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Full Length Research Paper

Glucose-6-phosphate dehydrogenase: The balance between energy production and genetic material repair in cyanogenic toxicity response

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The adult neurons are entirely dependent on aerobic metabolism involving the glycolytic pathway. The primary transport mechanism of glucose have been found to be dependent of exchange with glutamate, while the glutamate thus released is converted into glutamine by the surrounding astrocytes. In the metabolism of the glucose taken up by the neurons, glucose-6-phosphate dehydrogenase converts the glucose-6-phosphate into ribose sugar precursor for generation of genetic materials. In this study, we explain the basic of the rational for the conversion of glucose-6-phosphate (G-6-P) into ribose sugar as against the G-6-P proceeding into pyruvate formation for ATP generation. In toxicity studies where oxidative stress was induced by cyanide, we observed a decline in G6PDH levels. In analysis of these findings, it was observed that the G6PDH levels were secondary indicator of oxidative stress. The primary cause in the enzyme shift is for more G6P to proceed into energy production to compensate for the energy block created by cyanide while at the same time reducing the amount of G6P converted into ribose sugar for DNA repair.

Key words: Glucose, glutamate, DNA repair, G6PDH.

INTRODUCTION

Cyanide is a naturally occurring toxic substance that has been identified in a variety of food crops (Osuntokun, 1981). Cassava is the most widely consumed of these plants and it has been associated with the economic conditions in certain parts of the World; especially the tropics and sub-tropics (Okafor et al., 2002). Plants like cassava are called cyanophoric plants because they contain phytotoxins (cyanogenic glycosides). The term cyanide will usually refer to free cyanide (CN-) or hydrogen cyanide (HCN). For cyanide to exist in either state (as CN or HCN), it will depend on certain physical parameters such as pH.

It has been shown that in a medium of pH 7, most of the cyanide will be in the form of free cyanide (CN), while at pH of 11, 99% of cyanide will exist as HCN. Equilibrium is however achieved in the pH range of 9.3-9.5 (Nicholls and Soulimane, 2004).

Cyanide is highly reactive and forms salt readily with the alkali earth metals. The most reactive of these salts are those of sodium, potassium and calcium. They also dissociate easily in water to release free cyanide. The salts of copper, cadmium and molybdenum are less reactive and dissociate less easily and are often called “weak acid dissociable” (Isom et al., 1999).

The bio-activation of cyanide

Cyanide is readily absorbed and distributed following its oral administration, such that 9% activity can be recorded in the stomach, 0.9 activity in the brain and 84% activity in the urine 24 h after administration (in the form of

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thiocyanate-SCN). The basic form in which cyanide is excreted from the body is the form of SCN (Isom et al., 1999). The enzyme rhodenese has been implicated with the function of converting cyanide into SCN, thus the major defence of the body against cyanide toxicity is the enzyme rhodenese, which will convert cyanide to SCN in the presence of thiosulphates or sulphur containing amino acids. However, since the enzyme is present in large quantities but sequestered in sites that are not readily accessible, the rate limiting factor in the conversion of cyanide to SCN is thus the relative abundance of thiosulphates and SAA (Isom and Way, 1984). Other form in which cyanide is excreted is in the form of 2-iminothiozoldine-4-Carboxylic acid; a reaction product formed as a result of the reaction with L-cysteine. The reaction is reversible by co-incubation with curcumine (Isom et al., 1999).

CYANIDE IN ENERGY METABOLISM OF THE BRAIN

Cyanide has long been implicated with the ability to induce oxidative stress. It does so by virtue of its ability to inhibit cytochrome C oxidase, which is responsible for converting molecular oxygen into water to generate the proton gradient required to drive ATP production at complex V of the electron transport chain (Magistretti and Pellirini, 1996). When such a blockade occurs, oxygen radicals are generated at complexes I and III of the electron transport chain (ETC). In this context, we would like to describe oxidative stress in 2 typical systems (Ogundele and Olu-Bolaji, 2011);

(i) Type I: which is the type of oxidative stress observed in a system where oxygen is present but the transfer of the available is blocked
(ii) Type II: which is present in a system where oxygen is entirely absent; such is possible under low oxygen concentration in the circulatory system.

Oxygen radical generation is not characteristic of the Type I oxidative stress and not entirely characteristic of type II oxidative stress. The generated ROS in Type I then in turns induces lipid peroxidation. The most significant effect of lipid peroxidation can be felt on the membranes (lysosomal, nuclear, mitochondrial and cell membrane). The effect on nuclear membrane exposes the genetic materials to leaked endonucleases and phosphatases in the cytoplasm. The definitive response of the neurons to strike a balance between its energy requirement and repair of its genetic material is imperative (Denison et al., 2009).

Pivotal role of glucose-6-phosphate dehydrogenase (G6PDH)

G6PDH is an enzyme that has been used as a direct indicator of oxidative stress, especially as G6PDH: LDH ratio (de Graaf et al., 2001). G6PDH catalyses the conversion of glucose-6-phosphate into ribose sugar. This represents the diversion from early stages of glycolysis to the pentose phosphate pathway (PPP), thus G6PDH does not directly represent the glycolytic pathway. We can therefore say that G6PDH shunts glucose-6-phosphate (G6P) into RNA/DNA formation as against formation of high energy pyruvate. High levels of G6PDH will indicate a diversion of G6P into RNA production and reduction in the G6P meant for pyruvate formation; which will imply the neuronal metabolic system favouring repair of the genetic materials against energy requirements of the neuron. While a reduction in G6PDh observed during oxidative stress means a reduction in the rate at which G6P is converted into ribose sugar (DNA precursor), thus, the system favours energy production over the repair of genetic materials.

In cyanide toxicity, a definitive response is imminent; whether the neuron will strike a balance between the repair of its degenerating genetic materials and its energy requirement or favour one over the other poses a major scientific question in the field of cyanide induced cell death. At this point, we would like to visualise toxicity response in terms of the metabolic requirement for cell survival as against oxygen consumption to drive ATP production. A very important indicator of oxidative stress has been the G6PDH: LDH ratio, because G6PDh is preferred against hexokinase since its a rate-limiting step in the glycolytic pathway and LDH is a key enzyme in determining the fate of the glycolytic pathway to either proceed into formation of high energy pyruvate or stop as lactate (de Graaf et al., 2001). In a previous experiment, cyanide induced oxidative stress as shown in the G6PDh: LDH ratio which follows a similar trend as the level of superoxide dismutase (SOD). However, while constructing a toxicity response model (Figure 1), the reduced level of G6PDH against LDH can imply two things;

(1) Since G6PDH catalyses the conversion of G6P into ribose sugar, a reduction in G6PDh will allow more G6P to proceed to the end of glycolysis to form high energy pyruvate (a precursor of the tri-carboxylic acid (TCA) cycle)
(2) An increase in G6PDH level will imply that more G6P has been shunted to the PPP to generate ribose sugar for DNA production).

From the accounts of cell death, a similar event has been seen to precede apoptosis and necrosis, but the intensity of such an ‘initial event’ has been implicated in deter-mining the pattern and the adopted mode of cell death. DNA cleavage has been described as the most significant event for apotosis and necrosis (Katherine et al., 2001; Denison et al., 2009). The DNA cleavage pattern has been used to distinguish between the two modes of cell death genetically (Katherine et al., 2001). If

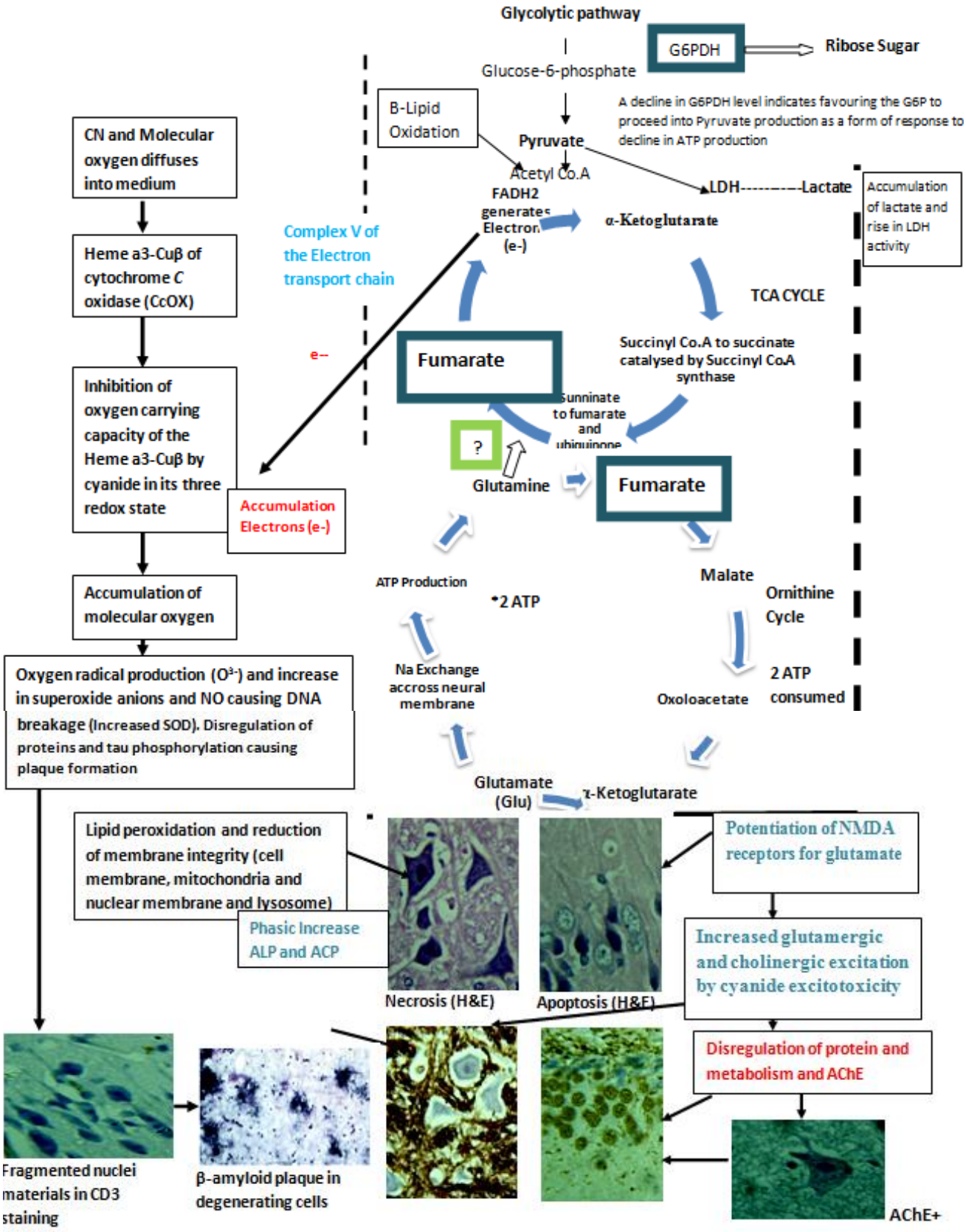

Figure 1. Proposed toxicity response model mechanism in cyanide neurotoxicity in the visual relay centres.

a definitive response to toxicity involves DNA breakage, is there a possibility of DNA repair machinery? A reduction in G6PDH usually termed as oxidative stress does not imply oxidative stress in its entirety but rather basic changes observed as result of effects of toxicity on the metabolic machinery of the neuron secondary to the oxidative stress. The level of G6PDh are not pre-determined but are dependent on the composition of the cytoplasm (neuronal metabolic system) such that when oxidative stress is induced the system will self-regulate to compensate for energy needs; thus, the G6PDH activity tilt the system as a regulator of energy need against DNA repair. When cyanide toxicity is induced, ATP production is impaired (indirectly by inhibition of cytochrome C oxidase), thus G6PDh levels will reduce to favour formation of pyruvate over ribose sugar for DNA repair, thereby leading to a deficiency in the DNA repair machinery. This is likely to precede the DNA cleavage characteristic of both modes of cell death (Figure 1).

The above explanation appears to be a missing link in the neglected science of necrosis. A rapid drop in G6PDh level and DNA repair machinery causes a rapid degradation of the cell, while a milder decrease in the G6PDh level can be found to induce apoptosis. This is evident in experiments performed by Katherine et al. (2001) which suggested dose dependence in the adopted mode of cell death of NP3 cells. Thus, to investigate or understand cell death pattern, the actual relationship between G6PDH and endonucleases activity should be investigated to account for the gap caused by reduced G6PDh level as a factor of DNA repair and DNA damage against the generalized term of oxidative stress. The action of cytochrome- c- oxidase (CcOX) at complex V is to transfer oxygen into water to generate the proton gradient required to drive ATP production. During the blockade of CcOX and Complex V, two major events will occur;

(i) Reduction in ATP production,
(ii) Production of oxygen radicals.

Both events will be characteristic of oxidative stress. The reduction in ATP will most likely have a direct effect on G6PDH, while the radicals will affect the membrane. We can also deduce that in a normal system, G6PDH will usually function to favour DNA repair since the neuron has more RNA than DNA. When oxidative stress is induced, reduction in ATP production will cause G6PDH to withdraw from DNA repair to favour ATP production from pyruvate to meet the energy requirement of the neuron under stress. It is also important to note that the generated radicals react with nitrogen to form NO and reactive nitrogen species (RNS). The NO thus formed is also an endogenous modulator of cell death (Isom and Way, 1984; Isom et al., 1999).

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