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Neurophysiological aspects of the trigeminal sensory system: an update

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Abstract: The trigeminal system is one of the most complex cranial nerve systems of the human body. Research on it has vastly grown in recent years and concentrated more and more on molecular mechanisms and pathophysiology, but thorough reviews on this topic are lacking, certainly on the normal physiology of the trigeminal sensory system. Here we review the current literature on neurophysiology of the trigeminal nerve from peripheral receptors up to its central projections toward the somatosensory cortex. We focus on the most recent scientific discoveries and describe historical relevant research to substantiate further. One chapter on new insights of the pathophysiology of pain at the level of the trigeminal system is added. A database search of Medline, Embase and Cochrane was conducted with the search terms 'animal study', 'neurophysiology', 'trigeminal', 'oral' and 'sensory'. Articles were manually selected after reading the abstract and where needed the article. Reference lists also served to include relevant research articles. Fifty-six articles were included after critical appraisal. Physiological aspects on mechanoreceptors, trigeminal afferents, trigeminal ganglion and central projections are reviewed in light of reference works. Embryologic and anatomic insights are cited where needed. A brief description of pathophysiology of pain pathways in the trigeminal area and recent advances in dental stem cell research are also discussed. Neurophysiology at the level of the central nervous system is not reviewed. The current body of knowledge is mainly based on animal and cadaveric studies, but recent advancements in functional imaging and molecular neuroscience are elucidating the pathways and functioning of this mixed nerve system. Extrapolation of animal studies or functioning of peripheral nerves should be warranted.

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Introduction

Knowledge about physiological aspects of the trigeminal system today is largely based on animal models (Akerman and Goadsby, 2015; Herta et al., 2017), cadaver studies (Ezure et al., 2001; Williams et al., 2003) or extrapolations from peripheral nerve functioning. Human studies are frequently limited to pathophysiology and lack proper study designs (Tanaka and Zhao, 2016; Goadsby et al., 2017). Neurophysiological research in this area is difficult due to the invasive character of most neurophysiological tests, the small caliber of fibers, high density of receptors, cross-connections between different cranial nerves, difficult access and ethical considerations. Advancements in imaging methodologies, e.g. diffusion tensor imaging and functional magnetic resonance imaging (fMRI), help us to understand the physiology and pathophysiology of the trigeminal system further (Mainero et al., 2007; Chen et al., 2016; Li et al., 2017). In this article, we aim to provide insights into and a thorough and clear overview of the most noteworthy studies and articles up to today on the neurophysiological sensory aspects of this complex neural system; important anatomic correlations will be reviewed where needed. The motor function of the trigeminal system and central nervous system functioning will not be extensively reviewed. A chapter on pathophysiology specifically at the level of the trigeminal nerve is added. To support the train of thought, we will start reviewing from the peripheral receptors going along the trajectory of the trigeminal up to the central nervous system.

In humans, the trigeminal system comprises the trigeminal ganglion (TG) having three divisions including ophthalmic, maxillary and mandibular nerves with sensory and motor functions. The trigeminal system peripheral receptors capable of receiving sensations are located in the trigeminal dermatomes of the face, the cornea, dura mater, tissues around mouth and nostrils, mucosal surfaces of the oral and nasal cavity including paranasal sinuses, teeth, gums and anterior two-third

of the tongue, as well as certain parts of the external ear (Baumel, 1974).

The trigeminal nuclei form the relay stations for their central projections. The ophthalmic, maxillary and mandibular nerves and their branches take somatosensory information from the head and face to the TG, where the roots of the TG laterally end up in mid-pons toward the trigeminal nuclei (Ezure et al., 2001). These nuclei are present in the midbrain (mesencephalic nucleus), pons (principal nucleus) and medulla/upper spinal cord (spinal nucleus). The sensory fibers coming from the TG are distributed to all three nuclei in a somatotopic way; their trajectory toward the spinal nucleus is known as the trigeminal spinal tract.

The distribution of different fibers shifts toward the nuclei and could explain certain pathological behaviors as illustrated by DaSilva and DosSantos (2012). Importantly, fiber demography and ratio, as well as the somatotopic arrangement of myelinated and non-myelinated fibers, has been implicated in several infectious and non-infectious injuries to the trigeminal system. These fibers are the conduit for the somatosensory information to the ventral posteromedial (VPM) nucleus of the thalamus, called the trigeminothalamic tract (Nash et al., 2010). After it synapses in the VPM it projects to the cortex of the postcentral gyrus (Corkin et al., 1970).

A histometric study from 1991 of three cadavers revealed the density and dimensional components of trigeminal fibers (Pennisi et al., 1991). The study showed that the number of fibers was highest in the mandibular division, i.e. 78 000, followed by maxillary with 50 000 and ophthalmic with 2600 fibers. The motor and sensory roots had 7700 and 170 000 fibers, respectively. Conduction velocities in the motor root were estimated at 55–68 m/s compared to 52 m/s for the sensory ophthalmic nerve and 54 m/s for the maxillary division. The ophthalmic and maxillary nerves showed a bimodal distribution of A δ and A β fibers, the last being predominant. Moreover, in the mandibular nerve, A α the ma were present to innervate the trigeminal muscles. Another noteworthy finding was the scarcity of perifascicular connective tissue of the sensory root, making it more susceptible to damage or compression.

Materials and methods

A literature search of the following databases was conducted: Medline, Embase and Cochrane, using the search terms ‘animal study’, ‘neurophysiology’, ‘trigeminal’, ‘oral’ and ‘sensory’. Articles were manually selected after reading the abstract and where needed the article. Reference lists also served to include relevant research. No constrictions were imposed based on publication year. However, we focused on recent advancements.

Results

Fifty-six articles were included after critical appraisal. Physiological aspects on mechanoreceptors, trigeminal afferents, TG and central projections are reviewed in light of reference works and recent research. Anatomic and embryologic insights are cited where needed. A brief description of recent discoveries of pathophysiology of pain pathways in the trigeminal area and dental stem cells is also discussed. Neurophysiology at the level of the somatosensory cortex is not reviewed. However, we do describe the projections toward the thalamus and primary cortex.

Embryologic considerations in the trigeminal system

The embryologic development of the TG and its branches at the second rhombomere is both from neural crest and placodal origin. Experimental animal studies have shown that the ganglion is formed by an anterior ophthalmic lobe and a posterior maxillomandibular lobe consisting of two cell types: large cells, heavily impregnated on silver staining, and small cells, which lightly stain. Previously, it was believed that placodal cells exclusively formed the ophthalmic lobe and the maxillomandibular lobe originated from mixed placodal and neural crest cell types; however, a study by Hamburger (1961) in chick embryos showed mixed origins for both lobes. This study confirmed the placodal origin of the large cell type and the neural crest origin of the small cell type, suggesting that the dual cellularity could be more important compared to the duality of lobe formation. Large cells are predominant and are functionally somatosensory exteroceptive, making the TG unique compared to the other cranial and spinal ganglia. The function of the small cells is still under debate but could be proprioceptive for the mastication muscles or special exteroceptive. Hamburger experimented with extirpation of the placodal or neural crest areas in chick embryos. He nicely demonstrated that even after extensive damage to the ganglia, the branching of peripheral nerves succeeded in almost all specimens and approached branching patterns of normal chick embryos. This argues for strong peripheral signaling and routing

of the branching process. In addition, his experiments confirmed the independent formation of ganglia when extirpation of neural crest or placode was performed; however, it seems that the neural crest cells, which are located centrally in the ganglion, guide the placodal cells in the development of the TG and act as a center of aggregation to induce the fusion of the ophthalmic and maxillomandibular lobe. Intriguingly, Hamburger also observed after extirpation of the placodal area new formation of placodal type cells, suggesting regeneration potential of the placode. Other studies showed the importance of the neural crest cells in correct migration of the placodal cells and axons to their target innervation fields (Barlow, 2002). The molecular mechanisms steering the cranial nerve development are being decrypted in the last decade. Hox genes, which are clustered in four groups, play a crucial role in rhombomere identity and neuronal signaling. A mouse model showed anteroposterior and dorsoventral differences in expression of the several Hox genes: anteroposterior levels group neurons to a specific cranial nerve, and dorsoventral levels influence the neuronal cell class such as motor versus interneuron (Cordes, 2001). Temporal and spatial expression patterns are paramount for correct nerve development. Considering more than 1000 different neural cell types in humans, we have only begun to understand the underlying cellular and molecular developmental pathways.

Somatosensory receptors of the trigeminal system

The three divisions emerging from the TG are involved in the somatosensory functions that inform the body about the external environment through several modalities including cutaneous sensory functions such as touch, temperature, pressure, vibration and proprioception (Stewart, 1989; Durick, 1995).

In describing the microscopic anatomical features of the sensory nerve endings, it is important to know about the various types of receptors that help in responding to various stimuli. Mainly there are three types of receptors in mammals in the areas being covered by the trigeminal system (Byers and Dong, 1989; McKemy et al., 2002; Trulsson and Johansson, 2002; Haggard and de Boer, 2014):

1. Exteroceptors: providing information from the environment,
2. Enteroceptors: providing information from internal organs,
3. Proprioceptors: providing information from the musculoskeletal system (position sense).

A recent study has summarized the types of mechanoreceptors, afferent types and their morphologies (Haggard and de Boer, 2014). Based on morphological characterization, the mechanoreceptors of soft tissues in the oral cavity and mucosal surfaces are Merkel cells (slow adapting type I), Ruffini endings (slowly adapting type II), Meissner corpuscles mainly perioral (rapidly adapting type I) and Pacinian corpuscles (rapidly adapting type II). Other receptors are Krause cold sensing receptors and free nerve endings that perceive superficial pain and tactile sensations.

Of importance, the periodontal ligament (PDL), tongue and mucosa have mainly Ruffini ending receptors (Trulsson and Essick, 2010). The periodontal afferents exhibit high sensitivity when exposed to low forces of the jaws. In parallel with true proprioceptors, they function as proprioceptors during the first contact of teeth, grinding food and speech. These receptors code force load and direction. When biting through food with high forces, less information is encoded, reducing the proprioception in these circumstances (Trulsson and Johansson, 2002). The importance of these periodontal afferents becomes apparent after tooth extraction or in edentulous patients where their function is lost. However, after implant placement, we can see a mechanism of 'osseoperception' where sensory-motor control partially recovers (Jacobs and Van Steenberghe, 2006). This can be explained by the presence of intraosseous and periosteal receptors near the implant sites. Other factors such as cortical plasticity and adaptation from different receptors are likely to participate in regaining sensory input. True proprioceptors have been reported in the sensory trigeminal transmission process: muscle spindles and Golgi tendon organs are found in several muscles of the trigeminal system and temporomandibular joint capsule; however, research on this matter is scarce (Davidson et al., 2003; Österlund et al., 2011; Saverino et al., 2014).

It has been reported that the periodontal Ruffini endings after injury regenerate faster when compared with such receptors in other parts of the body. The regeneration of Ruffini endings following cross-anastomosis with an inappropriate nerve was evaluated by immunohistochemistry for protein gene product 9.5 and S-100. Both these proteins are constitutively expressed by these receptors (Imai et al., 2003). The mechanoreceptors found in the dental pulp region are predominantly Pacinian corpuscles (rapidly adapting type II).

The nociceptor has mainly free nerve endings belonging to A and C afferent types and is widely distributed in the head and neck region. This will be discussed later on when reviewing the pathophysiology of pain.

The signals originating from the trigeminally innervated area are varied based on the tissue of origin and receptor type. Particularly, the tongue has a different distribution and types of mechanoreceptors compared with other regions. The response threshold varies, for example: mechanoreceptors of the deep tongue area are slowly adapting. Their activity persists during tongue movement when it is not in contact with anything (Trulsson and Essick, 2010).

To evaluate the distribution of receptors on the tongue, stereognostic evaluation of the tongue has been reported in various studies. An extensive review focusing on stereognostic methodologies alludes to three types of receptors in the oral mucosa. The sensory receptor on the tongue mucosa differs from the palate and to a lesser extent by the teeth and their PDLs (Jacobs et al., 1998). Based on the available scientific data, the oral somatosensory awareness theoretical model consists of three stages in sensory processing, including somatosensation, somatoperception and somatorepresentation. Furthermore, the mouth has a unique multisensory setup, where visual sensation is almost lacking with somaesthesis characteristics linked with evaluative properties (Haggard and de Boer, 2014).

Trigeminal ganglion and roots

After a sensory input triggers an action potential, the information is conveyed to the TG residing in a pouch-like structure known as cavum trigeminale (Meckel's cave). The three sensory divisions of the trigeminal system enter into the ganglion at the convex margin and are somatotopic organized within the TG. The sensory root emerges from the ganglion at the concave margin and attaches to the anterior pons surface through the middle cerebellar peduncle.

Transmission and processing of sensory signals by the three divisions having a joint gateway, the TG, is an active area of investigation. Histometric studies showed large differences in neuronal count between individuals ranging from 20 159 up to 156 702 nerve cells; the clinical relevance is yet not known (Ball et al., 1982). Various molecular moieties involved in the processing of signaling are being evaluated. A study evaluated the presence of beta-2 subunit of the mammalian brain voltage-gated sodium channel (SCN2B) in the rat TG and found its presence in various types of sensory neurons present in the TG (Shimada et al., 2016). Similarly, several other molecular moieties involved in nociception such as bradykinin receptors (B1 and B2) and purinergic receptor P2Y12 have been reported in the TG contributing toward its normal and pathophysiological processes (Kawaguchi et al., 2015a,b). Calcitonin gene-related peptide (CGRP), substance P and vanilloid receptor 1 have been identified and participate in nociception, see below (Hou et al., 2002, 2003).

Recent studies have defined the ultrastructure components of the TG further. It has been reported that telocytes are present within the ganglion. These mesenchymal stromal stem cells are CD34 positive suggesting their regeneration capabilities in the vicinity of neuronal-glial units (Rusu et al., 2016). Together with the glial satellite cells (GSC), they play an important supporting role for the TG neurons as well as responding to peripheral inflammation or injury.

Trigeminal nuclei and their projections

The human trigeminal system comprises three sensory nuclei and one motor nucleus (Sherwood et al., 2005). Sensory fibers coming from three divisions have their cell bodies in the TG. After that, the sensory and motor root enter the central nervous system through the middle cerebellar peduncle of the pons. At this position, there is segregation of all sensory fibers (DaSilva and DosSantos, 2012). The proprioceptive fibers pass through the TG without having their cell bodies there, but continue to the mesencephalic nucleus where their neurons are located; touch, pressure, and vibration conveying fibers move toward the principal sensory nucleus. Nerve fibers involved with temperature and pain sensation have a relatively smaller diameter than the other fibers and make their way to the spinal nucleus, usually designated as the spinal tract of trigeminal.

The trigeminal motor root has its distribution with the mandibular division. It has its own seperate motor nucleus where the primary neuron synapses. Several studies have focused on the functional and physiological aspects of the trigeminal nuclei. Notably, the motor nucleus received relatively more attention due to a role in ferrying the poliomyelitis virus (Williams, 1947). The polarity and projections of sensory and motor nerve fibers of the trigeminal system were initially defined through animal studies but can now be studied through fMRI and diffusion tensor imaging (Carpenter and Hanna, 1961; Erickson et al., 1961). The trigeminal sensory nuclear complex comprises four nuclei: main sensory nucleus (principal nucleus), oralis nucleus, interpolaris nucleus and caudalis nucleus. As in the TG, there is a somatotopic distribution of the fibers (Capra and Dessem, 1992). The principal nucleus receives tactile fibers with small receptive fields after synapsing secondary fibers mainly project to the

VPM nucleus of the thalamus. In contrast, the nerve fibers arriving at the oralis nucleus have large receptive fields and convey intra-oral sensory information. Cross-innervations with other nuclei and the spinal cord were observed in rat studies. The interpolaris nucleus has projections from intra-oral and skin tissue representing mechano- and nociceptors. Pathways to the central nervous system are diverse and broad; several projections to the cerebellum and superior colliculus are still under debate. The caudalis nucleus receives myelinated and unmyelinated afferents from all trigeminal divisions and projects mainly to the VPM; however, broader connections have been discovered. It receives most of the nociceptor inputs. The mesencephalic nucleus plays an important role in masticatory control and reflex arches. It projects to the VPM of the thalamus but has cross-connections with the principal nucleus which could assist in proprioception.

Trigeminal nuclei utilize a secondary ascending system also known as the ascending tract of the trigeminal nerve toward the thalamus and enter at the nucleus VPM of the thalamus (Yokota et al., 1988; Yoshida et al., 1991; Haque et al., 2012). The somatosensory information transmitted to the thalamic region travels in a bifurcated manner. The pain and temperature including deep pressure sensory messages are transmitted to both ventral posterior lateral (VPL) and ventral posterior inferior intralaminar nuclei of the thalamus, whereas the tactile, vibratory, muscle tensile and joint position somatosensory messages only end up in the VPL nucleus.

Molecular physiology of trigeminal nuclei is an active area of investigation. It has been reported that the SCN2B extends from the TG to the sensory nuclei of this system (Shimada et al., 2016). The transient receptor potential vanilloid type 1 is observed in the TG and spinal nucleus (Quartu et al., 2016).

Pathophysiology of injury and pain in the trigeminal sensory system

To develop a realistic integrated model, dissecting the mechanisms at molecular levels is important. Most information today is obtained by studying the pathophysiological molecular changes; however, the study of structural changes after nerve injury is under-evaluated. An extensive review by Holland (1996) describes morphological structural and electrophysiological changes after peripheral nerve injury including the chorda tympani nerve. Crush injuries were compared to transections for the chorda tympani, lingual nerve, inferior alveolar nerve (IAN), mental nerve, infraorbital nerve and ophthalmic nerve. Furthermore, changes of the TG and nuclei after injury were described. Crush injuries recovered faster with less central disruption than transection injury. All nerve injuries resulted in lower conduction velocities and sensory impairment. Reinnervation by other nerves was observed in rat studies. When re-apposition of cut ends is performed no cell death occurred; however, proximal degeneration and distal Wallerian degeneration were seen as well as axonal sprouting. Degenerative changes of brainstem nuclei were observed. Epineural suturing resulted in fastest recovery and less structural changes. If neural gaps were needed to be covered, stretching the nerve after release from its connective tissues resulted in better functional results compared to neural grafting. Nerve growth factor (NGF) plays an important role in neural guiding of axonal growth to its end target. NGF is also upregulated in the TG and nucleus. Neuropeptide Y expression in ganglion cells increases in response to injury as well as substance P. CGRP immunoreactivity is decreased in the caudal parts of the trigeminal nucleus.

Along with these thoughts, a study on human lingual nerve neuromas showed association with two proteins mainly Nav 1.8 and 1.9, which are voltage-gated sodium channels. The expression levels of Nav 1.8, which is supposed to be a sodium channel subtype, is linked to severity of pain (Bird et al., 2013). Furthermore, Nav 1.9 knockout mice models do not develop orofacial pain in a trigeminal neuralgia model (Luiz et al., 2015). Another study reported changes in the expression pattern of growth-associated protein 43 in the TG and transected region of IAN. Through compound muscle action potentials of the digastric muscle, the functional recovery of the nerve was evaluated. An increased myelination and axon density of regenerated fibers was associated with the overall recovery process (Ceber et al., 2015).

Despite structural differences in the areas covered by the trigeminal somatosensory system, it has similarities with the somatosensory system of the rest of the body. For example, both systems use a common channel, the Transient Receptor Potential Cation Channel Subfamily M member 8 (TRPM8), for recognizing cold sensations. However, the study of Zuo et al. (2013) related the TRPM8 with allodynia and hyperalgesia in an infraorbital chronic constrictive nerve injury rat model.

Intra-TG communication between nerve cells and GSC are being decrypted showing the mechanisms behind the response to peripheral inflammation, nerve injury and neuropathic pain (hyperalgesia, allodynia). After peripheral injury adenosine triphosphate (ATP) signal transduction induces activation of both cell types further contributing in an inflammatory cascade (Goto et al.,

2016). The vesicular nucleotide transporter regulates ATP release and could be a potential pharmacological target. Another channel, the subunit α2/δ-1 of the L-type channel of the dihydropyridine receptor, has shown to be highly selective for gabapentin and is abundantly present in the TG neurons. The subunit is massively upregulated after peripheral nerve damage. Other key molecules in pain transmission are CGRP and nitric oxide that are released after inflammation occurs, causing upregulation of neurokinin 1 (NK1) receptors. This upregulation causes a higher excitability of the TG neurons. The NK1 receptors are also present in the glial cells. Paracrine effects cause simultaneous release of IL-1 β that in turn suppresses voltage-gated potassium channels through protein kinase C/G-protein-coupled pathways, which ultimately increases the neural excitability. Studies showed the desirable effect of NK1 blockade at the TG to prevent central sensitization. Eugenol is a potential inhibitor of the voltage-gated potassium, calcium and sodium channels as well as the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. The HCN channels have been identified as key factors in mechanical allodynia (Yeon et al., 2011).

Looking at the central level we only start to understand the neurophysiology of pain perception and the important structural and molecular changes when acute pain passes into a chronic pain condition causing central sensitization (Sandkühler, 2009; Woolf, 2011). Stimulation of C-fibers releases amino acids and neuropeptides (substance P, galanin, CGRP, endomorphins, nociceptin, dynorphin A) in addition to posttranslational modifications such as phosphorylation of extracellular receptor-activated kinases. The chronic constriction model in rats revealed a decrease in substance P immunoreactivity 60 days after injury in the spinal dorsal horn bilaterally. Neuropeptides changes were observed up to 100–120 days after injury. GABA-immunoreactive neurons decline starting 3 days after injury and continue to decline bilaterally. Normal levels are seen 8 weeks after injury. The same is observed for glutamate decarboxylase immunoreactive cells. In combination with synaptic changes, e.g. long-term potentiation (LTP), central sensitization gradually becomes clinically apparent and reduces the chance for reversal. To summarize, we describe the electrophysiological pathway starting at the nociceptive fiber projecting to the TG after action potential firing. Excitatory postsynaptic potentials induce presynaptic transmitter release as well as an enhanced postsynaptic transmitter effect: LTP. Membrane excitability is modified causing lower resting membrane potentials and lower thresholds for action potential discharge. Sodium currents increase with a decrease in potassium currents. Synaptic inhibition by inhibitory interneurons is reduced by less transmitter synthesis and vesicular transport in addition to postsynaptic reduced receptor sensitivity. Inhibitory potentials can be reversed into an excitatory signal. The number of inhibitory synapses reduces in symphony with reduced release of inhibitory neurotransmitters. Descending tracts facilitate further in the release of postsynaptic potentials. Sprouting starts enhancing excitatory synapses further. Polysynaptic pathways start to form, causing epileptiform activity with burst-like discharges and synchronization. This increased excitability and synaptic plasticity leads to central sensitization causing hyperalgesia, allodynia, hyperpathia and aftersensations. Importantly, studies showed that this process starts as early as a couple of days after injury or inflammation and cascades further even when the nociceptor input has halted. This altered pain perception and processing has been evaluated in other pain conditions such as fibromyalgia, migraine-type headache, temporomandibular disorders, rheumatoid arthritis and others. Current therapies for these conditions target the peripheral pathologic pathways; however, new central-acting therapeutic options must be considered as many of these patients develop a chronic pain condition with unsatisfactory response to standard medications.

Repair mechanism of the nerve in the tooth pulp

After nerve injury occurs and irreversible damage is evident, limited treatment options are available at present. However, in the near future, the use of dental stem cells could provide a solution. We give a short overview of current knowledge of this matter. The presence of neuro-odontoblast synapses at the interface between the sensory nerves in the pulp and the odontoblast neurites implies that the odontoblast is able to act as a specialized receptor cell of the trigeminal system in the dental pulp. During ischemia or after avulsion of a tooth, these odontoblasts can undergo irreversible damage together with the other components of the dental pulp. The pulp chamber of tooth provides an environment where human stem cells respond to noxious stimuli with repair mechanisms. Migration of stem cells to the site of injury for differentiation into odontoblast-like cells is an important event for cell recruitment during regeneration (Martens et al., 2013). Multiple subpopulations of dental tissue-associated mesenchymal stem cells (MSC) can be isolated from the tooth and tooth-associated tissues. These include the stem cells from human exfoliated deciduous teeth. Tooth

germ progenitor cells and dental follicle precursor cells form the developing tooth. Alveolar bone-derived MSCs and gingival MSCs from the tooth-surrounding tissues and in and around the tooth itself periodontal ligaments stem cells, stem cells from the apical papilla and dental pulp stem cells (DPSCs) can be isolated. In the adult teeth, human DPSCs (hDPSCs) are activated after ischemia, after severe injury caused by mechanical trauma and dentinal degradation by bacteria. Severe damage to the tooth requires reparative dentinogenesis in which new dentin-secreting odontoblasts are formed out of hDPSCs. Studies have indicated that hDPSCs are not only capable of differentiating into odontoblasts *in vitro*, but that they are also able to form an organized dentin-pulp-like complex lined with odontoblast-like cells when seeded onto a scaffold and transplanted into immunocompromised mice. These observations suggest the potential role of hDPSCs in the repair of diseased and damaged dental tissues. Besides applications in tooth regeneration and repair, hDPSCs could also be clinically applied in other domains since they are capable of differentiating into functional neurogenic cells showing electrophysiological currents and the expression of neuron-related surface markers. Furthermore, since hDPSCs are isolated relatively easy from extracted third molars without any risk to the donor, have a higher proliferative and immunomodulatory capacity than bone marrow-derived MSC and retain their multilineage differentiation capacity after cryopreservation, these stem cells display several advantages over bone marrow-derived MSC with regard to future *in vivo* use and clinical applications in damaged nerve tissue.

Conclusions

The current body of knowledge is mostly based on animal or cadaveric studies. Moreover, neurophysiological aspects are under-investigated compared to pathophysiology. With the advancements in imaging technology, latest methodologies to study the behavior of a single nerve fiber through electromyography and availability of biomarkers, new opportunities to use integrated methods for studying various physiological aspects of complex neurological systems are abundant. This article describes the current advancements related to deciphering the elusive physiology of the trigeminal sensory system. We aimed to present an understandable overview of the current and evolving landscape of neuromolecular research supported by important historical reference works. Extrapolation of animal studies or functioning of peripheral nerves should be warranted as the trigeminal system is different on structural and molecular levels compared to peripheral nerves and across species.

Conflict of interest statement: The authors have no conflict of interest to declare.

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