Cranial Nerve Zero: A Comprehensive Review of Literature

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Abstract

Though it was definitively recognized over a century ago as an extra cranial nerve in humans, cerebral nerve 0 (CN 0) is still mostly absent from contemporary anatomy textbooks. Since the nerve's fibers were first observed entering the brain in the lamina terminalis of the species under examination, the nerve is known as the nervus terminalis. Since the CN 0 has been shown to secrete luteinizing hormone, it is assumed that the CN 0 is involved in reproductive activity. Because of its connection to the hypothalamic kisspeptin neuronal circuitry, CN 0 raises clinically important issues about the relationship between the system and neuropsychiatric symptoms and disorders, as well as the function of disruptions in this relationship.

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Introduction

The seemingly benign nerve known as nervus terminalis, also known as the terminal nerve, nerve nulla (n), cranial nerve zero "0" (CN 0) and cranial nerve XIII, has received very little attention in the literature, despite the abundance of publications outlining the standard 12 pairs of cranial nerves (CN). But for over a century, this nerve has been found in many vertebrate and invertebrate species, including humans [1]. Surprisingly, not much is understood about CN 0. NERVUS terminalis, nerve of Pinkus, tractus olfacto-commissuralis, new nerve, terminal nerve, nerve nulla (i.e., nothing, zero), and CN 13 were some of the previous names for CN 0 [1-4]. Fritsch first identified this mysterious nerve in elasmobranchs, a subclass of cartilaginous fish, or Chondrichthyes, in 1878. He called it a "supernumerary nerve." Roman numeral symbols were already being used at the time to classify CNs [2]. Since it was first identified in 1905 in humans among other species, this nerve is now often known as CN 0 [2]. This designation adheres to the predetermined numeric order of human CNs [1] and is congruent with the nerve's rostral display in relation to the other CNs. Additionally, the Federative Committee on Anatomical Terminology of the International Federation of Associations of Anatomists formally recognized CN 0 in the Terminología Anatómica [5,6]. In the human

brains of fetuses, newborns, and adults, CN 0 has been clearly identified [1]. Its embryology, histological structure, neurophysiology, and clinical importance have all been clarified by later research [4]. While terminal nerve has been thoroughly established in many vertebrate animals, their presence and functional relevance in humans are still debated. According to the literature, Cranial Nerve Zero does not occur in all individuals, but rather as a normal anatomical variance in a subset of the population. Histological and immunohistochemical studies have discovered this nerve in human fetuses and adults, generally placed near olfactory bulbs and tracts [2,7]. However, its discovery is uneven, most likely because to its tiny size and modest anatomical course, making it difficult to spot in routine dissections or imaging investigations. This variability has led to the conclusion that Cranial Nerve Zero is a supernumerary structure that may exist as a normal variation in certain people [8].

History of Cranial Nerves

A thorough investigation of the CN 0 in large mammals (such as horses) that included 14 people was reported by Johnston [9]. Johnston observed that while in certain human brains the nerve could be seen with the unaided eye, in other brains it required the use of a low power microscope. In conclusion, he expressed doubts about the nerve's vestigial status in humans due to its bigger size compared to numerous fish and amphibians. The gyrus rectus is where the adult human CN 0's intracranial path lies, according to Brookover and Johnston [9,10], who also observed that the nerve enters the brain near the medial olfactory stria. In his description of the nerve in the human fetus and baby, McCotter [11] noted that the peripheral route resembled that of the rabbit described by Huber and Guild [12]. The CN 0 in chimpanzees exits the brain through the pia, travels toward the cribriform plate, enters the dura, and exits the cranial chamber with the bundles of olfactory fibers, according to the well-known American morphologist Ayers [13]. He numbered the CN 0 as CN I because he believed it to be present in all vertebrates (in fact, he thought there were 14 CNs, including a "septal" nerve that is now known as the vomeronasal nerve). Pearson [14] provided a description of how the CN 0 developed in humans. According to Pearson, even if the human CN 0's primary roots are little, it is improbable that this nerve is entirely a vestige. Pearson [14] also mentioned that the majority of the olfactory nerve bundles often follow a deep (medial) course across the cribriform plate as a result of the CN 0 branches. While there were a few studies conducted in the middle of the 20th century that discussed the CN 0 in vertebrates, there was not much of an interest in the CN 0 at the time [15]. An exception to this rule is Larsell [16], who carried out exquisite histology studies on a number of species, demonstrating that the CN 0 is a mixed nerve with multiple functional components. Specifically, he demonstrated that the CN 0 probably has autonomic components that reach Bowman's glands and nasal blood arteries in addition to a sensory component. The development of immunocytochemistry in the 1970s made it possible to identify different chemicals, primarily peptides, in the central nervous system and peripheral nerves. Schwanzel-Fukuda and Silverman [17] used this method to show immunoreactive luteinizing hormone releasing hormone (LHRH) in the CN 0 neurons and ganglia of guinea pigs. "It is possible that some of the surgical and other experimental procedures used to highlight the significance of these two olfactory systems [vomeronasal and olfactory] also disrupted the nervus terminalis," they concluded. Transecting the CN 0 in male hamsters reduced the frequency of mating and increased the number of intromissions needed for ejaculation, as demonstrated by Wirsig and Leonard [18]. The anatomy and function of the CN 0 were the only focus of a symposium held at the New York Academy of Sciences (NYAS) in 1987. A separately published volume (519) of the Annals of the NYAS was the outcome

of the conference [15,17]. Based on a review of ten brains, Fuller and Burger [8] confirmed the presence of the CN 0 in adult humans. They called it "cranial nerve zero" and observed that it forms a plexiform network with a dispersed arrangement of ganglion cells in mammals, as opposed to a single massive fascicle as it usually does in lower animals. The nerve usually projects (in fetuses) to "the medial pre-commissural septum, including the medial septal nucleus, or at its junction with the tuberculum olfactorium, anterior olfactory nucleus, or anterior continuation of the hippocampus," according to a report by Brown [19] from the NY symposium. Female rats with lesioned CN 0 exhibited minor but statistically significant reductions in lordosis latencies, as demonstrated by Wirsig-Wiechmann [20]. Based on research on humans and animals, Wirsig-Wiechmann and Lepri [21] identified the following four traits as CN 0 neuron distinguishing characteristics: (1) in the adult, are located in the nasal cavity or subtly in the brain near the olfactory bulbs and receive input from the brain; (2) they originate from the neural crest and migrate from the olfactory placode area to nasal and rostral brain regions; (3) they send fibers to nasal mucosa and rostral ventral brains areas, primarily olfactory/limbic areas; and (4) they contain LHRH, acetylcholine, and an NPY-like peptide (figure 1).

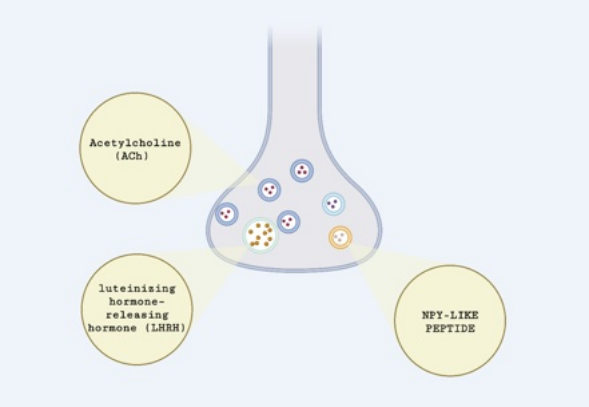

Figure 1: Illustration of cranial nerve zero (terminal nerve) highlighting its neurochemical components.

CN 0 LHRH neurons may play a neuromodulatory role in the forebrain and olfactory epithelium, modulating olfactory-mediated behavior, according to Oka [22] and later Whitlock et al. [23]. An essay titled "Sex and the Secret Nerve" [24] in Scientific American Mind discussed the CN 0. According to Fields, this nerve is highly significant in comparison to pheromones, but it is usually not discovered because it peels off with the dura during dissection.

Physiologic Variants

CN 0 functions differently from the traditional olfactory sensory role of detecting odorant molecules through the olfactory receptors, which are members of the G protein-coupled receptor families, while being located in close proximity to the CN I (olfactory nerve) [16]. According to a few accounts, the terminal nerve projects to several significant neuroanatomical structures, including the medial septal nucleus and the medial pre-commissural septum. Additionally, it sends fibers to the rostral ventral brain structures, mainly to limbic and olfactory regions (i.e., the amygdala and hypothalamus nuclei) and the nasal mucosa [15,21]. The limbic system's structures, including the hypothalamus, are accessible through these linkages. The "kisspeptin neuronal network" is the name given to a somewhat insignificant collection of neurons found in the preoptic and infundibular nuclei of the hypothalamus [25]. Puberty and human reproductive activities are under the central endocrinologic regulation of this hypothalamic neural circuit. The main way that the hypothalamic kisspeptin neuronal network neuron function is by stimulating the hypothalamus to secrete gonadotropin releasing hormone (GnRH), which in turn controls the release of the gonadotropin hormones luteinizing hormone (LH) and follicle stimulating hormone (FSH). In the end, these adenohypophysis hormones will affect how sex steroids are made and released by the gonads [26]. This

suggests that sexual behaviors are neuromodulated by the CN 0 through GnRH, which has an intriguing relationship with the hypothalamic kisspeptin neuronal network neurons. Although numerous exquisite investigations have detailed the human kisspeptin neuronal network efferent projections, little is known about the afferents of this significant hypothalamic cellular network. Maybe the key to solving this intricate scientific puzzle is the mysterious CN 0. Among other structures, the CN 0 projects to the amygdala, the hypothalamus, and the nasal mucosa. In the unlikely event that any of these projections make it to the preoptic, infundibular, or both hypothalamic nuclei, they might serve as an afferent source for the kisspeptin neuronal network neurons that control GnRH releases. Therefore, regulating the processes and behaviors of human sexuality. This idea is intriguing but just theoretical; yet, it deserves scientific study [27]. In addition, the theory that pheromones affect how people behave sexually has generated debate over the past few decades [28,29]. Naturally, this also includes the much more contentious vomeronasal organ (VNO), a highly distinct chemosensory organ found deep within vertebrates' nasal cavities, including humans [30-32]. The VNO has long been thought to oversee intra-specific chemical communication through the use of pheromones, which are chemical messages emitted by one member of the species and recognized by another. The existence of human pheromones and the VNO are still up for dispute. However, there is strong support for this from a number of credible research [33]. According to these findings, humans can create at least six of the same pheromone receptors found in mice thanks to their genetic makeup. Numerous descriptions of VNO in people have also been found in the literature. Human fetuses have the VNO by weeks six or seven; by week twenty-eight, its ducts have openings into the nasal cavity. Histologically, it is made up of a dense vascularization network, the lamina propria, and the olfactory epithelium. According to a recent study conducted in Bulgaria, roughly 27% of adults (males, 53%; females, 47%) have the VNO. Other populations (such as those in the United States, Canada, France, and Egypt) have observed similar findings [34]. Despite all these crucial factors, recent research on the VNO indicates that this sexually dimorphic structure in adults is only a vestige of our embryonic differentiation phases. This implies that this structure is unquestionably present but not physiologically active in adulthood. As such, there is insufficient empirical evidence to support the theory linking the VNO to the detection of pheromones in adult humans. A plausible theory, on the other hand, would involve the nasal mucosa nerve projections from CN 0, transducing the mysterious chemical signaling from adult human pheromones and modulating the hypothalamic GnRH secretory pulses via the kisspeptin neuronal network neurons, thereby regulating the secretions of sex steroids and gonadotropins in response to the chemical cues provided by the pheromones. But because the CN 0 projections to the hypothalamic kisspeptin neuronal network neurons are purely hypothetical, this conceptual cascade of neuroendocrinological events is purely theoretical. Given that the VNO might not be physiologically competent to detect biological pheromones in adults, the CN 0 could be a good fit for this distinct physiological role that is separate from the VNO [4]. Figure 2.

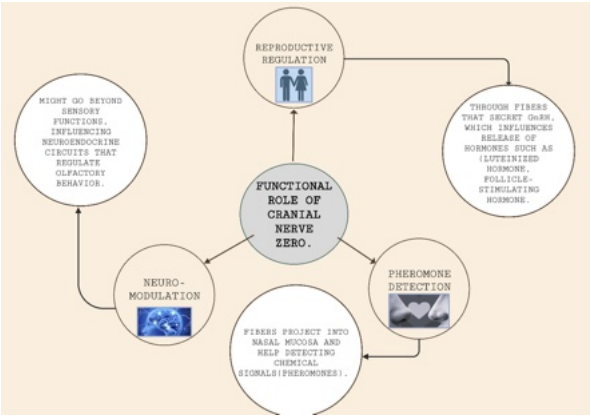

Figure 2: Illustration of CN-0, depicting its functional roles.

Embryology

Among vertebrates, CN 0 is one of the most mysterious nervous system structures. Like other CNs, it has embryonic roots in the neural crest and sensory placodes interacting synergistically during development [6,35]. An essential component of the embryo, the neural crest is made up of multipotent cells that can differentiate into a variety of cell types. These cells are responsible for the development of numerous nervous system components, such as ganglia, CNs, and peripheral nerves, as well as craniofacial tissues, such as cartilage and bones. The neurons of the nose that constitute the olfactory epithelium, the inner hair cells, and related tissues are examples of sensory structures whose growth is amplified by placodes, which are precursors of nervous tissue (24). At the front edge of migrating neural crest cells, the neural tube's terminal, and the adenohypophysis and olfactory placodes, CN 0 is formed [6]. Like the other human olfactory nerve systems, including the olfactory nerves (CN I), olfactory bulbs, and the VNO, CN 0 has a similar embryological origin [36,37]. It consists of one or two nerve bundles that go through the cribriform plate's anterior end [37]. Based on available data, it appears that these nerve fibers join the olfactory and vomeronasal processes nerves in the brain during embryological stages 17 and 18, also known as Carnegie stages 17 and 18 of human embryonic development [37-39]. In a previous investigation, parasagittal slices of 7-week-old (19-mm) human embryos were found to have the VNO and CN 0 fibers using standard histology techniques [2]. This nerve's anatomical organization is one of its distinctive and fascinating characteristics. Axons exhibiting immunoreactivity to the decapeptide GnRH comprise the nerve in most species, including humans [2,6]. The olfactory placode is the primary source of GnRH neuroendocrine cells and CN 0 nerve fibers, with contributions from the neural crest [6,17]. Nonetheless, research indicates that GnRH neurons could potentially originate from other embryological sources [40-42]. The hypothalamic GnRH neurons migrate from the placodal epithelium, carrying the central fibers of CN 0, CN I, and the VNO, as they differentiate and grow from outside the diencephalon into the forebrain [42]. Inadequate migration and genetic changes resulting in defective embryological processes can cause reproductive problems and other physiological disruptions, including anosmia in certain situations. Though the precise mechanisms controlling the migratory processes are yet unknown, several parameters influencing GnRH neuronal migration are currently understood [43].

Anatomy and Structure

In the human brain, CN 0 is detectable at all neurodevelopmental stages, including in embryos, fetuses, adults, and children [11,16,44]. In a prior study, ganglion cell bodies were found along the crista galli of the ethmoid bone at 10 weeks (76 mm, or the crown-rump length) [2] in human fetuses. According to a different study, it is located near the front edge of the ethmoid bone's perpendicular lamina (30 fetuses at 7–18 weeks; CRL: 25–160 mm). The anterior ethmoidal nerve, a branch of the ophthalmic division of CN V, has bundles of fibers that run along and cross posterior to its nasal branch. Additionally, clusters of tiny ganglionic cells were seen by the crista galli, the majority of CN 0's axons [37]. When the nerve reaches adulthood, it retains its plexiform structure, and ganglionic cells form in the ethmoid bone near the cribriform plate. The midbrain's lamina terminalis and medial olfactory gyrus are near the olfactory trigone, which the nerve fibers appear to pass by [2]. Although CN 0 shares physical similarities with the VMO nerve and CN I fibers (figure 3), it functions differently from both other structures. CN 0 is functionally linked to the neuroendocrine regulation of reproductive behavior, as well as other functions (such as smell, autonomic and vasomotor regulation, paracrine nitric oxide secretion, and im-

munologic defense mechanisms), because of its physiological correlation with GnRH expression [45]. In a variety of species, including humans, the axons of CN 0 facilitate the migration of GnRH neurons to the hypothalamus, hence enhancing the establishment of the hypothalamic-pituitary-gonadal axis. Furthermore, it has been proposed that the GnRH component of CN 0 is neuromodulatory, acting as a neurophysiological regulator over the olfactory epithelium to facilitate the detection of pheromones [46,47]. [48]

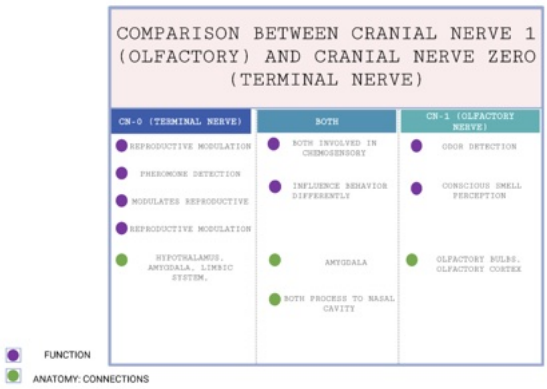

Figure 3: Comparison between cranial nerve 1 and cranial nerve zero

Function of CN0

It has long been unknown how the CN0 functions. It was the first convincing attempt to shed light on the function of the CN0 when Silverman demonstrated that the nerve and his ganglions contain neuroactive substances and are immunopositive for LHRH [17]. The LHRH that the terminal neuron produces is not a simple hormone; rather, it is a neuromodulator [49]. It's interesting to notice that the subgroups of CN0 neurons that express LHRH differ amongst animals [50]. Fibers from the CN0 grow into the adult retina of fish, frogs, and voles [51,52], but only in the early stages of embryonic development in other mammals, according to LHRH immunohistochemistry [53,54]. Thus, it is postulated that the terminal nerve controls vision in some animals. A separate investigation on goldfish indicated that the CN0 is the primary chemosensory pathway (pheromones-responder [55]. Reports state that in some animals, actions pertaining to mating, reproduction, and environmental adaptation are coordinated by the terminal nerve. Further research uncovered the role of CN0 in the formation of the human hypothalamic-pituitary-gonadal axis. Studies demonstrating the proximity of CN0 endings to blood arteries also suggest the possibility of autonomic and sensory functions, which may be performed in a manner akin to that of the trigemino-vascular system [56].

Pathology of CN0

The function of the CN0 is still unknown more than a century after it was discovered. Experimental evidence [50,57,58] suggests that LHRH cells migrate from the neural crest to the hypothalamus during vertebrate development, following the developing CN0 through the olfactory placode. The absence of LHRH cells in hypogonadism associated with Kallman's syndrome is believed to be the result of this migration failing, as shown by previous studies [59-61]. Another aspect of this illness is anosmia. Human Kallmann syndrome has been linked to deficiencies in the glycoprotein anosmin-1, which is encoded by the KAL1 gene [62,63]. These results point to a function of the CN0 in the maturation of the human hypothalamic-pituitary-gonadal axis [8,50]. Conversely, CN0 lesions have been found to play a limited role in modulating sensory processing during sexual interactions [20], and its projection to the retina in fishes has not been proven to play a role in reproductive behavior [64]. Current theory states that the CN0 would change the activity of the olfactory epithelium, making pheromones more detectable [65]. Research hypotheses suggest that the CN0 may trigger hormonal responses independently or in combination with other neuroanatomical circuits,

such as the kisspeptin neural network. These cells, which are mostly located in the preoptic and infundibular areas of the hypothalamus in females, exhibit an interesting sexual dimorphism that could have significant therapeutic ramifications [66]. The research on conditions associated with Cranial Nerve Zero is still limited, with much of the material being hypothetical or coming from animal studies. The nerve's small size and cryptic anatomical placement make it difficult to research in humans, restricting the availability of clinical data. However, advances in neuroimaging and molecular approaches may reveal fresh information on its functional and pathological roles in the future. More study is needed to determine if the terminal nerve contributes to specific clinical illnesses or if its failure occurs coincidentally in wider neurological disorders.

Clinical Aspects

For vertebrates to reproduce functionally, the GnRH neuronal circuit must mature normally. In humans, Kallmann syndrome and other forms of hypogonadism can be caused by disruptions in the nasal placode development and/or migration of the GnRH neurocircuitry. Hypogonadotropic hypogonadism, a rare genetic disorder known as Kallmann syndrome, usually results in anosmia and delayed sexual development [67,68]. Kisspeptin plays a crucial role in normal gonadotropin-releasing hormone physiology and in puberty, as clinical studies have shown that loss-of-function mutations in the kisspeptin 1 gene (KISS1) cause hypogonadotropic hypogonadism or precocious puberty (depending on the type of mutation) [69,70]. The KISS1 gene is mostly expressed in the hypothalamus of the central nervous system, where it serves as a crucial gatekeeper of the GnRH reproductive circuit and permits the integration of inputs from the central and peripheral neural systems [71]. Kisspeptin signaling is not limited to the hypothalamus region, either, as the KISS1 gene is expressed throughout the central nervous system (50). KISS1 has been found in the human substantia nigra, putamen, thalamus, medial and superior frontal gyri, cingulate, amygdala, medial and superior frontal gyri, nucleus accumbens, and Parahippocampal gyrus [72-75]. Furthermore, the limbic system's kisspeptin system plays a role in several circuits that govern olfaction, anxiety, fear, and other negative emotions [72,73,76]. In many species, kisspeptin's function in fear has not been thoroughly investigated. On the other hand, several zebrafish investigations have provided some preliminary evidence in favor of the theory that kisspeptin can reduce fear responses, perhaps through the serotonergic circuit [77,78]. The modulatory effects of kisspeptin on emotion have also been studied in relation to the serotonergic system. During an experimental swimming test, kisspeptin (dose dependent) administered intraventricularly reversed immobility, climbing, and swimming frequency in mice, indicating possible neuromodulatory effects [79]. Kisspeptin has also been linked to reward pathways and anxiety. Stress hormones are released by anxiety and are controlled by the hypothalamic-pituitary-adrenal axis. Nevertheless, peripheral kisspeptin treatment has no effect on this reaction in either humans or animals [80]. Remarkably, stress-induced plasma corticosterone in rodents reduces kisspeptin signaling in the hypothalamus, suggesting a potential link between the endocrinological components of anxiety and stress responses [81]. Furthermore, kisspeptin seems to counteract the physiological effects of morphine, indicating that it may play a role in controlling mesocorticolimbic dopaminergic activity [82]. Kisspeptin expression is functionally connected to the reward and addiction centers [83]. The regulation of mouse locomotion has long been associated with the dopaminergic projections that link the nucleus accumbens to the ventral tegmental region [84,85]. Kisspeptin may have a neuromodulatory effect on the mesocorticolimbic dopaminergic pathways, which attenuates locomotion [82]. Human kisspeptin receptor mRNA is reported to

be expressed in the prefrontal cortex [73]. A recent study involving peripheral administration of kisspeptin in healthy male individuals demonstrated increased prefrontal region activity (as assessed by functional magnetic resonance imaging) in response to negative-evoked visual stimuli. Furthermore, the researchers found that, according to psychometric tests, there was a decrease in depressive mood [86]. When considered as a whole, these results imply that the kisspeptin circuitry and signaling responses may modulate mood, anxiety, and reward through potentially affecting different limbic and paralimbic network architecture [72]. The brain's systems for processing sexual information are associated with a number of limbic and paralimbic structures. Human research has shown that the mechanisms leading to the autonomic responses required for the induction of sexual behaviors involve the sexual processing centers in the cingulate and thalamus (cognitive), amygdala and insula (emotional), and putamen and precentral gyrus (motivational). In related neural circuits, the kisspeptin neuropeptide and the kisspeptin neuronal network neural circuitry seem to have an interesting neuromodulatory role [86,87]. It is still unclear exactly what physiological processes kisspeptin uses to influence sexual behavior in addition to GnRH inductions. Nevertheless, the kisspeptin signaling pathways are intricate and require more research in regard to these characteristics, including possible interactions (i.e., anatomically, CN 0) [72].

Surgical Considerations

The olfactory tract and the placement of the CN 0 fibers are closely related. Its nerve components group together to form a dense plexus of fibers that are buried in the dura mater close to the CN I and other nerve fibers. This may help to explain why during imaging investigations, cranial surgery, and human dissections, CN 0 fibers have frequently been misidentified for CN I. In addition, the CN 0 fibers pass through the tiny cribriform plate (ethmoid bone) foramina on their way to the nasal cavity. Following that, the CN 0 fibers go down the nasal septum on both sides before bifurcating through the septal mucosa. Its fibers pass through the nasopalatine and olfactory nerve fibers in this area [4]. Therefore, surgeons should understand the anatomical complexity of CN 0 to overcome its damage, however, studies in the literature on how to overcome this damage are lacking. Therefore, it is recommended that further studies discussing this issue should be conducted. Important clinical considerations are raised by the anatomical placement of CN 0, particularly in relation to otorhinolaryngology (ENT) surgical procedures. Damage or lacerations to CN 0 during standard ENT surgical procedures may affect its potential functionality and structural integrity, given its potential neuro reproductive role. GnRH deficiency has been found to be caused by terminal nerve laceration in animal models. Nevertheless, no clinical research has been done on humans to support these results [4].

Conclusion

CN 0 is a neuroanatomical component that is largely conserved and functioning in most animals, including humans. However, neither the primary medical education materials (neuroanatomy, neuroscience, and clinical textbooks) nor the medical nor neuroscience communities (neuroendocrinology, neurology, and neuropsychiatry) usually identify and discuss CN 0. Recent studies have revealed that CN 0 is a well-established neuroanatomical structure that is important for the neurophysiology of human reproduction as well as the development of the GnRH system. In terms of embryology, it works in concert with other human CNs.

Conflict of Interest

The authors declare that they have no competing interests.

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