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REVIEW

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Trigeminocardiac reflex

A clinical phenomenon or a new physiological entity?

Abstract The trigemino-cardiac reflex (TCR) is defined as the sudden onset of parasympathetic dysrhythmia, sympathetic hypotension, apnea or gastric hypermotility during stimulation of any of the sensory branches of the trigeminal nerve. The sensory nerve endings of the trigeminal nerve send neuronal signals via the Gasserian ganglion to the sensory nucleus of the trigeminal nerve, forming the afferent pathway of the reflex arc. This afferent pathway continues along the short internuncial nerve fibers in the reticular formatio to connect with the efferent pathway in the motor nucleus of the vagus nerve. Clinically, the trigeminocardiac reflex has been reported to occur during craniofacial surgery, balloon-compression rhizolysis of the trigeminal ganglion, and tumor resection in the cerebellopontine angle. Apart from the few clinical reports, the physiological function of this brainstem-reflex has not yet been fully explored. From experimental findings, it may be suggested that the trigemino-cardiac reflex represents an expression of a central neurogenic reflex leading to rapid cerebrovascular vasodilatation generated from excitation of oxygen-sensitive neurons in the rostral ventrolateral medulla oblongata. By this physiological response, the adjustments of the systemic and cerebral circulations are initiated to divert blood to the brain or to increase blood flow within it. As it is generally accepted that the diving reflex and ischemic tolerance appear to involve at least partially similar physiological mechanisms, the existence of such endogenous neuroprotective strategies may extend the actually known clinical appearance of the TCR and include the prevention of other potentially brain injury states as well. This may be in line with the suggestion that the TCR is a physiological, but not a pathophysiological entity.

Key words trigemino-cardiac reflex · skull base surgery · brain stem · respiration · cardiovascular · cerebral blood flow

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Introduction

The trigemino-cardiac reflex (TCR) is a relatively unknown brainstem-reflex that has gained much attention to clinical medicine during recent years [14, 50, 51, 56]. There is poor understanding of the underlying mechanism and functional relevance of this reflex response. However, the oculo-cardiac reflex (OCR), which is a physiological subtype of the TCR, is a widely investigated and well-established clinical phenomenon, induced by mechanical stimulation of ocular and perioocular structures that are innervated by the ophthalmic division of the trigeminal nerve [9]. First described in cats and rabbits [32], the TCR is manifested by a sudden development of cardial dysrhythmia up to asystole, arterial hypotension, apnea and gastric hypermotility. A current theoretical explanation of the physiological mechanism of the TCR is that the sensory nerve endings of the trigeminal nerve send neuronal signals via the Gasserian ganglion to the sensory nucleus of the trigeminal nerve, forming the afferent pathway of the reflex arc. This afferent pathway continues along the short internuncial nerve fibers in the reticular formation to connect with the efferent pathway in the motor nucleus of the vagus nerve [33]. Efferent cardiac control is therefore

largely of parasympathetic origin. Such pathophysiological features are similar to the diving response, the most powerful autonomic reflex response that is known so far [11]. The diving reflex attenuates physiological homeostatic responses, such as the baroreceptor and the chemoreceptor reflexes. An increase in arterial blood pressure usually inhibits the ongoing activity of the sympathetic premotor bulbospinal neurons of the rostral ventrolateral medulla, yet, when coupled with nasal stimulation, these neurons actually increase their sympathothetic firing [38]. Also, despite the low arterial partial pressure of carbon dioxide which develops while an animal is submerged, in spite of stimuli that normally would increase respiratory drive the animal remains apneic [19]. Although it is known that the circuitry for the reflex is intrinsic to the brainstem [19], the exact brainstem circuitry of this response has not been identified.

In the light of the increasing interest of TCR in clinical medicine, especially in skull base surgery [14, 50, 51, 56] and in clinical electrophysiology, this seems to be the time to review the present knowledge and try to answer the question whether this reflex represents a physiological entity with defined anatomical and clinical correlation or is only a clinical phenomenon. Special attention will be given to the potential physiological functional relevance of the TCR.

Anatomical basis

The TCR represents a subgroup of the trigemino-vagal reflexes. However, vagolysis with high doses of atropine may not completely prevent the bradycardia caused by TCR. Initiation of this physiological reflex response results primarily from stimulation of receptors on trigeminal efferent fibers [11], including those in the anterior ethmoidal nerve [17] that innervate the face and nasal passages (see Fig. 1). The central circuit of the TCR is intrinsic to the brainstem, because the cardial responses are also maintained in decerebrate preparations [19]. The physiological background of this circuit has been the subject of very few investigations, The first relay of the circuit must be located in the ventral superficial medullary dorsal horn (MDH) since the cardial responses can be blocked there with injections of either lidocaine or kynurenic acid. This interpretation agrees with a prior study on awake rabbits in which the exposure of the nasal passage to formaldehyde vapour produced c-fos-expression in many tyrosine hydroxylase-immunoreactive neurons [23]. Thus, the parasympathetically mediated bradycardia, the sympathetically mediated vasoconstriction and the central inhibition of respiratory rhythm (apnea) must be modulated by the trigeminal system within the lower brainstem. However, the connections between the trigeminal system and brainstem autonomic neurons are unknown. Recently Esser et al. [20] have shown indirect neuronal projections from dorsomedial portions of the MDH via the dorsal medullary reticular formation to A1, C1 and A5 catecholaminergic cell groups in the brainstem, and implicate them in the pressor responses elicited after tooth pulp stimulation. The physiological and anatomical data of animal models have demonstrated that neither the nucleus of the tractus solitarius (NTS) nor the caudal C1 area play a major role in activating the sympathetic system when the nasal mucosa is stimulated since injections of the broad-spectrum excitatory amino acid receptor antagonist kynurenate into either of these areas failed to decrease the sympatho-activation produced by nasal stimulation [38]. This feature suggests that the trigeminal projections from MDH to the NTS and caudal C1 area may regulate a function other than sympathetic vasomotor outflow, perhaps respiration or the bradycardiac response. The NTS is well-known to be a relay for visceral afferent fibers entering the brain, but little is known of projections to it from a somatic relay nucleus. The NTS neurons just dorsolateral to the solitary tract receive prominent projections from the carotid sinus nerve [41] and are important for the baroreceptor reflex [63]. The labeled neurons in this location, therefore, may be important for modulating cardiovascular function. Following bilateral injections of 6-hydroxydopamine into the intermediate portion of NTS, animals demonstrate a prolonged bradycardia, but no changes in mean arterial pressure, indicating the baroreceptor reflex loop, which mediates bradycardia, is sensitive to impulses from catecholamine axons entering the intermediate NTS [28].

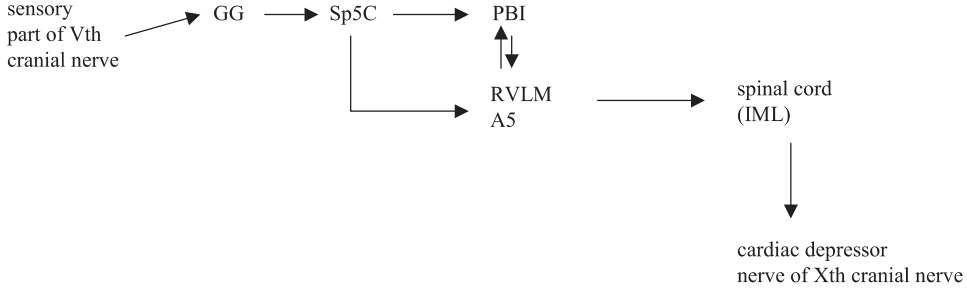

Fig. 1 Schematic diagram showing neuronal pathways involved in TCR (*GG* Ganglion Gasseri; *A5* catecholamine cell group; *IML* intermediolateral cell column of the spinal cord; *PBI* parabrachial nucleus, lateral; *RVLM* rostral ventral alteral medulla; *Sp5C* spinal trigeminal nucleus, pars caudalis)

Similarly the ventrolateral medulla represents a topographical locus for respiratory neurons, sympathetic premotor neurons, and preganglionic parasympathetic cardiac motoneurons [8]. The caudal ventrolateral medulla (CVLM), defined as that part of the ventrolateral medulla caudal to the obex that includes the nucleus ambiguous and the A1 group, contains both an important inhibitory relay of the baroreceptor reflex and mostly expiratory neurons of the caudal ventral respiratory group [22]. The NTS and CVLM are thus reciprocally connected [60]. The Pre-Bötzinger area lies in the ventrolateral medulla rostral to the obex yet caudal to the rostral part of the ventrolateral medulla (RVLM; rostral C1 area), placing it in the intermediate ventrolateral medulla (IVLM) [8, 47]. Neurons in this topographical location have been implicated in respiratory rhythm generation [8, 47]. It is not known whether the apnea seen after stimulation of the sensory part of the trigeminal nerve is mediated by the projections from the MDH and the IVLM (defined as the area of the ventrolateral medulla between the caudal end of the compact formation of the nucleus ambiguous and the obex), or, if the apnea is induced by impinging on respiratory motoneurons. However, it has been reported that the apnea seen after electrical stimulation of the anterior ethmoidal nerve is mediated in the dorsolateral pons [17]. The RVLM is well known to be important in both respiratory and cardiovascular function. The Bötzinger group of respiratory neurons lies just dorsal and lateral to the excitatory premotor sympathetic neurons [8]. The effect that nasal stimulation has on the respiratory neurons in the Bötzinger group has yet to be explored fully, but all respiratory neurons recorded from the area to date are silenced by sensory trigeminal stimulation [37, 38]. The RVLM contains the rostral C1 adrenergic cell group [48], neurons that provide bulbospinal projections to the intermediolateral cell column in the spinal cord and provide sympathetic tone [24, 55]. Approximately 62 % of the responding neurons, which are normally markedly inhibited or silenced by an increase in blood pressure, demonstrate an increase in firing, when the sensory part of the trigeminal nerve is stimulated, despite an increase in blood pressure [37, 38]. The dorsolateral pons is an important relay for visceral information from the NTS and has been designated the pneumotaxic center and pontine taste area. Trigeminal projections to the A5 area have received little attention, but it seems that A5 neurons project to a system of neurons in the brain important for central cardiovascular regulation and particular in the baroreceptor reflex mechanism, and are generally sympathoexcitatory [21].

Physiological effects of trigeminal stimuli

From animal models it is well known that approximately two thirds of the sensory trigeminal nerve is composed of unmyelinated C-fibers and that the majority of myelinated fibers are of small diameter and are involved in a nociceptive pathway. Microneurographic studies have demonstrated that activation of a single C- or Aδ-fiber could evoke a 'burning' or 'stinging' sensation [27]. Thus, summated potentials like the electrical pain-related potential probably do not pick up just a single fiber's activity [64]). This could explain the detection of CO_2 by the trigeminal system just below or near the electrical pain-related potential threshold, but hardly explains the large difference between the detection and the electrical pain-related potential threshold as noticed in the study of Thürauf et al. [64]. Other studies have identified α-gustducin, the subunit of the trimeric G-protein complex specific for such receptor cells [1]. In the context of these findings, the thresholds for detection, electrical pain-related potential and pain determination has led to the possibility that the detection of CO_2 clearly below electrical pain-related potential and pain thresholds may be mediated by a subset of trigeminal afferents, e. g. trigeminal afferents innervating α-gustducin positive chemosensory cells [64]. This would imply that the electrical pain-related potential can be employed to distinguish functionally subsets of trigeminal primary afferents, i. e. it summates trigeminal nociceptive activation, but not activation of trigeminal innervated solitary chemosensory cells [64].

The nature of the stimulus is the most important risk factor in inducing the TCR. During surgery, abrupt and sustained traction is more reflexogenic than smooth and gentle traction [9]. Other potent stimuli can also induce the TCR, including needle insertion, balloon inflation of the trigeminal ganglion, and tumor resection within the cerebellopontine angle [53].

Mechanical stimulation

Although there are some variations in the projection pattern for the different branches of trigeminal nerves, a horseradish peroxidase study has shown that projections in the cat are generally distributed widely over the sensory trigeminal complex (namely the main sensory nucleus and spinal nucleus) [35]. This conclusion has been validated electrophysiologically in experimental animals [5, 18] and humans. The field potential studies by Dong et al. [18] have furthermore demonstrated that the parallel inputs from the trigeminal nerve activate these nuclei nearly simultaneously. In addition to small diameter Aδ- and C-fibers, which are believed to carry nociceptive information, tooth pulp is innervated by large-diameter A-β myelinated axons [61], whose con-

duction velocities in the peripheral portion up to the Gasserian ganglion can be as much as 58–62 m/s in the cat [4, 12, 16]. Because of their fast conduction, these A-β fibers activate main sensory nucleus, subnuclei oralis, nucleus interpolaris and nucleus caudalis of the cat within a span of 0.4 ms [18]. These earlier anatomical and electrophysiological studies have suggested that stimulation of the snout may also activate the A-β-fibers which project to the sensory trigeminal nuclei with short latencies. It is now known that the nucleus caudalis as well as the main sensory nucleus contain neurons responsive to low-threshold mechanoreceptors [30, 56]. These receptors produce short-latency responses in the main sensory nucleus and spinal nucleus via A-β fibers [18, 30].

Chemical stimulation

The neuronal pathways involved in mediation of reflexly increased arterial blood pressure elicited by electrical stimulation of the mandibular incisor were studied following microinjections of cobalt chloride or lidocaine into the brainstem to block neuronal pathways of TCR [3]. Lidocaine blocks synaptic transmission by blockade of voltage sensitive sodium channels on neuronal cell bodies and fibers of passage [49] whereas cobalt chloride blocks synaptic transmission by binding to calcium channels on synaptic terminals. Microinjection of cobalt chloride or lidocaine in the dorsomedial Sp5C of rats, RVLM, and A5 regions have demonstrated effective attenuation of the reflex cardiovascular responses and of the reflex pressor responses [3]. Bilateral injection into the Sp5C were consistently more effective in blocking the reflex pressor response (70–100 % attenuation) than ipsilateral injections (68–78 % attenuation). Thus, it appears that primary afferents carrying nociceptive inputs from the mandibular incisor terminate bilaterally in the dorsomedial Sp5C with an ipsilateral predominance [3]. This study confirms previous reports which have revealed that autonomic responses elicited by noxious stimulation of trigeminal sensory neurons are mediated initially in the superficial laminae of the Sp5C [7]. Panneton [42] demonstrated that injection of 2 % lidocaine into the medullary dorsal horn reversibly blocked bradycardia and apnea elicited by nasal inhalation of ammonia.

Chemical blockade of synaptic inputs in the RVLM completely eliminates the reflex pressor response whereas approximately 50 % attenuation of the reflex pressor response was observed following bilateral injections of chemical blockers into the lateral parabrachial nucleus [3]. This finding suggests that the attenuation of the reflex pressor response observed following injections of chemical blockers into the RVLM region may have resulted from blockade of direct projections from the spinal trigeminal nucleus (primarily pars caudalis) to the RVLM and indirect projections which relayed in the lateral PB prior to reaching the RVLM.

Electrical stimulation

Dutschmann and Herbert [17] electrically stimulated the anterior ethmoidal nerve in the rat and reported bradycardia, hypertension and apnea. However, in their studies, the bradycardia was of a slower time course than is normally seen during nasal stimulation [36]. This suggests that the bradycardia seen in this study may have been due to a reflex activation of the arterial baroreflex in response to increased arterial pressures. Electrical stimulation of the sensory part of the trigeminal nerve is presumably a noxious stimulus [3]. By contrast, McCulloch demonstrated that electrical stimulation of the anterior ethmoidal nerve – probably of the small diameter fibers contained within the nerve – was followed by a heart rate decrease by 54 %, primarily within the first beat following the onset of the electrical stimulus [38]. The magnitude and time course of this bradycardia was similar to that seen during voluntary dives or nasal stimulation. The relative contribution of unmyelinated C-fibers and small diameter myelinated fibers (Aδ) in the production of this reflex response remains still undetermined. These findings are consistent with a study in which Allen et al. demonstrated c-fos-immunoreactive neurons in the dorsomedial Sp5C following electrical stimulation of the trigeminal nerve [2]. The c-fos-immunoreactive neurons were localized in the spinal trigeminal nucleus bilaterally.

Clinical appearance of TCR

The TCR and its interactions normally serve protective and purposeful functions, but may – under certain circumstances – become exaggerated and put the patients at risk. The clinical importance of the TCR lies in the fact that its clinical features range from sudden onset of sinus bradycardia, bradycardia terminating asystole, asystole with no preceding bradycardia, arterial hypotension, apnea, and gastric hypermobility [13]. Independently of these clinical signs and symptoms, the clinical occurrence of the reflex can be demonstrated by (mechanical) stimulation of the peripheral or the central part of the trigeminal nerve. The clinical occurrence of TCR after stimulation of the central part of the trigeminal nerve was first described by the author [54].

Craniofacial surgery frequently involves osteotomies and soft-tissue manipulation of the region innervated by the mandibular, maxillary, and ophthalmic divisions of the trigeminal nerve. Several craniofacial procedures have been noted to induce the TCR including the LeFort

I osteotomy, as well as midface fractures reduction, elevation of complex zygomatic fractures and distraction of insufflation of the temporomandibular joint [6, 31, 32, 44]. The incidence of reflex bradycardia during craniofacial procedures has been reported to be as high as 1.6% [43].

Over the last 20 years, advances in skull base surgery have allowed access to the cerobellopontine angle or the pituitary fossa. A significant decrease in heart rate and blood pressure during surgical resection of tumor near the trigeminal nerve in the cerebellopontine angle has been reported [49, 51], even in the pituitary fossa [48] and during balloon-compression rhizolysis of the trigeminal ganglion [14, 49]. Several factors have been postulated as predisposing patients to the TCR based on cases of the OCR [9]. These factors include hypercapnea, hypoxemia, light anesthesia, children with high resting vagal tone, narcotics such as sufentanil and alfentanil, preoperative beta-blockers and calcium channel blockers [31, 56].

Cause-effect association

A cause-effect association can be concluded by examining the effectiveness of the different measures used to prevent the response [10], although their value is restricted by the retrospective view of most of the studies, To the best of the author's knowledge this includes only surgical cases; but there are certainly other clinical situations in which the TCR may appear. Thus the TCR can be prevented by avoiding stimulation of the afferent pathway, as described above, or by blocking the nerves that conduct the afferent impulses [51]: anticholinergic medication to block muscarinic receptors of the heart was an effective prophylactic measure, and no further episodes of dysrhythmia were detected. The remaining surgical procedure could be completed uneventfully in all cases. This cause-effect relationship speaks for the evidence of a TCR and that the stimulation of the trigeminal root may represent the afferent pathway.

Validity of the suggested pathway

The above-mentioned anatomical basis and the suggested pathway of the afferent way of TCR have one important restriction: they are only theoretical. Only one report has dealt with the confirmation of the suggested pathway by experimental methods [42]. Different virus subtypes have been used to map transneuronal projections in the CNS of synaptically-linked neurons. The great advantage of using viruses for tract tracing studies is their ability to migrate and jump synapses, and then replicate, thus amplifying their signal transneuronally. Viruses primarily transport in a retrograde fashion, outlining motoneurons and their premotor afferents [62]. However, more recent experiments have shown that the herpes simplex virus 1 (HSV-1), strain 129, migrates through neurons in the trigeminal system in anterograde direction [38]. This strain of HSV thus can be used to outline the primary, secondary and higher order neurons along an afferent pathway [38]. This allows the use of the HSV-1 on a purely sensory nerve to map a circuit for a reflex such as the diving response. In addition, biotinylated dextran amines have been used as an anterograde tracer; these show fine details of terminal structures produced with a fast and simple reaction that results in a permanent product. This technique was used to demonstrate direct projections from the ventrolateral part of the MDH and to check the validity of the transneuronal viral method. The injections were placed into lamina I and II of the ventral MDH, the area labeled after the injections of HSV-1 into the anterior ethmoidal nerve. This same area receives primary afferent projections from the anterior ethmoidal nerve, and is where the cardiorespiratory response to nasal stimulation can be reversibly blocked [42] and where neurons are activated and display c-fos immunoreactivity to nasal stimulation [34]. The injections of BDA into the MDA validated the data seen from the viral experiments. Such projections could be the trigeminal homologue of the described spinal-autonomic projections [14].

The interpretation of these results provides substantial evidence that the TCR, as described above, represents a physiological brainstem reflex. This is certainly true for the well-known subtype of OCR and it may be the case for the TCR as the whole group. This implies that the TCR is not only a clinical phenomenon, but also a new physiological entity.

Central neurogenic neuroprotection: part of the trigeminal-cardial reflex

The TCR is a specific example of a group of related responses generically, defined by Wolf as oxygen-conserving reflexes [63]. Within seconds after reflex initiation, there is a powerful and differentiated activation of sympathetic nerves. The consecutive elevation in CBF is not associated with changes in CMR_{O2} or CMR_{glc} and hence represents a primary cerebrovascular vasodilatation. The brain can protect itself from ischemia by distinct (endogenous) physiological mechanisms, which probably involve two separate systems of neurons in the CNS [50]. The one which mediates a reflexive neurogenic neuroprotection, emanates from oxygen-sensitive sympathoexcitatory reticulospinal neurons of the RVLM. These cells, excited within seconds by reduction in blood flow or oxygen, initiate the systemic vascular components of the oxygen conserving diving reflex. They profoundly increase rCBF without changing

CMR_{O2} and CMR_{glc} and, hence, rapidly and efficiently provide the brain with oxygen. Upon cessation of the stimulus the systemic and cerebrovascular adjustments return to normal. The system mediating reflex protection projects via as-yet-undefined projections from RVLM to upper brainstem and/or thalamus to engage a small population of neurons in the cortex which appear to be dedicated to transducing a neuronal signal into vasodilation. Two lines of evidence indicate that the RVLM neurons are essential for the expression of the cerebrovascular vasodilation elicited by hypoxia. First, electrical stimulation of RVLM in intact or spinalized rats site-specifically and dose-dependently elevates rCBF, but not CMR_{O2} or CMR_{glc} [23]. In this manner these data replicate hypoxic vasodilatation [59]. The response can only be attributed to stimulation of the reticulospinal sympathoexcitatory neurons since these are the only neurons in the region excited by over 50 % the elevation of CBF produced by hypoxemia. The fact that such lesions do not affect the vasodilatation elicited by hypercarbia indicates that the response is stimulus selective [59]. Thus, much of the cerebrovascular vasodilatation elicited in the cerebral cortex by hypoxemia is a reflex which results from excitation of oxygen-sensitive brainstem neurons, and not by a direct effect of hypoxia on blood vessels [29] nor by stimulation of arterial chemoreceptors whose activity, while regulating blood flow to most vascular beds, is without effect on the cerebral circulation [27]. It also appears to relay the central neurogenic vasodilatation elicited from other brain regions, including excitation of axons innervating the fastigial nucleus (FN). This mode of protection would be initiated under conditions of global ischemia and/or hypoxemia because the signal is detected by medullary neurons.

That the brain may have neuronal systems dedicated to protecting itself from (ischemic) damage, at first appearing to be a novel concept, is, upon reflection, not surprising since the brain is not injured in naturalistic behaviors characterized by very low levels of rCBF, such as diving or hibernation [25, 52]. Such neuroprotective adaptations may also underlie preconditioning strategies [52]. The diving reflex, hibernation and ischemic tolerance appear to involve at least partially similar physiological mechanisms because most of the signals, transducers and effectors, that are well-established in ischemic tolerance, have also been demonstrated in hypoxia-tolerant or hibernating animals [25]. A better and more detailed understanding of the pathways, transmitters, and molecules engaged in such protection may provide new insights into novel therapies for a range of disorders characterized by neuronal death [52]. Recent clinical studies suggest such an endogenous neuroprotective effect in human brain [52, 66].

Conclusion

From neuroanatomical and physiological studies, direct projections from neurons in the superficial MDH to several brainstem autonomic areas, the ventrolateral medulla, the A5 area and peribrachial complex can be demonstrated. These projections undoubtedly play a key-role in apnea, bradycardia and selective vasoconstriction. Further investigations are needed to characterize exactly these projections. The functional relevance of the TCR may lie in mediating a reflexive neurogenic neuroprotection that emanates from oxygen-sensitive sympathoexcitatory reticulospinal neurons of the RVLM. These cells, excited within seconds by reduction in blood flow or oxygen, initiate the systemic vascular components of the oxygen conserving reflex. They profoundly increase rCBF without changing CMR_{O2} or CMR_{glc} and, hence, rapidly and efficiently provide the brain with oxygen. Such potential endogenous neuroprotective strategies may extend the clinical appearance of the TCR over those actually known, to include the prevention of other potentially brain injury states as well. This may be in line with the suggestion that the TCR is a physiological, but not a pathophysiological entity.

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