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MORPHOPHYSIOLOGICAL ASPECTS OF THE TERMINAL NERVE: LITERATURE REVIEW

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INTRODUCTION

The terminal nerve, also described as cranial nerve zero[1], is a cranial nerve composed of pseudounipolar neurons. Its cells originate from the cranial neural crest, the final portion of the neural tube, and the olfactory[1,2,3] and adenohypophyseal[2] placode. In mammals, this nerve goes to the telencephalon, where it receives olfactory and somatosensory afference from the tegmental nucleus of the midbrain[2,4,5], being an important component of the GnRH system, but independently of the preoptic nucleus[5]. These interferences modulate the neuronal electrical activity of the terminal nerve, whose fibers are related to the olfactory and vomeronasal nerves[2], acting on reproductive behavior[2,4] through the secretion of GnRH[6]. Furthermore, the terminal nerve seems to receive input from sensory processing neurons related to visual and somatosensory information[6,7].

Based on this information, this study aimed to review the most current literature on the terminal nerve, addressing its anatomy, development, and main functions.

ANATOMICAL REVIEW

The terminal nerve (TN) was first described in dogfish shark in 1878 by Fritsch; in 1895, it was described in detail by Pinkus and named Pinkus' nerve[8]; however, it was only recognized with its current name in 1905. In 1987, it was named nerve zero because it is located rostrally to the other twelve cranial nerves described[6,9,10,11]. This nerve arises from the olfactory placode and it is also suggested that the neural crest contributes to its formation[6, 9, 11, 12].

The TN, composed of ganglion cells, forms one or two groups (ganglia) at the base of the crista galli that give rise to both afferent and efferent plexiform fibers[8,9,11,13] and are distributed in the nasal cavity, but also have intracranial course[13]. In mammals, the terminal nerve is mixed with the vomeronasal nerve (VN) and because of this, it is difficult to distinguish it anatomically in most animals. However, it is located medially to the olfactory nerve[9,13]. The vomeronasal nerve (VN) arises from the vomeronasal organ, while the TN is found in the rostral and dorsal portions of the nasal cavity[12,13]. Both nerves reach the medial region of the cribriform plate of the ethmoid bone, where they cross into the cranial cavity[12,13,14]. In the region of the olfactory bulb and accessory olfactory bulb, both the VN and the TN mix with some olfactory nerves (ON) before making a connection in this region, and after making synapses, they run to the olfactory and vomeronasal areas in the lamina terminalis of the brain cortex[13], and preoptic and precommissural areas[9,12,13,15]. The TN runs through the ventral region of the brain[15] parallel to the olfactory tract, initially close to the dura mater and later crossing the subarachnoid space to join the pia mater in the straight gyrus[13]. In fish, it also runs to the retina[9,12,13,15]. The TN is found bilaterally as a tiny unmyelinated plexus and forms autonomic nerve bundles that reach Bowman's glands and the nasal blood vessels[9,12,15].

The terminal nerve complex has been described in most vertebrate groups, including lampreys and lungfish, teleost fish, amphibians, reptiles, birds, and several mammalian groups, including rodents and primates[11]. It has also been described in cetaceans, animals that lack an olfactory bulb or olfactory epithelium[3,14], and in human embryos and adults, which lack a functional vomeronasal organ[3,11].

In both birds and mammals, GnRH-1 neurons are detected during embryonic development in various regions of the nasal pit, including the respiratory, olfactory, and

vomeronasal epithelia. In some species, such as rats, these neurons develop and migrate from the nasal cavity to the brain or hypothalamus[3].

The Prokr2 gene and its ligand Prok2 are candidates to elucidate gaps in knowledge about the relevance of the role of the terminal nerve, olfactory bulb formation, and GnRH migration since humans that do not express the gene present atrophy of the genital system and hypoplasia of the olfactory bulb. In rodent embryos, Prokr2 expression was detected in an early transient class of neurons that prefigure the primary olfactory pathway before the growth of olfactory sensory axons or expression of olfactory receptor genes[3].

OLFACTORY FUNCTIONS

The terminal nerve has been described as a modulator of the olfactory epithelium[9] in addition to providing sensory pathways for olfaction[8] since some peptides found in the terminal nerve have this function[12,16]. GnRH from the TN alters the excitability of olfactory receptors, possibly causing these cells to respond more promptly and vigorously to odors[16,17]. However, this response appears to be seasonal, being more efficient in winter and fall than in summer. This activity is probably increased during the breeding season[16]. In addition, the TN exerts a level of neurophysiological regulation on the olfactory epithelium, making pheromones more easily detected[8,12].

In several vertebrates, TN axons have connections with the prosencephalon in association with the medial olfactory tract, raising the possibility that pheromone-mediated responses are detected by the TN or in combination with the olfactory system[18]. The TN also plays a role in the chemosensory modulation of sperm release in goldfish, according to a study by this author.

NON-OLFACTORY FUNCTIONS

Although their function is still uncertain, TN fibers have been described as facilitating the migration of luteinizing hormone-releasing hormone-producing cells to the hypothalamus, participating in the development of the hypothalamic-gonadal axis[11] and producing non-hypophysiotrophic GnRH, playing neuromodulatory roles and regulating sexual behaviors in mammals[3,8,12,19] independently of the olfactory and vomeronasal connections in the olfactory bulb[8]. This GnRH production causes the neurohypophysis to secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in females and testosterone in males[8]. Furthermore, TN neurons show reactivity to FMRFamide-like neuropeptides, which are related to the inhibition of the action potential for GnRH release[20]. Studies indicate that interruptions in the migration of GnRH-1 neurons or any alteration in the release of this hormone negatively affect sexual maturation and function, social behavior, and fertility[3,14].

In addition to hormone production, the neurons of the terminal nerve seem to receive inputs from sensory neurons processing olfactory, visual, and somatosensory information[6,7]. Morphological analyses show that the neurons of the TN project to the interplexiform layer of retina, where there is the expression of GnRH receptors, suggesting that the TN modulates dopaminergic cells and induces modulation of color contrast by ganglion cells[6,22,23,24]. This indicates that the terminal nerve plays a key role in the integration of multiple sensory inputs[6,24,25].

In addition to being related to the neuroendocrine regulation of reproductive behavior and modulation of several sensory pathways, TN also participates in autonomic and vasomotor regulation, paracrine secretion of nitric oxide, and immune defense mechanisms[12].

FINAL CONSIDERATIONS

Although the terminal nerve was described over a century ago, many studies attribute several functions to it in addition to the olfactory function and its relationship with reproductive behavior via the production of GnRH by its neurons. There is no doubt that the role of this nerve is very complex, as it makes numerous interconnections with other brain systems. Nevertheless, much preliminary evidence in the literature has to be elucidated, in addition to clarifying the molecular mechanisms of the olfactory and non-olfactory functions of this nerve. Additionally, more studies are needed to describe its ontogenetic development and a more reliable anatomical description, since many discrepancies are found in this information, especially in its connections with the various regions of the telencephalon.

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