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ORIGINAL RESEARCH

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Frey's syndrome: A review of the physiology and possible role of neurotrophic factors

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Abstract

Objectives: Frey's syndrome (FS) describes the phenomenon of gustatory sweating and is a cause of significant social embarrassment for sufferers. It has been attributed to aberrant growth of parasympathetic salivatory fibers in the auriculotemporal nerve toward overlying sweat glands. However, the exact mechanism behind this growth is unknown. This review aims to expand and elucidate the theory of aberrant regeneration in FS.

Methods: A review of the recent literature on nerve regeneration was conducted in order develop further insights into the etiology of both adult onset and pediatric FS.

Results: Neurturin, a neurotrophic factor released by both salivary and sweat glands, was identified as a possible key player in the etiology of FS.

Conclusion: Further research into the role of neurturin could help to elucidate the pathogenic mechanisms underlying the condition and might reveal neurturin to be a potential target for pharmacological intervention.

Level of Evidence: NA (Basic Science Review).

KEYWORDS

auriculotemporal nerve, Frey's syndrome, neurology, neurotrophic factor, neurturin

1 | INTRODUCTION

Frey's syndrome (FS), also known as auriculotemporal or gustatory sweating syndrome, describes transient sweating or flushing over the auriculotemporal region during eating.[1] Symptoms of excess sweating usually occur a few seconds after mastication, and last for a few minutes.[2] FS is most commonly seen after parotidectomy, and intraoperative damage to the auriculotemporal nerve (ATN) is thought to trigger this syndrome.[2] The most common explanation of FS is aberrant regeneration of autonomic fibers within the ATN toward nearby sweat glands,[3] resulting in gustatory sweating rather than gustatory salivation. However, the exact method by which these nerves regenerate erroneously is yet to be established.[4] FS can also present in early childhood, although its etiology and incidence in this population is currently unknown.[5]

Aberrant nerve growth resulting in a functional, yet abnormal reflex is quite unusual in nature. A similar phenomenon is seen in crocodile tears syndrome, where mastication triggers lacrimation in sufferers.[6] These syndromes highlight the sometimes-imperfect nature of nerve generation and regeneration. Understanding how this process of erroneous innervation may occur will help define the process of nerve development itself. Therefore, this review aims to re-evaluate the etiology of FS to identify the precise mechanism behind the aberrant generation of nerves in pediatric and adult FS.

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International Review Board approval was not required for this article as it is wholly literature based.

2 | REVIEW OF THE PHYSIOLOGY OF FS

The involvement of the ATN in FS was first suggested by Lucja Frey in 1923. She hypothesized that parasympathetic fibers within the ATN must grow to innervate sweat glands after discovering that drugs which inhibited the parasympathetic system also inhibited the gustatory sweating reflex.[7] In 1927, Andre Thomas elaborated on the mechanism of FS with his theory of aberrant regeneration,[8] later reinforced by Ford in 1933.[6] This theory postulates that sectioned parasympathetic fibers within the ATN regenerate in sympathetic pathways.

This theory of aberrant regeneration is widely accepted[4,9,10] and conforms with the period of latency before symptoms are noted. However, there are still some unanswered questions surrounding this theory. For instance, this theory suggests that parasympathetic fibers occasionally regenerate accidentally along sympathetic pathways, yet Minor's test shows the incidence of FS after parotidectomy to be around 95%.[11] Minor's test involves applying iodine and starch to the temporal region of the face and giving the patient a salivatory stimulus to chew such as a lemon sweet.[2] If gustatory sweating occurs, the iodine and starch mix together resulting in a purple color change. The test is very sensitive and picks up subclinical levels of gustatory sweating, indicating that after parotidectomy FS nearly always occurs. This high incidence of FS suggests that parasympathetic fibers must somehow be drawn to the sympathetic pathways rather than accidentally regenerating along them. Furthermore, the theory of aberrant regeneration does not explain the incidence of pediatric FS in otherwise healthy children.

There are a few different theories on how gustatory sweating may occur which do not involve the aberrant regeneration of parasympathetic ATN fibers. One theory is that gustatory sweating is a pre-existing reflex, which is usually inhibited by the ATN.[12] If this theory was correct, one would expect symptoms to present as soon as the ATN was cut and regress once it had regenerated. However, the opposite is the case as symptoms present after a period of latency during which the ATN regenerates.[13]

Another theory is that when the parotid gland is stimulated scar tissue causes aggravation of sympathetic nerve endings, leading to sweating over the region of the gland.[4] However, FS has been shown to occur when the whole parotid gland has been excised, so could not itself excite sympathetic nerve endings.[13] A more convincing theory is that sectioned parasympathetic nerve endings could catch on the scar tissue when stimulated and themselves cause the release of acetylcholine and sweating in the nearby glands.[4,12] A teenage girl developed slight gustatory flushing at 13 after fracturing her mandibular condyle 7 years prior and in this instance the theory of scar irritation caused by pubescent shift in mandibular bone structure is more plausible than extremely late onset aberrant regeneration.[14] However, this theory does not explain why pediatric FS occurs in 2-month old babies without previous trauma or scar formation.

The most plausible cause of FS remains the theory of aberrant regeneration, however, this theory needs to be expanded to explain the high incidence of FS after parotidectomy and the incidence of FS in children. Neurotrophic factors could provide the missing link in this theory and explain why parasympathetic fibers are attracted to sympathetic pathways.

3 | POSSIBLE ROLE OF NEUROTROPHIC FACTORS IN FREY'S SYNDROME

Neurotrophic factors play a key role in the development of the nervous system. In utero the target (the gland, muscle, or tissue a neuron innervates) determines the number of neurons supplying it by regulating the cell death of neurons. This is achieved through the target releasing a limited amount of "neurotrophic factor" which is necessary for the survival of the neurons. The neurons then compete for this factor and only those that receive it survive and innervate the target, whilst the rest die through programmed apoptosis.[15] The number of nerve fibrils which originally project from a ganglion far exceed the number that eventually come to innervate the target, thus programmed apoptosis is a natural part of neuronal development.[16]

Further experiments have shown, however, that these neurotrophic factors have a more complicated role than first expected.[17] Growth cones on the end of developing neurons receive these factors or "axon guidance cues" and respond according to the receptors the neurons express.[17] These factors have differing roles in neuron development, such as survival and maintenance of the neuron, influencing neurotransmitter expression and guiding growth of the neuron toward its target.[17]

The group of neurotrophic factors important to note for the development of the autonomic system, particularly in the light of FS, are the glial cell-derived neurotrophic factors (GDNFs).[18] The GDNF family ligands are the group of neurotrophic factors that bind to the GDNF family receptors (GFRs) on developing neurons. The ligands so far discovered are GDNF, neurturin (NRTN), artemin, and persephin. These bind to GFRα one to four respectively.[18] These factors are important for the growth and target innervation of the autonomic nervous system and thus the neurons concerned in FS.

4 | THE PARASYMPATHETIC SYSTEM

Experiments have identified the neurotrophic factors responsible for the development and maintenance of cranial parasympathetic ganglia and neurons.[19-21] These have found that initially GDNF, which binds to GFRα1 receptors, is necessary for the formation of the ganglia.[21] Following this, NRTN which binds to the GFRα2 receptor, is fundamental for the growth and target innervation of parasympathetic neurons emerging from these ganglia.[20] In GFRα2-deficient mice, there was significant reduction in parasympathetic innervation to the

parotid gland, but not the number of neurons in the otic ganglion.[20] In other words, the parotid gland releases the neurotrophic factor NRTN, which is necessary for the growth of parasympathetic neurons from the otic ganglion.

Indeed, this has been further proved through research into NRTN gene therapy as a protective agent of parasympathetic innervation to salivary glands during radiotherapy.[22] A common side effect of radiotherapy used to treat head and neck cancer is salivary gland hypofunction. Research suggests that if a NRTN adenovirus is given to the patient after radiotherapy, the salivary glands will produce NRTN mRNA. NRTN then promotes growth and maintenance of parasympathetic secretomotor neurons and protects the glands from hypoplasia.[22] This suggests that NRTN is a powerful agent in the protection of parasympathetic secretomotor fibers and has even been recommended to aid their recovery after nerve injury.[21] Therefore, if NRTN was released after nerve damage, it could be suggested that parasympathetic neurons might regenerate toward the direction of its secretion.

5 | THE SYMPATHETIC SYSTEM

While the parasympathetic system is characterized by cholinergic neurons, the sympathetic system is typically adrenergic.[16] Sweat gland innervation, however, is the exception to this rule as sweat glands are innervated by cholinergic sympathetic neurons.[2] This is why FS results in sweating if parasympathetic cholinergic neurons aberrantly regenerate to innervate sweat glands.[12]

It was originally thought that all the developing sympathetic neurons exhibited an adrenergic phenotype and switched to cholinergic once they had contacted sweat glands.[23] New research, however, suggests that a proportion of developing neurons in the sympathetic ganglia expresses a partly cholinergic and partly adrenergic phenotype.[24] This cholinergic phenotype is stabilized as the neuron develops through the influence of neurotrophic factors.[25] When the cholinergic neuron reaches the sweat gland, it is further stabilized through depolarization of the neuron.[26]

Research has proven NRTN to be one of the factors that aid stabilization and target innervation of cholinergic sympathetic neurons.[25] In GFRα2 knockout mice, there was a 50% to 70% reduction in cholinergic innervation to sweat glands.[25] Thus NRTN, released by sweat glands and supplying vessels, is vital for the stabilization and final target innervation of cholinergic sympathetic neurons.

6 | IMPLICATIONS FOR FREY'S SYNDROME

From the above evidence, it can be concluded that NRTN is released by sweat glands and causes growth, development, and target innervation of parasympathetic secretomotor neurons. Therefore, NRTN could provide the missing link between sweat glands and nearby salivatory neurons in FS. Sweat glands will release NRTN both in utero and after damage or injury, such as after parotid gland surgery.[27] Furthermore, when a nerve is sectioned the Schwann cell bands that remain after Wallerian degeneration will also release neurotrophic factors such as NRTN.[28] Therefore, it could be suggested that NRTN will be secreted if the ATN is damaged or injured such as in adult onset-FS.

Minor's test demonstrates that the incidence of FS after parotidectomy is high, suggesting that to some degree parasympathetic fibers nearly always aberrantly regenerate toward sweat glands.[11] During the operation, all or part of the parotid gland is excised and the neurons supplying it are sectioned.[29] Since their target organ is removed, these neurons should die through apoptosis. However, the sweat glands are now directly above the sectioned parasympathetic neurons. Thus, it could be hypothesized that these neurons will receive NRTN released by denervated sweat glands and regenerate toward them. This could explain why the incidence of FS after parotidectomy is so high.

7 | IMPLICATIONS FOR PEDIATRIC FREY'S SYNDROME

Pediatric FS can be split into unilateral and bilateral forms. Unilateral pediatric FS is highly associated with instrumental delivery,[30] during which pressure is exerted on the temporal region of the face. This could damage the underlying structures such as the facial nerve and explains the occurrence of transient facial nerve palsy seen after forceps delivery.[31] The pressure is rarely enough to cause nerve palsy though it can commonly cause facial marks and abrasions.[32] However, even light pressure on this area could damage superficial structures such as sweat glands. In theory, these glands would then release NRTN and stimulate nearby salivatory fibers to generate aberrantly toward them.

In cases of bilateral FS, there is often no history of injury to the ATN. This might suggest that in this situation the nerves grow aberrantly without mechanical force. One possible explanation for this might be that if sympathetic neurons fail to innervate sweat glands then parasympathetic salivatory neurons "take over" to innervate them instead. This might occur if sympathetic neural crest cells were delayed in migrating such as in familial dysautonomia[33,34] or if there was a lesion in the sympathetic cervical trunk as seen in some cases of Harlequin syndrome.[35] Indeed, a patient with Harlequin syndrome who had decreased thermoregulatory flushing on the left side of the face, also had a marked increase in gustatory flushing on the same side.[35] This demonstrates that in the absence of sympathetic innervation parasympathetic secretomotor fibers will grow to innervate sweat glands and associated vessels.

8 | DISCUSSION AND FUTURE DEVELOPMENTS

During neuronal development, neighboring target organs will often produce the same neurotrophic factor as each other.[15] Therefore,

why does the aberrant generation only occur in FS? The answer is that many factors may contribute to enabling aberrant generation in FS, making it unique in circumstance. For example, only 4% of sympathetic neurons are cholinergic,[36] so parasympathetic neurons could only functionally innervate 4% of sympathetic targets (sweat glands). Furthermore, sweat glands are densely innervated by a plexus of neurons and when denervated demonstrate reactive hyperinnervation,[37] resulting in hyperhidrosis. This hyperinnervation is seen in neuropathic disorders such as diabetes (where FS also presents)[37] and disorders of sympathetic innervation such as familial dysautonomia.[33,34] Therefore, when sweat glands in the facial region become denervated, they will release high volumes of neurotrophic factor, which results in the growth of nearby parasympathetic secretomotor neurons and the common cholinergic phenotype results in a functional yet abnormal gustatory sweating reflex.

Many surgical techniques have been proposed to prevent FS occurring which aim to create a barrier between sectioned parasympathetic fibers and overlying sweat glands. The most successful methods at preventing FS are temporoparietal fascial flaps, acellular dermal matrices and free fat grafts, with more traditional techniques such as the sternocleidomastoid and superficial musculoaponeurotic system flaps proving less efficient barrier techniques.[38] Recently, a new technique involving a de-epithelialized sub mental flap has been recommended for reconstruction of parotidectomy defects but has not yet been tested as a method to prevent FS.[39] It could be suggested that creating a physical barrier reduces the incidence of aberrant regeneration by blocking the growth of parasympathetic neurons toward sweat glands. However, there is little existing evidence of the long-term efficacy of these techniques, therefore, it cannot be known whether they prevent FS or simply delay its onset.[11,40] In theory, if either the release of NRTN or its attachment to receptors on salivatory neurons could be inhibited, then FS could be effectively prevented rather than simply delayed.

NRTN provides an explanation for the incidence of FS in children and adults, adding to the theory of aberrant regeneration rather than contradicting it. However, there have been no experiments on the possibility of aberrant regeneration of these neurons following NRTN release from nearby sweat glands. Further research into this possibility would have to occur before definitive conclusions could be drawn. Importantly, however, this theory does provide new pharmacological targets (namely, NRTN and/or its receptor GFRα2/RET) for the prevention of FS.

9 | CONCLUSION

FS is a fascinating neurobiological phenomenon, which has never before been studied in this context. NRTN has been identified as a common factor in both sympathetic innervation of sweat glands and parasympathetic innervation of salivary glands.[20,25] Therefore, it may provide the missing link in the theory of aberrant regeneration for pediatric and adult FS. Further research on the influence of NRTN is required to test this hypothesis.

10 | IN MEMORY OF LUCJA FREY (1889-1942)

Lucja Frey lived and studied in what is now Lviv, for much of her life, moving briefly to Warsaw to complete her medical degree in 1923, the same year she published her paper on FS.[41] She was the first female academic neurologist in the whole of Europe and published 43 papers on topics such as the neuropathology of multiple sclerosis, topography of the brain and Charcot joints.[2] Tragically, following invasion by Nazi soldiers in 1941, she was forced to move to the Lwow ghetto and on 20 August 1942, she and all the other workers and patients in the ghetto hospital were shot.[41] Her husband and two young children also died during the war. Much of her work was destroyed but her legacy lives on in the syndrome named after her, Frey's Syndrome. She continues to inspire young female scientists across the globe nearly one hundred years after she published her first paper.

CONFLICT OF INTEREST

There are no conflicts of interest to declare.

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