Commentary

Oxygen-Conserving Implications of the Trigemino-Cardiac Reflex in the Brain: The Molecular Basis of Neuroprotection?

Bernhard J Schaller,[1] Nora Sandu,[2] Jan F Cornelius,[1] Andreas Filis,[3] and Miguel A Perez-Pinzon,[4] for the Trigemino-Cardiac-Reflex-Examination-Group (T.C.R.E.G.)

[1]Department of Neurosurgery, University Hospitals of Paris, Paris, France, and [2]Department of Neurosurgery, University Hospital Lausanne, Lausanne, Switzerland; [3]Case Western Reserve University, Minimally Invasive Neurosurgery Lab, University Hospital, Cleveland, Ohio, United States of America; and [4]Cerebral Vascular Disease Research Center, University of Miami Miller School of Medicine, Miami, Florida, United States of America

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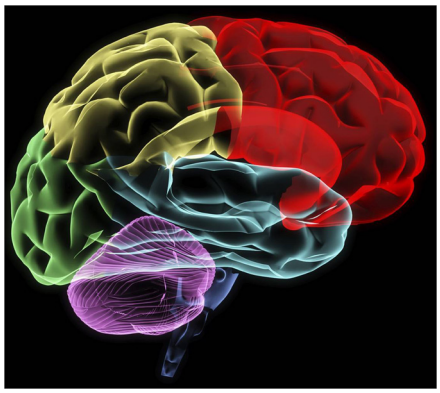
Online address: http://www.molmed.org
doi: 10.2119/molmed.2009.00013

The trigemino-cardiac reflex (TCR) is defined as a sudden dysrhythmia with arterial hypotension accompanied by apnea or gastric hypermotility after stimulation of any of the sensory branches of the trigeminal nerve (1). The sensory nerve endings of the trigeminal nerve transmit neuronal signals via the Gasserian ganglion to the sensory nucleus of the trigeminal nerve (2). This initiates adjustments in the systemic and cerebral circulation to adjust the cerebral blood flow in a manner that is not yet well understood (3). Extensive investigations in animals have documented the involvement of supramedullary regions of the brain in cardiovascular regulation (4–6). It appears that the cerebrovascular response as part of the TCR is generated by the activation of the reticulospinal neurons of the rostral ventrolateral medulla (RVLM) to elevate cerebral blood flow (CBF) reflexively and most likely slow cerebral metabolism as part of an oxygen-conserving reflex. The existence of such endogenous neuroprotective strategies also may have an important physiological role namely by stabilizing the brain function and by the prevention of permanent cerebral ischemic damage. However, examinations of higher influences on basic cardiovascular control mechanisms in man are still sparse.



Diving reflex is an example of a peripheral TCR. The main stimuli eliciting the diving reflex is the chilling of the face. The most pronounced physiological adjustments are bradycardia and peripheral vasoconstriction, but also the initiation of apnea. Cardiac output is redistributed to favor blood flow to the heart and brain, while blood flow to most visceral organs, inactive muscle groups, and the skin are reduced. The TCR therefore causes redistribution in blood supply. Transcranial Doppler ultrasonography (TCD) studies give a reproducible value of brain perfusion by continuous non-invasive real-time sampling (7). With TCD, it can be shown that the CBF rises in the middle cerebral artery (MCA) in healthy subjects during facial cooling with normal ventilation when resting in a supine position without any change in the systemic blood pressure (7). This may suggest a neuroprotective effect of the TCR and therefore some kind of an oxygen-conserving effect. Despite this preliminary data it is yet unknown how exactly CBF and cerebral metabolism are affected by the TCR.

The oxygen-conserving reflexes are sympathetically mediated vasomotor responses of a small population of neurons that reside in the subnucleus of the C1 area of the RVLM (11,12). These neurons mediate sympathetic and cerebrovascular responses to hypoxia and play a critical role in modulating circulatory control, maintaining arterial pressure,

Address correspondence and reprint requests to *Bernhard Schaller, Rämelstrasse 12, CH-4106 Therwil, Switzerland. E-mail: bernhard.schaller@yahoo.de.*
Submitted March 2, 2009; Accepted for publication March 3, 2009; Epub (www.molmed.org) ahead of print March 6, 2009.

and mediating the vasomotor component of cardiovascular reflexes (8). In fact, exposure of excised slices from the RVLM to either hypoxia or sodium cyanide (which inhibits mitochondrial respiration), results in neuronal excitation (9). Extensive studies have been carried out on the mechanisms by which these reflexes mediate vasomotor responses in response to hypoxia. For example, two K^+_{ATP} channel inhibitors injected into RVLM, tolbutamide and glibenclamide, elevated arterial pressure and rCBF, potentiating the hypoxic responses (10). Finally, the RVLM neurons are the principal relay for the cerebrovascular dilation mediated by the cerebellar fastigial nucleus (FN) (8). In fact, direct electrical stimulation of the cerebellar FN protected the CA1 region of the hippocampus and reduced infarct volume by 50% after global (11) and focal (12) cerebral ischemia, respectively.

Interestingly, it seems that the same neuronal centers, the rostral neurons in the ventrolateral medulla, play a major role in protecting the brain of ischemic insult whether the underlying event is acute, chronic, or intermittent. In fact, in the case of TCR, the brain is protected instantly by a reflex-mediated response of the cardiovascular system. If hypoxemia is chronic or intermittent, brain protection results from long-term adaptive changes on the cellular and molecular level that occur in the same cell groups of import in the acute changes mediated by the TCR, suggesting an oxygen-conserving part of the TCR. The exact relationship between reflective, acute changes of physiological parameters and long-term changes on the molecular level are unclear; more basic research has to be done to underline this hypothesis.

DISCLOSURE

We declare that the authors have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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