglion receives input via second-order, pre-ganglionic fibers from the ciliospinal center of Budge, located within the ILM, containing fibers from thoracic nerves T1–T8 [3]. Fibers of the SCG ascend into the head and neck along branches of the internal carotid artery [4]. These post-ganglionic, sympathetic, unmyelinated fibers are thought to pass over the tentorium cerebelli and travel to the caudal aspect of the pineal gland in man (Fig. 1). In some, the left and right nerves join inside the gland at the midline. In cats, Rodríguez-Pérez [5] found that only a few fibers cross

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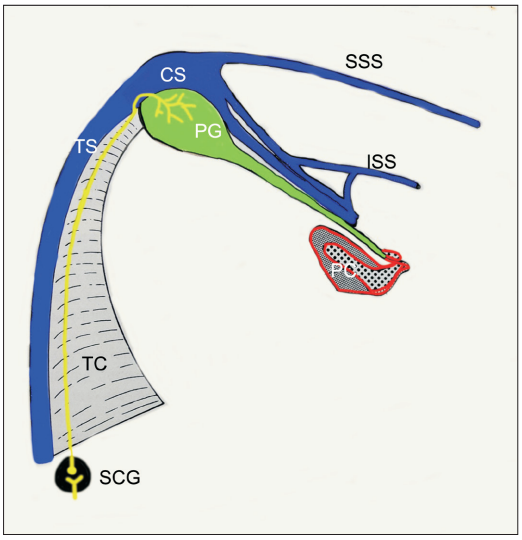

Fig. 1. Schematic drawing of the nervus conarii (yellow) in a rat (after Kappers and Schadé [6]). Note the TS, CS, SSS, ISS, TC, SCG, PC, and PG. TS, transverse sinus; CS, cavernous sinus; SSS, superior sagittal sinus; ISS, inferior sagittal sinus; TC, tentorium cerebelli; SCG, superior cervical ganglion; PC, posterior commissure; PG, pineal gland.

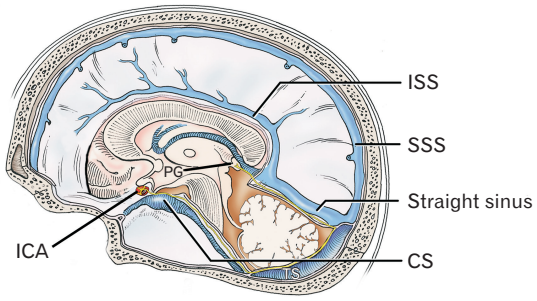

Fig. 2. Schematic drawing illustrating one proposed pathway of the nervus conarii (yellow) for reaching the PG from the sympathetic nerve plexus around the ICA in man. The nervus conarii travels from the sympathetic nerve plexus around the cavernous part of the ICA and then posteriorly medial to the superior petrosal sinus (unlabeled) along the tentorium cerebelli (cut). It then extends along the tentorium cerebelli near the transverse sinus and then by the straight sinus at the junction of the tentorium cerebelli and falx cerebri anteriorly to the vein of Galen (unlabeled) to terminate on the pineal gland. Note the TS. PG, pineal gland; ICA, internal carotid artery; TS, transverse sinus; ISS, inferior sagittal sinus; SSS, superior sagittal sinus; CS, cavernous sinus.

the midline. Fibers from the nervi conarii then branch out to innervate bundles of pinealocytes [6, 7]. Kappers [8] performed a ganglionectomy in rats and this led to degeneration of the epiphyseal neuronal network and thus demonstrated that the nerve fibers traveling within the nervi conarii are not epiphyseofugal but rather epiphyseopetal. This also demonstrated that almost all nervous innervation to the pineal gland originated from the superior cervical ganglion. Bowers et al. [9] confirmed this by injecting over 250 rats with horseradish peroxidase and found that most if not all of the 440 axons that penetrate the pineal gland originate from the superior cervical ganglion. However, Kenny [10] found that in the macaque, parasympathetic nerve fibers in the greater petrosal nerve traveled to the pineal gland and that these fibers were presynaptic. Pastori [11], in man and various other mammals, identified a ganglion conarii (Pastori's ganglion conarii) at the posterior aspect of the pineal gland. However, subsequent authors have been unable to identify such a ganglion. Some have speculated that if the findings of preganglionic parasympathetic nerve fibers as shown by Kenny [10] do reach the pineal gland, then such a ganglion might serve this system.

Function

The function of the pineal gland is poorly understood, but it is responsible for the cyclic release of melatonin in the circadian rhythm. Light enters the retina and triggers a signaling cascade, with one particular pathway involving the superior cervical ganglion that assists in the regulation of melatonin production [12]. As previously mentioned, there is a multi-circuit system composed of the retina, hypothalamus, intermediolateral cell column, and superior cervical ganglion coordinating the pineal gland function. Dafny [13] showed that a fast and slow pathway provide innervation to the pineal gland. The fast pathway comes from the habenular posterior commissure complex and has a short latency, while the slower pathway starts at the superior cervical ganglion and moves through the nervi conarii. The pineal gland lacks true neurons, so its function(s) appear to be reliant on these fast and slow pathways as described by Dafny [13]. Kappers and Schadé [6] have mentioned that although the mammalian pineal gland receives autonomic innervation, almost exclusively via the superior cervical ganglion, non-mammalian vertebrates with a pineal organ or accessory pineal organ have only sensory fibers emanating from these structures. This is contrasted to the pineal gland of mammals where no sensory cells are seen.

One study observed only insignificant phase delay changes as a result of cutting the nervi conarii. This led to the understanding that the circadian rhythm relies on multiple inputs [14]. To release catecholamines to the pineal gland, the

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postganglionic fibers release granular vesicles. Machado [15] found that the numbers of large and small granular vesicles in the nervi conarii varied throughout the lifespan of the rat. He was also able to show that the large granular vesicles originated from dense material in the smooth endoplasmic reticulum, while the small ones formed in the nerve endings.

Neurotransmitters

Melatonin production occurs via a biochemical pathway that is initiated through phototransduction which ultimately stimulates the noradrenergic neurons of nervi conarii to release noradrenalin. Some nervi conarii axon terminals have been found to terminate in the perivascular spaces of the pineal gland to then activate the pinealocytes to produce melatonin. Noradrenalin triggers pinealocytes to produce the arylalkylamine N-acetyltransferase (AA-NAT), one of the enzymes critical to melatonin biosynthesis [16, 17]. Pinealocytes take-up tryptophan upon its activation to begin the process of producing melatonin [18]. Klein et al. [19] refer to AA-NAT as the melatonin rhythm generating enzyme among other enzymes known to have a role in melatonin synthesis. As the main cell of the pineal gland, pinealocytes also produce serotonin which could also be a precursor for melatonin production [4]. Using a sensitive fluorescence-microscopic method, Bertler et al. [20] demonstrated 5-hydroxytryptamine levels in the rat pineal gland and in the postganlionic sympathetic fibers that made up the nervi conarii. These sympathetics are predominantly noradrenergic, but the study showed that the postganglionic fibers take up this neurotransmitter. The re-uptake of noradrenalin is to maintain the circadian rhythm by preventing noradrenalin from continuously stimulating the pineal gland [16, 17]. Bulc and Lewczuk [21] observed projections from the nervi conarii into the pineal gland containing substance P and calcitonin gene-related peptide. The nerve fibers entered the parenchyma to create "basket-like structures" around pineal gland cells. This author also found fibers positive for substance P and negative for calcitonin gene-related peptide dispersed through the pineal gland; fibers with substance P were predominantly in the distal and middle regions of the pineal gland, and no fibers were identified with calcitonin gene-related in the absence of substance P.

Conclusion

Based on animal studies, the nervus conarii provides sympathetic nerve stimulation to the pineal gland and these fibers apparently arise from superior cervical ganglion. This innervation may be to activate pinealocytes in the pineal gland to produce melatonin. Others have also found substance P and calcitonin gene-related peptide from the nervus conarii ending in the pineal gland. Additional studies are necessary to better elucidate this nerve's function, especially, in humans.

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Conceptualization: JI, ASD, RST. Data acquisition: KG, TW. Data analysis or interpretation: KG, TW, JJC, AC. Drafting of the manuscript: KG, TW. Critical revision of the manuscript: JJC, AC, ASD, JI, RST. Approval of the final version of the manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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