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Short Commentary

Hypothesis on the use of Galactose in Prolonged Cardiac Arrest to Restore Neuronal Bioenergetics

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ABSTRACT

Cardiac arrest survivors are prone to brain injury, secondary to ischaemia/reperfusion. Several studies on both human and animal models have shown an association among intra-arrest hyperglycemia and poor neurological recovery. However, the optimal blood glucose levels have not been established by the 2020 American Heart Association Guidelines for Advanced Cardiac Life Support. Glucose can become harmful for the brain, likely due to critically low brain ATP levels, caused by sustained cardiac arrest, that hinder its utilization. In fact, glucose must be phosphorylated to enter the glycolytic pathway. By contrast, D-galactose can become the substrate of Hexose-6-Phosphate-dehydrogenase (H6PD, E.C. 1.1.1.47) expressed in the myelin sheath. H6PD conducts a pentose phosphate pathway acting on several phosphorylated and non-phosphorylated hexoses, utilizing both NAD^+ and $NADP^+$. Here, the compassionate early use of intravenous galactose is proposed to sustain the cellular bioenergetics in cardiac arrest, followed by perfusion with 50% glucose plus 50% galactose, the latter mimicking breast milk. It is supposed that early use of galactose in prolonged cardiac arrest would supply the myelin H6PD of galactose that can become its substrate also its non-phosphorylated form. Such pentose phosphate pathway would produce reducing equivalents that may feed the electron transfer chain expressed in the sheath, restoring the proper bioenergetics conditions in turn allowing glucose utilization.

INTRODUCTION

Prolonged cardiac arrest is a major cause of death [1]. Moreover, cardiac arrest survivors can suffer permanent disability due to brain injury secondary to ischaemia and reperfusion [2]. Duration of cardiac arrest and of Cardiopulmonary Resuscitation (CPR, the procedure attempting to restore tissue perfusion), influences outcome, along with Blood Glucose (BG) levels. Elevated BG levels in patients resuscitated from out-of-hospital ventricular fibrillation were shown to predict poor outcome [3]. A number of studies showed an association among hyperglycemia and poor neurological recovery [4-6]. The effect of dextrose on neurological outcome and Return of Spontaneous Circulation (ROSC) was studied on 100,029 patients and it was found that those receiving dextrose had lower rates of survival and worse neurological outcome, compared to patients who did not receive it [7]. A study conducted on 145 nondiabetic ventricular fibrillation cardiac arrest survivors reported that high blood glucose levels over the first 24 h after ROSC were independently associated with unfavourable neurological recovery [2]. More recently, a study showed that intra-

arrest blood glucose administration was not correlated with improved outcomes for in-hospital cardiac arrest patients [8]. Postischemic hyperglycaemia was shown to cause neuronal damage [2], hampering the cerebral bioenergetics recovery. Typically, post-resuscitation disease includes disturbances of cerebral blood flow and oxygen extraction [9]. However, the optimal BG range has not been established, and the 2020 American Heart Association Guidelines for Advanced Cardiac Life Support (ACLS) did not address the issue of intra-arrest BG levels normalization by dextrose usage during cardiac arrest resuscitation [10]. Similar results were reported in animal studies, showing that cerebral hypoxia/reperfusion damage is worsened by hyperglycaemia [11,12]. Glucose administration before cardiac arrest in cats worsened neurologic outcome [13]. These data appear quite surprising, considering that the brain relies essentially on glucose for its bioenergetics [14]. The human brain, accounting for about 2% of the body weight uses 20% of the body glucose.

We may wonder why and how glucose, a beneficial nutrient, can become harmful. Firstly, we must consider the pathophysiological circumstances, in which the subjects find themselves, i.e.: prolonged cardiac arrest. In those conditions, ATP levels would be too low to allow glucose utilization. In fact, glucose is an expensive nutrient, which, after entering the cell via the Glucose Transporter (GLUT) family of proteins, must be phosphorylated by hexokinase enzymes to effectively be trapped inside the cell and enter the glycolytic pathway [15]. As discussed previously, glucose, an essential nutrient under steady state conditions, would cease to be favourable in case of absolute ATP deficiency [16]. Upon ATP shortage, glucose would only end up in depleting the meagre ATP reserves of the cell. Interestingly, in the high-risk preterm newborn, hyperglycemia was shown to be independently associated with mortality and poor outcome [17]. In infants with hypoxic ischaemic encephalopathy, hyperglycaemia or labile BG levels are associated with brain injury [18]. Also, in neonates with encephalopathy, worse global brain function is associated with hyperglycemia [19].

D-galactose (D-Gal) is the C-4 epimer of glucose that forms the disaccharide lactose binding with D-glucose. It metabolism was reported to occur in in the liver and also in the brain and [20]. In fact, D-Gal can pass the blood brain barrier and enter the neurons across GLUT3 [21]. It is widely accepted that D-Gal is metabolized through three routes: the Leloir pathway, involving galactokinase, galactose-1-phosphate-uridylyltransferase, UDP-galactose-4-epimerase, its conversion to galactonate, followed by the pentose phosphate pathway, and its reduction to galactitol, similarly to bacteria [22]. The involvement of hexose 6-Phosphate Dehydrogenase (H6PD), a luminal enzyme of the Endoplasmic Reticulum (ER) that bears a favourable K_M for both phosphorylated and unphosphorylated D-Gal, is not considered as an alternative pathway, although such route would be exclusive of eukaryotes, that possess an ER. The importance of D-Gal metabolism is evidenced by its disorders, such as classic galactosemia, caused by mutation in the galactose-1-phosphate uridylyl transferase gene (OMIM #230400), which mainly affects the brain causing cognitive impairment [23]. Interestingly, D-Gal administration exerts opposite effects depending on the dosage [16]. D-Gal has been used to generate animal liver and brain aging models [24], the latter displaying oxidative damage and mitochondrial dysfunction [24]. On the other hand, oral D-Gal supplementation at low doses has been proven beneficial in neurologic diseases [4,5]. D-Gal has been utilized *in vitro* to boost the oxidative metabolism, bypassing glycolysis and to increase the expression of the proteins of the oxidative phosphorylation (OxPhos) [25]. The biological importance of D-Gal in human physiology likely transcends its role in newborn nutrition and metabolism [26]. D-Gal has been proposed to play a role in neuronal bioenergetics role entering the myelin sheath and becoming the substrate of the Hexose-6-Phosphate-dehydrogenase (H6PD, E.C. 1.1.1.47), therein expressed [27]. H6PD is an Endoplasmic Reticulum (ER) enzyme conducting a pentose phosphate pathway [28], able to oxidize several phosphorylated and non-phosphorylated hexoses [29], including D-Gal and 2-deoxy-D-glucose, using NAD^+ or $NADP^+$ as substrates [30]. H6PD was shown to contribute to the brain ^{18}F-Fluoro-*deoxy-D-glucose* uptake [31]. H6PD activity on D-Gal was assayed in purified myelin, where it would sustain its metabolism [27]. In fact, myelin was shown to conduct an extra-mitochondrial OxPhos [32], that would supply ATP to the axoplasm via connexons [33]. As the respiratory Complex I is expressed in myelin [34], H6PD would provide reducing equivalents in the form of either NADH, which would enter the

myelin ectopic Electron Transfer Chain (ETC), sustaining the extra-mitochondrial oxidative metabolism, or NADPH, thanks to its versatility in the utilisation of pyridinic nucleotides. The latter would act in the detoxification of free radicals [35]. A beneficial role of small amounts of orally administered D-Gal on neuropathological processes has been reported [20,36]. D-Gal ameliorated congenital face recognition deficit (prosopagnosia) [37], and the central symptoms of a patient with multiple sclerosis-like demyelinating brain lesions [38]. D-Gal was proposed as a novel neuroprotective treatment for Alzheimer's disease, for its direct effects on the brain, and the gastro-intestinal tract. In particular, it was shown that D-Gal can normalize cerebral glucose hypometabolism [39]. It was reported that administration of D-Gal prevents the cognitive deficits induced by reduced brain metabolism caused by streptozotocin treatment in rats [36]. The therapeutical applications of D-Gal would be still in their infancy [26].

Following this line of thought, and considering the role played by oxidative stress during the ischemia/reperfusion phase of ROSC, the compassionate early use of intravenous D-Gal to sustain the cellular bioenergetics in the prolonged cardiac arrest, rather than simple saline, is here proposed. No studies have approached this topic, as the involvement of H6PD in the metabolsim of D-Gal, and of myelin as a metabolic supportive sheath is not universally accepted. Perfusion could then be switched to saline containing 50% glucose plus 50% D-Gal, mimicking the carbohydrate content of human milk [40]. In fact, at the dawn of human history, a putative hypoxic newborn could exclusively rely on milk (actually, colostrum, which however bears the same glucidic percentage as mature milk), to survive. Notably, breast milk contains equal parts of beta-D-Gal and either alpha- or beta-glucose in the form of lactose. In fact, it is well known that early initiation of breastfeeding is essential for all infants, especially for the high-risk ones. Consistently, the American Academy of Pediatrics (AAP) recommends initiating feeds within the first hour of life for infants at risk [41]. In case of prolonged cardiac arrest, the subject suffering this condition would be clinically dead, and its neuronal ATP content next to none, which justifies the need to avoid glucose in an early resuscitation phase, differently from an hypoxic but still alive newborn, to avoid the ATP-consuming activation of hexokinase.

In conclusion, the early use of D-Gal in cardiac arrest would rely on H6PD ability to utilize non-phosphorylated D-Gal in the myelin sheath, overcoming the impaired energy charge. In a subsequent phase, the restoration of the ATP cellular physiologic content would allow the neuron to utilize also D-glucose. This would allow to re-establish proper bioenergetics conditions, that would progressively allow the use of glucose. In fact, due to the differential affinity of hexokinase for D-Gal with respect to glucose, some unphosphorylated D-Gal may reach the ER and become an early substrate of H6PD. The latter activity would allow the finely tuned loading of reducing equivalents on either NAD^+ or $NADP^+$, to sustain the metabolic extra-mitochondrial or antioxidant cellular needs, both required in case of hypoxia/reperfusion damage.

CONFLICT OF INTEREST

Author declares no conflict of interest.

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