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Ischemic postconditioning in cerebral ischemia: Differences between the immature and mature brain?

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ABSTRACT

Ischemic postconditioning (postC), defined as serial mechanical interruptions of blood flow at reperfusion, effectively reduces myocardial infarct size in all species tested so far, including humans. In the brain, ischemic postC leads to controversial results regardless of variations in factors such as onset time of beginning, the duration of ischemia and/or reperfusion, and the number of cycles of occlusion/reperfusion. Thus, many major issues remain to be resolved regarding its protective effects. Future studies should aim to identify the parameters that yield the strongest protection, as well as to understand why the efficacy of ischemic postC differs between models. This review will focus on initial hemodynamic changes and their consequences, and on specific features such as NO-dependent vascular tone and/or prolonged acidosis in cerebral ischemia-reperfusion in order to better understand the dynamics of ischemic postC in the developing brain.

1. Introduction

The term "postconditioning" (postC) was first introduced in 1996 by Na et al. (Na et al., 1996). Zhao et al. were the firsts to report the application of postC to limit reperfusion injury in experimental acute myocardial infarction (Zhao et al., 2003). Ischemic postC combining brief periods of ischemia alternating with brief periods of re-flow applied at the onset of reperfusion following sustained ischemia effectively reduces myocardial infarct size in all species tested, including humans (Ovize et al., 2010; Staat et al., 2005). Interest in this field has been rekindled with several studies suggesting that postC might reduce injury to organs other than the heart, such as the brain (Zhao et al., 2006) and the kidney (Sun et al., 2004).

A Number of reviews has been published in the last few years, but while most of them have focused on signaling pathways induced by ischemic postC–we refer the reader to the excellent review by Zhao et al. (Zhao, 2009)–here we will discuss about early physiological parameters that could account for successful or unsuccessful postC in experimental models of cerebral ischemia. For translation to humans in cardiology, the recommended algorithm for postC and protection takes into account at least 3 factors: the delay after which the first re-occlusion is established; the duration and number of re-occlusion; and the duration of interspersed reperfusion (Ovize et al., 2010). A similar postC algorithm [time onset of occlusion, duration of occlusion and/or reperfusion, and number of cycles (Ovize et al., 2010)] has also been evaluated In cerebral ischemia, but has yielded contradictory effects, suggesting that specific and timing cell death features differ according to the different models used, and/or the developmental stage, leading to efficiency or not by using a same postC protocol. The effectiveness or ineffectiveness of the postC algorithm could depend on i) the patency of collaterals, ii) NO-dependent vascular tone, and iii) intracellular acidosis. Knowledge of these intrinsic anatomical, functional and physiological features, which vary from one model to another, even in the same species, should improve our

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understanding of the dynamics of ischemic postC during brain development.

2. Developmental physiological and vascular characteristics

During normal brain development (Table 1), physiological parameters indicate that paCO2 decreases between 7 day-old (neonatal) and 15 day-old (juvenile) rat becoming normocapnic as the adult rat. Structural changes in postnatal microvasculature as evidenced by increased cortical vessel branching between P15 and P25, endothelial cell proliferation around P10 (Harb et al., 2013), and increased vascular density between P8 and P21 (Fernandez-Lopez et al., 2013) may contribute to differential changes in blood-flow modulation in response to ischemia-reperfusion. Furthermore, CO_2-mediated vasoreactivity (in the internal carotids) is impaired in the neonatal rat, and appears in the juvenile rat, similar to that measured in the adult rat (personal data), suggesting impairment of the endothelial function (see below).

3. Collateral network and postconditioning

Native collaterals are preexisting arteriole-to-arteriole anastomoses that connect adjacent arterial trees and that limit the ischemic tissue damage that occurs with sudden or progressive arterial obstruction. Collateral circulation and the associated compensation in downstream perfusion have been recognized for their potential in myocardial ischemia research long before preconditioning or partial/gradual reperfusion. The establishment of collateral blood-supply may also occur during cerebral ischemia and/or after reperfusion.

3.1. Collateral recruitment during cerebral ischemia

In the neonatal P7 rat brain during ischemia (Bonnin et al., 2011) a rise in mean blood-flow velocities (mBFVs, as measured using ultrasound imaging) both in the contralateral internal carotid artery and basilar trunk (BT) was observed. Mean BFVs were increased in the BT during occlusion of both left and right common carotid arteries (Bonnin et al., 2011). This rise in mBFVs during ischemia (Table 1) reflects the patency and efficacy of collateral support through the circle of Willis (primary collateral network). Blood-flow supply is then rerouted towards efficient cortical arterial anastomoses between vascular networks from anterior (ACA) to middle (MCA) and, posterior to middle cerebral arteries (secondary collateral support). In contrast, such a rise in mBFVs was not detected during ischemia in a similar stroke model applied in the adult rat (Lapergue et al., 2011), suggesting inadequate collateral support during ischemia. In the adult rat (in a model of transient MCA occlusion), good collateral flow during MCA occlusion provides complete protection from ischemic injury in variable areas of the cortex and striatum, if reperfusion is achieved. Conversely, poor collateral status is associated with a greater extent of both ischemic core and penumbra (Beretta et al., 2015). Maps of blood flow on the surface of the frontoparietal cortex (using laser speckle contrast imaging) and measures of speckle contrast in multiple regions of interest (ROI) indicate that partial blood flow in branches of the MCA is maintained through anastomoses the develop between distal segments of the ACA and MCA during thromboembolic MCAo both in the adult rat (Armitage et al., 2010) and in the immature rat (Leger et al., 2013).

3.2. Hemodynamic changes during reperfusion

The restoration of blood flow–reperfusion–to the ischemic territory in the adult rat brain is characterized by a significant hyperemia within the penumbra immediately after the removal of occlusion (Pinard et al., 2000), which could be related to the substantial vasodilation of the local vascular network. Ischemic postC was reported to either interrupt hyperemia (Zhao et al., 2006) or shorten hyperperfusion time (Wang et al., 2008), or both (Gao et al., 2008), resulting in reduced infarct volume. These studies suggest that abrupt reperfusion may exacerbate ischemic injury, and that ischemic postC is a valuable strategy to reduce infarct. Studies have reported collateral blood flow after several hours of reperfusion, but not immediately after arterial re-flow (when anastomoses are not longer perfused) in adult rodents (Armitage et al., 2010), and in humans (Liebeskind, 2009). In contrast in neonatal rodents, we have demonstrated that the carotid arteries are gradually perfused during early re-flow, as shown by ultrasound imaging, laser speckle contrast imaging, and [^{14}C]-iodo-antipyrine autoradiography (Leger et al., 2013). This absence of hyperemia could reflect a lower magnitude of vasodilation in response to the potent redistribution of blood-flow through the collateral network initiated during ischemia (Bonnin et al., 2011), and its maintenance during early re-flow (Leger et al., 2013). This important difference between immature and mature hemodynamic responses may be consistent with data demonstrating that neonatal animals had larger caliber midline collaterals than adult animals 6 months after bilateral CCA occlusion (Choy et al., 2006 Table 1).

Regardless of the ischemic postC protocol used, infarct volumes are not reduced in P7 rat pups after 72 h of recovery (Leger et al., 2012). The hyperemic episode could, however, depend on the duration of ischemia. In a model of asphyxial cardiac arrest in P17 rats, early subcortical hyperemia has been shown to occur during the first 15 min of the return of spontaneous circulation after 8.5 and/or 9 min of asphyxia, but not after 12 min of asphyxia (Manole et al., 2009), suggesting that important differences in reperfusion patterns develop with an increase in the duration of injury. A hyperemic episode has also been reported in four-week but not one-week-old rats (Table 1) after cerebral hypoxia-ischemia (Qiao et al., 2004). A very recent study strengthens the role of ancillary perfusion by showing that the infarct-limiting effects of ischemic postC are influenced by the anatomical pattern of the arteries involved in the blood supply to the brain in a model of MCA embolism in the adult rat. In this study, the ischemic postC protocol consisting of 5 episodes each of 10 s of ischemia and 10s of re-flow [previously shown to be protective (Zhao et al., 2006)] was effective in limiting infarct size limitation only in animals with the typical bifurcating MCA branching pattern. In animals with a multiple branching MCA pattern or a combination of multiple branching with bifurcation, which presumably have better collateral blood supply to the affected MCA territory, ischemic postC was ineffective (Shcherbak et al., 2012).

Together, these data suggest that ischemic postC interrupts and reduces both primary hyperemia and secondary hypoperfusion leading to a more progressive re-flow as observed in the immature brain with early collateral recruitment. The onset of collateral recruitment appears to be a potent neuroprotective agent against tissue injury.

4. NO-dependent vascular tone and postconditioning

Increased collateral blood-flow suggests the existence of effictive vascular reserves after ischemia and reperfusion, whatever the organ studied. One important determinant of vascular tone is nitric oxide (NO) (Charriaut-Marlangue et al., 2013), produced by NO