

*Editorial*

## **Ketogenic Diet Provides Neuroprotective Effects against Ischemic Stroke Neuronal Damages**

**Sheyda Shaafi, Javad Mahmoudi, Ali Pashapour, Mehdi Farhoudi, Saeed Sadigh-Eteghad, Hossein Akbari\***

*Neurosciences Research Center (NSRC), Tabriz University of Medical Sciences, Tabriz, Iran.*

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### **Abstract**

Ischemic stroke is a leading cause of death and disability in the world. Many mechanisms contribute in cell death in ischemic stroke. Ketogenic diet which has been successfully used in the drug-resistant epilepsy has been shown to be effective in many other neurologic disorders. The mechanisms underlying of its effects are not well studied, but it seems that its neuroprotective ability is mediated at least through alleviation of excitotoxicity, oxidative stress and apoptosis events. On the basis of these mechanisms, it is postulated that ketogenic diet could provide benefits to treatment of cerebral ischemic injuries.

### **Introduction**

Nowadays, Ischemic stroke is one of the major health problems worldwide.<sup>1</sup> It leads to approximately, 6000000 death annually<sup>2</sup> and according to WHO estimations the number of stroke victims will raise to 7.8 million in 2030.<sup>3</sup> In the brain, arterial occlusion disrupts blood flow and causes glucose and oxygen deprivation. This results in the occurrence of ischemic stroke<sup>4</sup> and initiation of divergent sequence of cellular dysfunctions in a limited area of brain.<sup>5</sup> Despite some immediate medical interventions such as thrombolytic therapy, treatment of acute ischemic stroke is a real challenge for health professionals and majority of patients experience various permanent disorders.<sup>6</sup> Stroke leads to degeneration of neurons, vascular endothelial cells and other supportive cells within the necrotic core of ischemic injury.<sup>7</sup> Decline in blood flow has an axial role in the pathophysiology of stroke and development of its irreversible insults. Indeed immediately after stroke, the central part of brain parenchyma faced to the marked blood supply decline, becomes depolarized, enlarged and eventually undergoes necrotic procedure. This necrotic tissue is surrounded by a zone of moderate injured tissue, termed as ischemic penumbra.<sup>2</sup> Accordingly, in normal circumstances the blood flow to brain is 55ml/100gr/min. If it falls to 18ml/100gr/min, neurons will become electrically functional and following cerebral stroke it falls to 8ml/100gr/min and the neuron fail to survive. Within the penumbra zone, blood follow is between 18mg/100gr/min and 8 ml/100gr/min.<sup>5</sup> From the functional aspect this region of cerebral ischemia is silent but it still metabolically active<sup>2</sup> hence, it may have

capacity to recover and medical interventions.<sup>2,5</sup> It is important to keep in mind that regenerating capacity of ischemic penumbra is not over lasting and declines over the time. Indeed, over the time some of pathologic conditions predispose its damages, although main mechanisms underlying of this procedure is not well established but it may contributed to three main cellular and molecular events: excitotoxicity, oxidative stress and Ischemia/reperfusion injury.<sup>2</sup>

Ketogenic diet was formulated in 1920 and then became popular for treatment of intractable epilepsies.<sup>8</sup> The ketogenic diet has high amounts of fat and low content of carbohydrates and proteins. Hence it provides inadequate levels of carbohydrates for metabolic procedures.<sup>9</sup> In contrast, cells within the peripheral and central nervous systems, by using of fat content of this diet alternatively compensate their metabolic needs.<sup>10</sup> Indeed, following oxidation of high amounts of fatty acids, high rates of acetyl-CoA are produced which this process, consequently leads to generation of keton bodies (acetoacetate,  $\beta$ -hydroxybutyrate and acetone) within the liver mitochondria.<sup>9,10</sup> Eventually, keton bodies are entered into the blood stream and when plasma amounts of ketone bodies rise, these molecules are consumed as an energy source in peripheral and brain tissues.<sup>10</sup> Although, in normal conditions, cerebral tissue consumes glucose as a major metabolic molecule<sup>11</sup> But, brain is able to consumption of ketons as an alternative fuel and this ability of brain is triggered by some conditions such as certain diets, fasting and extensive physical exercise.<sup>12</sup> The capability of brain to consumption of ketons instead

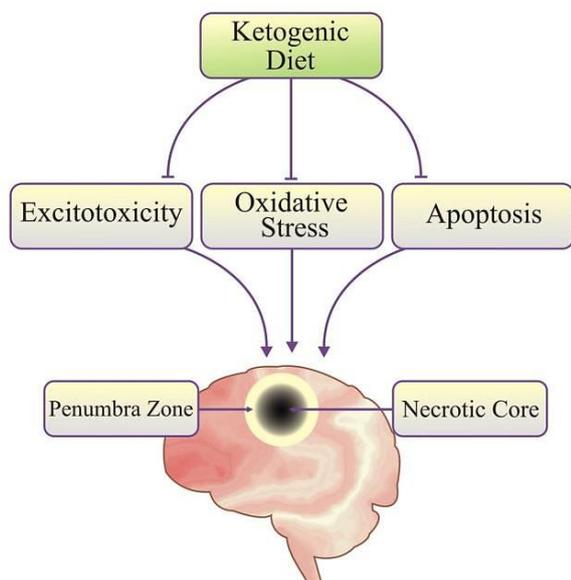
\*Corresponding author: Hossein Akbari, Fax: +98 (411) 3340730, Email: hn\_akbari@yahoo.com

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of glucose is considered as a form of cerebral metabolic adaptation.<sup>11</sup>

Emerging data from the preclinical investigations have proposed additional therapeutic options for KD, besides its effects on the drug-resistant forms of epilepsy. There is evidence that show KD is able to protect neurons and improves functional outcomes in some experimental models of neurodegenerative conditions such as: Alzheimer's disease,<sup>13</sup> Parkinson's disease<sup>9,14</sup> and Huntington's disease<sup>15</sup> and spinal cord injuries.<sup>16</sup>

As shown in Figure 1 and as mentioned above oxidative stress, excitotoxicity and apoptosis are three pathologic process involved in many neurologic disorders ranging from neurodegenerative disease to ischemic stroke.<sup>17</sup> Experimental finding suggested that adverse out comes of these events can be reduced by KD; therefore it may exert promising effect against ischemic damages. In this paper we focused on the different roles of these events in ischemic stroke and pointed out the benefites of KD against these pathologic conditions.



**Figure 1.** Mechanisms underlying of ischemic stroke and inhibitory effect of ketogenic diet against development of ischemic insults.

### Excitotoxicity

Following ischemia, Failure in energy metabolism occurs, leads to accumulation of glutamate as a highly toxic agent for neuronal cells, in the synaptic cleft and initiation of glutamate excitotoxicity cascade.<sup>2</sup> In this process, glutamate through activation of its receptors increases  $Ca^{2+}$  levels within the neurons. Increased intracellular  $Ca^{2+}$  amounts activates several neurotoxic mechanisms such as: impairment of mitochondrial function,<sup>9</sup> production of free radicals<sup>18</sup> and stimulates apoptotic proteins.<sup>19</sup>

Invitro finding suggests that keton bodies are able to protect some kinds of neurons from the excitotoxicity adverse effects and increase their survival time.<sup>18</sup> Therefore it seems that, KD may have regulatory role in energy metabolism and glutamate excitotoxicity.

### Oxidative stress

Oxidative stress has pivotal role in ischemia/reperfusion injuries, worsens the cerebral ischemic conditions and extends the penumbra zone damage. As mentioned, following reperfusion period, significant amount of free radicals are generated by mitochondria and thereby these agents are eliminated by some kinds of free radical scavengers. Over the progression of ischemic injury, the imbalance between production and scavenging of free radicals is occurred which leads to increasing of ischemic insults.<sup>20</sup>

Studies have been shown that KD improves the neurons free radical elimination ability. This effect, in part may mediated through increasing of glutathione levels and improvement of mitochondrial antioxidant capacity and protection of mitochondrial from the oxidative stress induced destruction.<sup>14</sup> Moreover, invitro studies have been established that keton bodies through regulation of NADH oxidation reduce free radical induced oxidative stress in neuronal cells.<sup>18</sup>

### Apoptosis

Neurons in the penumbra zone are affected by apoptosis or programmed cell death after several hours or days. The gradual progression of this type of neuronal death may create an opportunity to recover alive neurons from the ischemic damage.<sup>21</sup> As noted above, excessive generation of free radicals disrupts mitochondrial function consequently leads to leakage of pro-apoptotic factors such as cytochrome c in to the cetoplasmic space<sup>18</sup> and activation of caspase proteases-mediated apoptosis.<sup>22</sup>

Studies have demonstrated that keton bodies reduce some apoptotic biomarkers.<sup>9,18</sup> As believed, many different biogenic molecules are involved in apoptosis, but approximately in all cases the main pathway leads to apoptosis is the activation of caspase proteins. Results from animal studies have demonstrated that KD is able to block at least one of the caspase proteins and exert neuroprotective effect.<sup>23</sup>

Consequently, it may be postulated that administration of KD could provide benefits in treatment of cerebral ischemic injuries and provide golden opportunity to healing of remaining neurons in the penumbra zone.

### Conflict of interest

Authors declare no conflict of interest.

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