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Metabolic Shift toward Succinate Oxidation and Cerebral Reperfusion Injury Following Perinatal Hypoxia-Ischemia

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Editorial

Perinatal Hypoxic-Ischemic (HI) brain injury is one of the predominant causes of permanent neurological handicap in newborn infants [1]. Despite considerable progress in neonatal intensive care and the introduction of neonatal neuro-critical care, our current understanding of this disease does not allow for the development of mechanism-targeted neuroprotective interventions. HI-brain injury is initiated by acute oxygen and substrate deprivation secondary to the collapse of cerebral circulation. HI produces a severe bioenergetic crisis leading to cellular demise if nutrient and oxygen supply are not restored in appropriate time. If cerebral circulation is reestablished, then reperfusion initiates full or partial brain recovery. At the same time, reperfusion can also serve as a critical stage of HI injury. Recently, it has been shown that one of the leading mechanisms of reperfusion injury is oxidative stress in which mitochondria are recognized as the primary sites for excessive production of Reactive Oxygen Species (ROS) [2]. Since mitochondrial ROS production occurs primarily early on during reperfusion, metabolites fueling ROS production should also be oxidized in the same time period [3]. In normoxic brains, mitochondria are mostly fueled by the oxidation of NAD-linked, complex-I dependent substrates [4]. In post-ischemic neonatal and adult brains, there is an almost 30-fold elevation of FAD-linked substrate, succinate, and a decrease in the NAD-linked substrates except for alpha-ketoglutarate [4,5]. As reperfusion progresses, both FAD- and NAD-linked substrates are restored to normoxic levels [4]. The reperfusion-driven decline in succinate is coupled with gradual elevation of fumarate. This suggests that accumulated succinate is actively metabolized during the initial stage of reperfusion. Indeed, experiments with *ex-vivo* isolated brain homogenates fuelled with glucose demonstrated preferential oxidation of succinate at the onset and during the initial reperfusion [4]. This post-ischemic shift in mitochondrial substrate oxidation is of critical mechanistic significance, because oxidation of succinate creates Reverse Electron Transport (RET) from complex-II to complex-I which dramatically increases ROS production compared to conventional, complex-I-dependent Forward Electron Transport (FET, from complex-I to complex-IV) [5-7]. Our previous reports have demonstrated that partial inhibition of the reperfusion-driven recovery of mitochondrial complex-I significantly reduced mitochondrial ROS generation and attenuated HI-brain damage [8,9]. Furthermore, it has been shown in cardiac and brain ischemia-reperfusion injury that the extent of damage was strongly linked to accumulation of succinate [5]. These data suggest that at the onset of reperfusion, the recovery of mitochondrial metabolism is driven by the oxidation of succinate which reactivates ATP generation via FET, but simultaneously generates an excessive amount of ROS via RET. Significantly greater tolerance of complexes-II, III and IV to ischemic depression compared to complex-I explain FET-dependent recovery of ATP generation upon reperfusion [10]. Succinate supported RET, however, requires active complex-I to provide electron flux from complex-II to the electron acceptor, NAD^+ [11,12]. Complex-I is the most sensitive mitochondrial complex to ischemic depression [13]. Therefore, at the onset of reperfusion, when complex-I is depressed, succinate oxidation mostly contributes to bioenergetics recovery (ATP production), as FET does not depend on complex-I activity. However, once complex-I reactivates (at five minutes of reperfusion), succinate oxidation begins to support elevated production of ROS via RET [14]. This concept of reperfusion injury explains the mechanism of neuro- and cardioprotection exerted by transient inhibition of complex-I recovery during initial reperfusion reported by us and others [9,15,16]. Thus, there three most critical biological conditions that have been reported in support of RET-dependent mechanism of excessive mitochondrial ROS release in reperfusion: 1) reactivation of complex-I, 2) accumulation of succinate and 3) preferential oxidation of succinate in mitochondria [4,5,9]. Considering post-ischemic inhibition of complex-I activity, preferential mitochondrial oxidation of accumulated succinate is critical for ATP replenishment at the initiation of reperfusion. The supplementation of succinate upon reperfusion has been shown to reduce myocardial infarction [17]. In the model of perinatal HI-

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brain injury succinate accumulation was linked to improved neo-angiogenesis and neuro-recovery governed by G-protein coupled receptor 91 [18]. Thus, post-ischemic accumualtion and preferential oxidation of succinate in neonatal HI-brain injury contributes to both bioenergetics recovery and reperfusion-driven oxidative stress. Considering normalization of succinate levels with reperfusion the elevation of complex-II (succinate-dehydrogenase) product fumarate and recovery of NAD-linked substrate concentrations and NAD-linked mitochondrial respiration with reperfusion, this preferential succinate oxidation must be transient [4,8,19]. We propose that at the initiation of reperfusion, transient pharmacological inhibition of complex-I reactivation could be considered as the initial therapeutic maneuver against reperfusion injury. This strategy does not alter bioenergetics recovery, because complex-I does not participate in succinate supported ATP production. However, it should be restricted only to the reperfusion stage when succinate is actively metabolized. This stage could be defined by the detection of cerebral succinate content and its normalization using MRI-spectroscopy. In conclusion, further studies to understand pro-survival and pathogenic mechanisms induced by post-HI accumulation and preferential oxidation of succinate in the developing brain are critically important to develop a novel concept of metabolic resuscitation which should be initiated with a return of circulation in the ischemic brain.

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