J. Cell. Mol. Med. Vol 13, No 4, 2009 pp. 644-647

Oxygen-conserving reflexes of the brain: the current molecular knowledge

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Received: August 16, 2008; Accepted: January 6, 2009

Abstract

The trigemino-cardiac reflex (TCR) may be classified as a sub-phenomenon in the group of the so-called 'oxygen-conserving reflexes'. Within seconds after the initiation of such a reflex, there is neither a powerful and differentiated activation of the sympathetic system with subsequent elevation in regional cerebral blood flow (CBF) with no changes in the cerebral metabolic rate of oxygen ($CMRO_2$) or in the cerebral metabolic rate of glucose (CMRglc). Such an increase in regional CBF without a change of $CMRO_2$ or CMRglc provides the brain with oxygen rapidly and efficiently and gives substantial evidence that the TCR is an oxygen-conserving reflex. This system, which mediates reflex protection projects *via* currently undefined pathways from the rostral ventrolateral medulla oblongata to the upper brainstem and/or thalamus which finally engage a small population of neurons in the cortex. This cortical centre appears to be dedicated to reflexively transduce a neuronal signal into cerebral vasodilatation and synchronization of electrocortical activity. Sympathetic excitation is mediated by cortical-spinal projection to spinal pre-ganglionic sympathetic neurons whereas bradycardia is mediated *via* projections to cardiovagal motor medullary neurons. The integrated reflex response serves to redistribute blood from viscera to brain in response to a challenge to cerebral metabolism, but seems also to initiate a preconditioning mechanism. Better and more detailed knowledge of the cascades, transmitters and molecules engaged in such endogenous (neuro) protection may provide new insights into novel therapeutic options for a range of disorders characterized by neuronal death and into cortical organization of the brain.

Keywords: oxygen-conserving reflex • diving reflex • trigemino-cardiac reflex

In the last few years, the so-called 'oxygen-conserving reflexes (OCR)' [1] have been gaining increasing interest, especially among neurosurgeons and other neuroscientists [2–8]. This term was coined by the research work of Wolf *et al.* [1] and Andersson *et al.* [9], who studied oxygen consumption in resting human beings. They found that apneic situations with bradycardia were associated with a slightly smaller reduction in arterial O_2 saturation than apneic situations without bradycardia.

A typical example of these OCRs in natural life is the 'dive reflex' observed in diving mammals. It is a protective OCR aimed to keep the body alive during submergence in cold water, preparing itself to sustain life [1, 3, 10, 11]. It is elicited by contact of the face with cold water and involves breath-holding, intense peripheral vasoconstriction, bradycardia, decreased ventilation and increased mean arterial pressure, maintaining the heart and the brain adequately oxygenated at the expense of less hypoxia-sensitive organs [10, 12].

Human beings are not able to hold their breath for as long as diving mammals. This might be due to a less-developed diving response [1]. However, the dive reflex is considered playing a major role in the etiopathogenesis of sudden infant death syndrome (SIDS) or crib death, whose underlying pathological substrates are considered to be mostly congenital in nature and involving the brainstem [13, 14]. Another example of OCRs in human beings represents the trigemino-cardiac reflex (TCR) which was first reported by Schaller *et al.* [14] during surgery in the cerebellopontine angle. It was observed that electrical, mechanical or chemical manipulation of the trigeminal nerve on its intra- or extracranial course may provoke drop in mean arterial blood pressure and bradycardia [8, 14, 15].

Very little is known of these two principal clinical examples of reflexogenic aberrance, and the international literature seems far away to provide the exact pathophysiology of TCR and dive-reflex. It appears, however, that the dive reflex may rather be a

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doi:10.1111/j.1582-4934.2009.00659.x

sub-phenomenon and that the TCR is the superordinate principle [2–5]. Understanding both these OCRs would be of enormous clinical importance to resolve major problems, especially during surgery or invasive procedures, but also the dreaded SIDS.

The importance and frequency of the TCR and its sub-phenomenon, the diving reflex, prompted us to evaluate in more details the current knowledge of their molecular bases, as well as of their clinical implications.

It is generally accepted that the diving reflex and ischemic tolerance involve, at least in part, similar physiological mechanisms [8, 12, 15]. As regards TCR, this seems to be the higher principle, with the diving reflex being one specific clinical manifestation among others when stimulating the trigeminal nerve. The discovery of those endogenous neuroprotective strategies underlines the clinical importance of TCR. Even though no convincing experimental data exist, TCR may be a specific example of a group of related responses generally defined by Wolf as 'OCRs' [2]. Within seconds of the initiation of such a reflex, there is a powerful and differentiated activation of the sympathetic system [2]. The subsequent elevation in cerebral blood flow (CBF) is neither associated with changes in the cerebral metabolic rate of oxygen ($CMRO_2$) nor with the cerebral metabolic rate of glucose (CMRglc). Hence, it represents a primary cerebral vasodilatation [2]; a state in which the arterial blood pressure seems not to have any influence. However, a temporary reduction in peripheral consumption of O_2 resulting in a slower O_2 uptake from the alveolar space to the blood, would temporarily conserve O_2 for the benefit of the central nervous system and the heart, which cannot sustain their metabolism without O_2.

It has been largely shown that various noxious stimuli may, when applied below the threshold of brain damage, induce tolerance in the brain against a subsequent deleterious stimulus of the same or even another modality; these phenomena are called 'ischemic pre-conditioning' and 'cross-tolerance', respectively [14, 16]. They probably involve separate systems of neurons of the central nervous system [8]. One of these two systems which mediate reflexive neurogenic protection emanates from oxygen-sensitive sympatho-excitatory reticulospinal neurons of the rostral ventrolateral medulla oblongata. These cells, excited within seconds by a reduction in CBF or $CMRO_2$, initiate the systemic vascular components [17]. They profoundly increase regional CBF without changing $CMRO_2$ or CMRglc and hence rapidly and efficiently provide the brain with oxygen [17]. The exact projections are currently undefined. They are thought to project from the rostral ventrolateral medulla oblongata to the upper brainstem and/or thalamus and finally project to the small population of cortical neurons. These appear to be dedicated to reflexively transduce a neuronal signal into cerebral vasodilatation and synchronization of electrocortical activity [17]. Reticulo-spinal 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 of the brainstem to hypoxia and ischemia [18]. The systemic response to excitation of rostral ventrolateral medulla oblongata neurons, however, results from activation of a network of effector neurons distributed elsewhere in the central nervous system [18]. Thus, sympathetic excitation is mediated by projections to spinal pre-ganglionic sympathetic neurons whereas bradycardia is mediated by projections to cardiovagal motor medullary neurons [8, 17]. The integrated response serves to redistribute blood from viscera to brain in response to a challenge to cerebral metabolism [18].

The second mechanism that protects the brain itself from ischemia is represented by the intrinsic neurons of the cerebellar fastigial nucleus and mediates a conditioned central neurogenic neuroprotection. This mechanism is activated by excitation of the intrinsic neurons of the fastigial nucleus and is independent of the first mechanism. These two mechanisms initiate the systemic components of the oxygen-conserving TCR within seconds of excitation [18]. The CBF is significantly increased without changing $CMRO_2$ and thus, the brain is rapidly provided with oxygen.

These mechanisms described above need a pre-exposure that can be seen clinically by a repetitive stimulation of the TCR, for example during operation [14]. That the brain may have neuronal systems dedicated to protecting itself from ischemic damage at first appears to be a new concept. However, upon reflection, this is not surprising given that there exist naturalistic behaviours characterized by very low levels of regional CBF, such as diving or hibernation [12]. The exact mechanisms of neurogenic neuroprotection are unknown, but such neuroprotective adaptation may be part of preconditioning strategies [19]. Probably, these reflexes, like the TCR, may prevent other brain insults as well – which therefore remain unrecognized.

Accordingly, it can be suggested that the TCR represents a 'physiological' entity rather than a pathological one. Better and more detailed knowledge of the cascades, transmitters and molecules engaged in such endogenous protection may provide new insights into novel therapeutic options for a range of disorders characterized by neuronal death and into cortical organization of the brain. Hypoxic or anoxic tolerance is found ubiquitously in nature, especially in diving species and hibernating species [20, 21]. A common feature in most anoxic-tolerant species or during hibernation is a pronounced metabolic depression [22]. For example, it is now well accepted that during diving, turtle brains undergo metabolic depression, which is characterized by a depression in electrical activity [23, 24].

One question that arises in the field of ischemic preconditioning (IPC) is whether it induces metabolic depression in a similar manner as that observed in diving vertebrate species or during hibernation. Up to now, there are no studies that have directly demonstrated that electrical activity in mammalian brain is particularly depressed after IPC. But the evidence points towards that fact. It is well established that inhibitory pathways are enhanced after IPC. For example, several groups have demonstrated that glutamate release during ischemia was ameliorated by several forms of preconditioning [25–27], and down-regulation of the excitatory receptors alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) [28] and N-methyl-D-aspartic acid (NMDA) [29] also occurred. In contrast to glutamate, increases in gamma-aminobutyric acid (GABA) release were observed after IPC

[26, 27]. These results also suggest that IPC, like in diving species, promotes a metabolic rate down-regulation in brain, thus reducing energy consuming pathways.

In the diving reflex, however, adapted species must be metabolically prepared to respond to a potential hypoxic insult. It is possible that activation of the diving reflex by shifting blood flow to the brain, provides additional time that allows the brain prepare for the eventuality that anoxia ensues, by activating signalling pathways similar to those observed as triggers of IPC.

Two good candidates to trigger a neuroprotective cascade during the diving reflex and IPC are adenosine and the activation of the ATP-sensitive potassium channel. Several studies have demonstrated the role of the adenosine A1 receptor in both anoxia tolerance in diving species and in IPC [29–37]. Activation of the K^+_{ATP} channel, likely plays a role in at least some of the mechanisms of IPC [29, 38]. However, the precise K^+_{ATP} channel involved remains undefined. Recently, two ATP-sensitive potassium channels have been described. One of these channels resides in the plasma membrane; the other resides in the mitochondrial inner membrane. The mtK^+_{ATP} has been suggested to be the key channel involved in IPC [39, 40]. It has been suggested that opening of the mtK^+_{ATP} channel may depolarize mitochondrial membrane potential promoting an increase in the electron transport chain rate, and thus increasing ATP production [41]. These two triggers are the logical result of the oxygen-sensing mechanism, because they are both linked to ATP levels. Once they are activated, a number of signalling pathways ensue that orchestrates the anoxic-/ischemic-tolerant phenotype. For a more in-depth description of some of these signalling pathways and genes expressed after IPC see Gidday *et al.* [16].

Further improvement in knowledge may be assigned by state-of-the-art imaging methods in the next few years: first in animal models, then in human beings and finally during operations. Recent clinical studies suggest the existence of such an endogenous neuronal protective effect in the human brain [42, 43] and represent a rational basis for the development of neuroprotective drugs. Given the potential hazard of inducing ischemic tolerance by the TCR in human beings, a trial may not be advisable, and proof of testing of agents that safely mimic the effects of the TCR may be required.

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