Review paper

Trigemino-cardiac reflex: A recently discovered "oxygen-conserving" response? The potential therapeutic role of a physiological reflex

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Abstract

The trigemino-cardiac reflex (TCR) is defined as a sudden onset of parasympathetic dysrhythmia, sympathetic hypotension, apnea or gastric hypermotility during the 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. By this physiological response, adjustments of the systemic and cerebral circulations are initiated to change the cerebral blood flow in a manner that is not yet understood. It appears that the cerebrovascular response to hypoxemia is, to a large extent, due to this reflex and is generated by the activation of neurons of the rostral ventrolateral reticular nucleus; the existence of such endogenous neuroprotective strategies may extend beyond the actually known clinical appearance of the TCR and include the prevention of other potential brain injury states as well.

Key words: trigemino-cardiac reflex; rostral ventrolateral reticular nucleus of the medulla; oxygen-conserving; ischemia.

Since the initial report of the trigeminal cardiac reflex (TCR) occurring during tumor operations in the cerebellopontine angle in humans [1], there has been an increasing and continuing debate about this response to trigeminal irritation. Other articles have additionally described this reflex during skull base operations in the region of the petrosal sinus, of the falx and microvascular decompression of the trigeminal nerve [2, 3]. The physiological function of this reflex has not yet been fully understood [2, 4]. The only electrophysiological studies that exist are those of extramedullary recorded medullary neurons during electrical stimulation of the trigeminal ethmoidal nerve [cited in 5] and are thus of limited value for the centrally induced TCR. Therefore, there is only a vague definition of the TCR that is manifested by a sudden development of cardial dysrhythmia up to asystole and arterial hypotension after central or peripheral stimulation of any division of the trigeminal nerve [6]. Our initially introduced criteria of the occurrence of the TCR with a simultaneous reduction of mean arterial blood pressure and heart rate of more than 20% of the baseline level after stimulation of any division of the trigeminal nerve is now generally accepted [1].

Due to a lack of sufficient clinical and experimental data, there is an operational definition based mainly on anatomical data of the physiological

background of the TCR: 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 [6]. This afferent pathway continues along the short internuncial nerve fibers in the reticular formation to connect with the efferent pathways in the motor nucleus of the vagus nerve [6]. The vagus provides parasympathetic innervation to the heart, vascular smooth muscle and abdominal viscera. Vagal stimulation via these connections after trigeminal nerve activation is thought to account for the reflexive response.

The TCR represents a phylogenetically old reflex that has not, until recently, gained much interest in the neurological literature. In particular, the effects of the TCR on cerebral vasculature are incompletely defined. Since it is generally accepted that the diving reflex and ischemic tolerance involve, at least partially, similar physiological mechanisms [6-8], the existence of such endogenous (neuro)protective strategies may stress the clinical importance of the TCR; thus, the definition of the TCR may also include the diving reflex. The latter has been much better investigated to date.

Even though there are no convincing experimental data, the TCR may be a specific example of a group of related responses generally defined by Wolf as "oxygen-conserving reflexes" [9], since the autonomic manifestations of the TCR seem to be both parasympathetic and sympathetic [6]. Within seconds after reflex initiation, it is followed by a strong and differentiated activation of sympathetic nerves and of the rostral ventrolateral reticular nucleus of the medulla [9]. Protecting the brain from a lack of oxygen supply may be an important function of the rostral ventrolateral reticular nucleus of the medulla [10]. The consecutive elevation in the cerebral blood flow is not associated with changes in the cerebral metabolic rate of oxygen (CMR_{02}) or the cerebral metabolic rate of glucose (CMR_{glc}) and hence represents a primary cerebrovascular vasodilation [9, 11]. An experimental excitation of the rostral ventrolateral reticular nucleus of the medulla, electrically or chemically with L-Glu, is followed by changes in the arterial blood pressure and regional cerebral blood flow and leads to a synchronization of the EEG [5]. The observation that electrical or chemical stimulation of the rostral ventrolateral reticular nucleus always changes these two physiological parameters in parallel suggests that the evoked changes in the regional cerebral blood flow and EEG are linked in some manner and share, at least in part, common projections [9]. Such increased cerebal blood flow resulting from a stimulation of the rostral ventrolateral medulla might reflect vasoconstriction of systemic vascular beds, redistributing cardiac output toward the brain, without an actual change in cerebral vascular resistance. In this context, it would be important to know whether the TCR increases or decreases total peripheral resistance to blood flow.

The TCR underlines the essential role of the rostral medulla in the organization and integration of the cerebrovascular adjustment to hypoxia and/or cerebral ischemia [9]. It appears that, to a large extent, the cerebrovascular response to hypoxemia is due to this reflex and is generated by an activation of the neurons of the rostral ventrolateral reticular nucleus. This observation is supported by the fact that a stimulation of the rostral ventrolateral reticular nucleus, like by hypoxemia, causes elevated regional cerebral blood flow without changing the cerebral metabolism [11, 12] and that bilateral lesions of the rostral ventrolateral reticular nucleus reduce, by up to 50%, the elevation of the cortical blood flow elicited by hypoxemia, without affecting the cerebrovascular response by hypercapnia or impairing cerebrovascular autoregulation [5, 11]. Because the rostral ventrolateral reticular nucleus does not innervate the cerebral cortex [13], the intracerebral pathway mediating cortical vasodilation is indirect, and the first synapse resides in the medullary vasodilator area, which is innervated directly from the rostral ventrolateral reticular nucleus [14]. An excitation of the medullary vasodilator area elicits changes in the arterial blood pressure, regional cerebral blood flow and EEG that are quantitatively identical to those evoked from the rostral ventrolateral reticular nucleus [15]. Bilateral lesions of the medullar vasodilator area block the cerebrovascular and electrocortical responses to stimulation of the rostral ventrolateral reticular nucleus, as well as hypoxia-induced cerebral vasodilatation [15]. The vasodilatation effects of medullary vasodilator area excitation is relayed by the subthalamic nucleus to other areas of the brain [15]. The integrated response functions to redistribute blood from the viscera to the brain in response to a challenge to the cerebral metabolism.

It is generally accepted that various noxious stimuli given below the threshold of brain damage are able to induce tolerance in the brain against a subsequent deleterious stimulus of the same or even another modality that is called "cross tolerance" [16] and that this phenomenon probably involves separate systems of neurons of the central nervous system [6]. The one which mediates a reflexive neurogenic protection emanates from oxygen-sensitive sympatho-excitatory reticulospinal neurons of the rostral ventrolateral medulla oblongata. The system mediating reflex protection projects via as-yet-undefined pathways from the rostral ventrolateral medulla oblongata to the upper brainstem and/or

thalamus and finally engages a small population of neurons in the cortex which appear to be dedicated to reflexively transducing a neuronal signal into cerbrovascular vasodilatation and synchronisation of electrocortical activity [10]. Reticulospinal neurons of the rostral ventrolateral medulla oblongata are "premotor" neurons and, as such, are critical for detecting and initiating the vascular, cardiac and respiratory responses to brainstem hypoxia and ischemia. The systemic response to the excitation of rostral ventrolateral medulla oblongata neurons, however, results from the activation of a network of effector neurons distributed elsewhere in the central nervous system. Thus, sympathetic excitation is mediated by an excitatory projection to spinal preganglionic sympathetic neurons and the bradycardia via projections to cardiovagal motor medullary neurons [6, 10].

It may be hypothesized that the sympathoexcitatory reticulospinal neurons of the rostral ventrolateral medulla may represent a key element of the endogenous neuroprotective pathways, which relays a cerebrovascular response of different origin to other areas of the brain. A better and more detailed knowledge of the cascades, transmitters and molecules engaged in such endogenous protection by the TCR may provide new insights into novel therapeutic options for a range of disorders characterized by neuronal cell death. Recent clinical studies suggest such an endogenous neuronal protective effect in the human brain [17] and represent a rational basis for the development of neuroprotective drugs [18]. Given the potential hazard of inducing ischemic tolerance by the TCR in humans, a trial may not be advisable and proof may require the testing of agents that safely mimic the effects of the TCR.

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