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Photic sneeze reflex: another variant of the trigeminocardiac reflex?

Tumul Chowdhury[1], Zohara Sternberg[2], Eugene Golanov[3], Riccardo Gelpi[4], Thomas Rosemann[5] & Bernhard J Schaller*[,5]

[1]Department of Anaesthesiology & Perioperative Medicine, University of Manitoba, Winnipeg, MB, Canada
[2]Department of Neurology, Buffalo University of New York, NY, USA
[3]Department of Neurosurgery, Houston Methodist Hospital, Houston, TX, USA & Weill Cornell Medicine, NY, USA
[4]Department of Cardiovascular Pathophysiology, School of Medicine, University of Buenos Aires, Buenos Aires, Argentina
[5]Department of Primary Care, University of Zurich, Zurich, Switzerland
*Author for correspondence: bernhardjschaller@gmail.com

The photic sneeze reflex (PSR) is a condition of uncontrollable sneezing episodes in response to bright light. This reflex often manifests as a mild phenomenon but may cause devastating consequences in some situations (aeroplane pilots, car drivers, etc.). Its exact mechanism is poorly understood. Interestingly, the roles of the fifth and tenth cranial nerves, brainstem nuclei and inciting patterns closely mimic a well-known brainstem reflex, known as the trigeminocardiac reflex (TCR). In this critical review, we hypothesize that the PSR can be a variant of the TCR. This concept will lead to a better understanding of the PSR and sharpens the TCR characteristics and open the doors for new research possibilities.

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The photic sneeze reflex (PSR) is a phenomenon of uncontrollable sneezing episodes following sudden exposure of the sunlight. It is usually a mild reaction, but sometimes imposes significant consequences in particular occupation [1]. The exact mechanism is poorly understood. Various mechanisms have been proposed [2]. Strikingly, roles of the fifth (CN V) and tenth cranial (CN X) nerves, brainstem nuclei and inciting patterns mimic another brainstem reflex, known as, the trigeminocardiac reflex (TCR), which is defined as the sudden onset of parasympathetic dysrhythmia, sympathetic hypotension, apnoea or gastric hypermotility during the stimulation of any of the sensory branches of the CN V [3–10]. Recently, it has been highlighted that the TCR phenomenon has a wide array of clinical implications in both experimental and clinical neurosciences [11–22]. Interestingly, recent literature explores the role of the TCR in various conditions, including sudden infant death syndrome, sleep disorders, rhinitis and stroke [23–31].

In this critical review, we hypothesize that the photic sneeze reflex can be a part of the TCR or at least mechanisms of both the reflexes share a common pathway and need to be explored based on existing literature.

The photic sneeze reflex

The PSR [32] is considered as a condition of uncontrollable repeated sneezing episodes in response to such stimuli as wavelength-independent bright light or periocular (surrounding the eyeball) injection. This condition is also including so-called 'autosomal dominant compelling helio-ophthalmic outburst syndrome (ACHOO)' and affects 18–35% of the population in the USA [1], but its exact mechanism is not well understood [2]. A recent German study reported much higher (up to 57 percent) prevalence of ACHOO [33]. In general, the PSR seems to be a mild pathophysiological phenomenon. However, more dramatic and severe consequences can develop if PSR occurs in aeroplane pilots or car drivers [1]. The pathophysiology of this phenomenon is still unknown [1].

One hypothesis of the PSR occurrence is based on the crosstalk between the second nerve (CN II) and CN V at the mesencephalon after an intense light stimulation [34]. A second theory called 'parasympathetic generalization' is based on the hypothesis that adjacently located parasympathetic branches are co-activated during the PSR [34] and neurally transmitted to the brain region relevant for the initiation motor execution of a sneeze [34,35]. Other

Table 1. Similarities between the photic sneeze reflex and the trigeminocardiac reflex (source: own table).

Characteristics	TCR	PSR	Synthesis
Initiation/triggering	Sensible CN V; temperature, mechanical [33–36]	Sensible CN V; temperature, light, mechanical [35]	The trigger is the same for both reflexes. It is not clear of the light alone is a factor of PSN, or it is instead the temperature alone
Symptoms	CN X; heart (dominant), lung, stomach [3]	CN X, lung (dominant) [30,35]	The afferent arc is the same, even the TCR is heart dominant, and the PSN is lung dominant
Risk	Cardiac arrest [3]	NA	The cardiac arrest is an over reaction of the efferent TCR pathways; for the PSN, nothing similar is described
Pathophysiology	CN V, CN X, brainstem [3] Abnormal medulla oblongata [57]	CN V, CN X, brainstem [30] Abnormal medulla oblongata [58]	Changes in the medulla oblongata may be the basis of both reflexes
Genetic	Polymorphisms and/or mutations of specific genes [59]	ACHOO syndrome [32]	In the TCR, there is no genetic syndrome known, even it is a genetic involvement proposed by serval groups base on pathoanatomical studies [3,57]. But a genetic involvement of reflex occurrence is a substantial part of both reflexes
Management	Avoidance; atropine [8,11,13]	Avoidance [35]	Both reflexes do not know an adequate treatment; atropine any complete protection [6]
Benefit	Annoying 'holdover' of evolution; oxygen conserving reflex [4]	Annoying 'holdover' of evolution; protect nasal respiration [1]	Both reflexes are a holdover of evolution to preserve a sufficient oxygen supply to the brain

ACHOO syndrome: Autosomal dominant compelling helio-ophthalmic outbursts of sneezing; CN V: Trigeminal nerve; CN X: Vagus nerve; NA: Not available; PSR: Photic sneeze reflex; TCR: Trigeminocardiac reflex.

cases of parasympathetic generalization are already well described as emotional involvement on parasympathetic outflow [36]. A third theory suggests that PSR occurrence is related to a parasympathetic hypersensitivity, particularly within the nasal mucosa [34–36].

The trigeminocardiac reflex

The TCR was initially defined as "the sudden onset of parasympathetic-sympathetic disbalance, apnoea or gastric hypermotility during stimulation of any of the sensory branches of the CN V" [3]. The generally accepted afferent pathway of the TCR model elucidates that the sensory CN V endings send neuronal signals via the Gasserian ganglion to the sensory CN V nucleus [4,37–40] and continue along the short internuncial nerve fibres in the reticular formation [4,41]. Here, the signals connect with the efferent pathway in the motor branches of CN X nucleus [4,41].

In clinical neuroscience, the TCR has been reported to occur during skull base surgery and in different neurological disorders [5,42–55]. Apart from these numerous clinical reports published during the last 20 years, the physiological mechanisms and function of the TCR have not yet been fully explored, even so, detailed neurobiological studies exist [41]. Probably the most studied particular exemplification of TCR is the so-called diving response [29,56]. Experimental findings demonstrate that the TCR is a coordinated systemic neurogenic reflex integrating central and peripheral mechanisms leading to rapid cerebral vasodilatation, adjustments of parasympathetic and sympathetic activity resulting in changes in blood pressure, redistribution of blood flow, bronchial diameter, mucosal secretion along with changes in cardiac output and plethora of other autonomic changes [5,41]. Specifics of autonomic changes patterns seem to vary depending on the stimuli triggering TCR [5,41,49].

Is the photic sneeze reflex a subtype of the trigeminocardiac reflex?

There are many similarities between the common origin of PSR and TCR (see Table 1). The CN V initiates both, and both can be induced by temperature and light [1–5]. Both phenomena are triggered by the excitation of the CN V [1–5]. Importantly, only sensory branches of the CN V are involved in both reflex pathways.

Studies related to the PSR suggest a cross-talk between the CN II and the CN V that makes the afferent pathways [60]. Some studies suggest that the hypersensitivity of the CN V is a common factor for TCR [3–5] and photic sneeze reflex [1,2]. The brainstem seems to be a plausible site providing the cross-talk between optic input and CN V [32,33]. At the brainstem, various efferent pathways, including cranial nerves V, VII, IX, XI, XII are interconnected with vagal outflow [10]. Ophthalmic and maxillary branches of the CN V often activate the PSR pathway [1,2], and the TCR can be activated by all the three sensory branches of the CN V [8]. Also, both reflexes are accompanied by parasympathetic over activity [1,5]. These speculations are supported by the observation of similar SR during ocular anesthesia, especially at the light plane, under propofol sedation due to the stimulation of the CN

Table 2. Causal relationship in the trigeminocardiac reflex.	
Plausibility	The appearance of the TCR must be explainable by an adequate stimulation of the trigeminal nerve The TCR appears promptly after the stimulus is applied
Reversibility	Stimulus cessation abolishes the reflex, and cardiopulmonary parameters return to baseline
Repetition	Reapplication of the stimulus on cranial nerve V will result in similar hemodynamic changes
Prevention	A lighter stimulus of the same type does not result in the same severe TCR Trigeminal nerve bock abolishes the TCR Application of anticholinergic drugs blocks the occurrence of the reflex

TCR: Trigeminocardiac reflex.
Adapted and published with permission from [55].

V [35,36,60]. These conjectures are supported by our observations that the light plane of anesthesia is a risk factor for more occurrences of TCR episodes [37,38].

The PSR is also a genetic variant called 'ACHOO' [32]. The abnormal TCR is often postulated to be based on a genetic variance. For an example, the best hypothesis of the pathogenesis of sudden infant death syndrome (SIDS), which is a variant of abnormal TCR, is the so-called 'triple risk model', which suggests that the SIDS is based on interactions of different variables related to exogenous stressors and infant vulnerability [37]. In this context, it is suggested that environmental factors serve as triggers acting during a period of particular sensibility modulated by intrinsic genetic characteristics [37]. While it is undoubtedly true for the SIDS, it may take place in TCR and ACHOO-Syndrome as well. Importantly, tobacco smoking, a risk factor for SIDS [37] is also associated with PSR [1,2,32,33]. This view finds additional support in the fact that both phenomena (SIDS and ACHOO) are common in the younger age group [1–5]. Also, the increased parasympathetic tone seems to be a common factor in both conditions [1–5]. Therefore, it is reasonable to suggest that TCR pathways may be indirectly associated with the PSR.

And now what are the consequences?

The mechanisms of two well-established phenomena are only partially understood. The TCR pathways currently are being a subject of numerous studies. However, the mechanism of PSR remains underinvestigated. On the contrary, triggers initiating the phenomena are better understood in the case of PSR [1,2,34] and only partially for the TCR [3–5]. The basis of both aspects is the CN V with the strong connections to other epiphenomena of the reflex (e.g., 'parasympathetic generalization'). But how can we prove that it is the part of the same reflex arc? There is the need for a causal relationship of the both as described previously for the TCR [55,61].

Plausibility, reversibility, repetition and prevention (see Table 2) – as criterion best established for the TCR [55] (see Table 2) – are also all fulfilled for the PSR and are designed to help clinicians to discriminate better and especially more rapidly between the very nonspecific pain reaction and the more specific TCR reaction. Adequate stimulus like light exposure, physical stimulation of the CN V, various CNS pathologies confirm the plausibility of the PSR [35]. Every stimulus cessation stops the PSR, or repetition of the stimulus leads to the PSR [35]. Therefore, the cause–effect relationship for the PSR is proven. In connection with the above-described connections between TCR and PSR pathways, the PSR and the TCR may be linked. As an inductive consequence of this critical evaluation and a definite causal relation, there can be hypothesized that the PSR is a subtype of the TCR.

Molecular basis

The molecular mechanisms responsible for TCR and PSR are unknown. Nevertheless, the hemodynamic byproducts of these two reflexes share a resemblance with those of the neurodevelopmental disorder, the Rett Syndrome (RTT). The disease is associated with a variety of autonomic nervous system abnormalities including overactive parasympathetic tone [62], and spontaneous cardiac rhythm abnormalities which may lead to complete cardiac conduction block [63], contributing to sudden death in a quarter of all deaths in RTT individuals [64].

These abnormalities are related to the suboptimal function of the MeCP2 in cholinergic neurons and are partly reversed by atropine [62]. Silencing of MeCP2 early during development result in defects in peripheral innervation of sensory CN V [65], and MeCP2 loss is associated with an overall increase in neuronal activity, especially in the area of brainstem with a role in cardiorespiratory function [66].

Whether MeCP2 or allelic variations have a role in TCR or PSR is unknown. However, the increase in neuronal activity is related to the alterations in the activity of several voltage-gated sodium channels [67]. The dysfunction of

Box 1. Implications for future research.

Parasympathetic generalization
Influence of emotions on TCR
Genetic variant leading to TCR

Data taken from [Chowdhury T *et al.*, Unpublished Data].
TCR: Trigeminocardiac reflex.

some of these channels has also been attributed to the parasympathetic hyperactivity, an electrical malfunction of the ventricles and sudden death in intractable epilepsies [68].

Trigeminal fibers are known to mediate the chemesthetic sensations due to their innervation in the mucous membranes of the nasal cavity, nasopharynx, oral cavity and cornea, through the activation of the transient receptor potential vanilloid 1 (TRPV1) channel [69]. TRPV1 is a multimodal channel, and a member of the transient receptor potential (TRP) family of nonspecific cation channels, whose activation can be the result of a combination of multiple factors [70].

Stimuli such as capsaicin, temperatures above 43°C [71] and light [72] can activate these channels through direct stimulation of free CN V fibers endings, suggesting the involvement of these channels in PSR activation. It would be interesting to demonstrate the involvement of these channels in TCR, as additional evidence for the common pathways responsible for the activation of these two reflexes.

Here too, the voltage-gated sodium channels are the main classes of ion channels which underlie the action potential generation and propagation of the TRPV1 of CN V nociceptive neurons, resulting in various sensations including pain in the orofacial area [73]. Nevertheless, the type of the CN V influences the activation of TRPV1 and voltage-gated sodium channels, as CN V neurons are classified based on cell size, shapes of the action potential, duration of the action potential and isolectin B_4 binding sensitivity to tetrodotoxin [74]. The inhibition of TRPV1 and voltage-gated sodium channels are among mechanisms contributing to the analgesic action of the anesthetic eugenol in the orofacial regions [74].

These molecular similarities of RTT and TCR/PSR might help to a better grouping of clinical features of the different known subgroups of the TCR based on molecular differences.

Future perspective

The hypothesis that the PSR might be a subtype of the TCR has several implications for the TCR/PSR research (see Box 1). Since the beginning of the TCR research nearly 20 years ago, it was postulated that there must be a genetic prerequisite that makes patients prone to the abnormal TCR [10,11]. In case of the specific form of the PSR, ACHOO Syndrome, the hereditary nature is proofed [1,2,32,33]. As a consequence, there is an urgent need of a 'risk model' potentially including this genetic prerequisite and helping to further prospectively select those patients in whom and in which severity of the abnormal TCR could occur [75]. As a conceptual innovation of the here presented work, the hypothesis of a multiple risk model of the TCR/PSR occurrence is supported. A genetic involvement explains the fact that individual patients are more prone to the TCR/PSR occurrence than others with the same characteristic. In times of personalized healthcare, such a model is necessary to make the next step in the treatment of the TCR.

The 'parasympathetic generalization' as mentioned for the PSR further supports a cross-classification on different stimuli in certain brain regions providing evidence for a shared neural code for processing specific triggers and underlying an evolutionary significance of the TCR/PSR occurrence.

On the other hand, this possible link between the PSR and the TCR stresses the importance of the TCR again. The TCR is one of the essential protective reflexes [5,21], and its abnormalities might be the cause of various neurological diseases [27,51]. Understanding the mechanisms and functional significance of TCR opens new therapeutic opportunities in clinical neurosciences [51,61], for example, protecting neurons from injury. In this context, a recent Australian work [75] shows that prevention by a remote action (Philtral Pressure Technique) may be successful at least in some cases. This research opens the old question again, whether such manoeuvre could not be used more therapeutically [4].

Besides the previous TCR research, one important point seems that emotions can influence PSR as already described for other autonomous reflexes. This hypothesis might explain why the TCR and its subgroups are better documented during surgery [76–78]. But it also opens the window to further (potential) risk factors [79–81], a better

understanding of neuroanatomy [82,83] and might explain the influence of positive psychology on the course of different neurological diseases [84–86]. In such a context, the TCR also helps to understand the physiology of the nervous system better and to develop new models of it [87–92].

The more detailed development of diagnostic or treatment strategies must take into account the functional and molecular properties as discussed here and must consider the therapeutic target, brain region, and perhaps cell type or time of application. More directly target therapeutics that are administered as early as possible in the course of the TCR is likely to be the most effective.

Conclusion

The TCR is a general neural reflex, of which specific appearance and characteristics depend on the particular conditions and triggers. However, more and more clinical and experimental data suggest that there must also be genetic variants that make patients prone to abnormal TCR, which can be dangerous and damaging. Based on a critical literature review and cause relationship, the present hypothesis indicates the possibility that the PSR may be a part of the TCR. Moreover, the existence of the PSR-specific ACHOO syndrome may provide the key to explore the genetic variances underlying the diversity in TCR presentations and supports the concept of a multiple risk model of the TCR/PSR. A fuller understanding of the TCR based on our increasing knowledge of neurobiology together with clinical aspects could lead to effective treatment of TCR/PSR shortly.

Executive summary

- The trigeminocardiac reflex (TCR) is a well-known brainstem reflex. The photic sneeze reflex (PSR) seems to have some parallels to the TCR so that there is the hypothesis that PSR is a subtype of the TCR.

Photic sneeze reflex a subtype of the trigeminocardiac reflex?

- PSR and TCR have both many parallels which underline the here presented hypothesis that the PSR is a variant of the TCR. Notably, the connection of the PSR to genetic variants highlights the theory that this must also be the case in the TCR. Besides that, the influences of emotions and parasympathetic generalization might be a topic of further research. All in all, the present article underlines the importance of TCR in clinical and basic neuroscience again.

Molecular basis

- Either for PSR nor TCR, there is nothing know about a molecular basis. Here, there is suggested the involvement of cholinergic neurons, voltage-gated channels and multimodal channels based on conceptualization.

Future perspectives

- The better understanding of subtypes of the TCR will lead to a better knowledge of the TCR as there are currently still some blind spots in the understanding of this reflex.

Author contributions

T Chowdhury developed the hypothesis, assisted substantially in data collection, screening, reviewing, analyzing, contacting the authors, compiling and writing the manuscript. Z Sternberg reviewed and screened the data, and helped substantially in writing the manuscript. E Golanov collected and screened the data and helped in to draft the manuscript. R Gelpi and T Rosemann assisted in writing and editing the paper. B Schaller developed the hypothesis, assisted in writing, reviewing and editing the manuscript.

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