

# Modulatory role of ketogenic diet on neuroinflammation; a possible drug naïve strategy to treatment of Parkinson's disease

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## Abstract

Parkinson's disease is the second common neurological disease associated with elderly. Neuroinflammation contributes in neuronal death in Parkinson's disease (PD). The ketogenic diet (KD) is low in carbohydrates, adequate in protein, and high in fat, has been used in intractable epilepsy and seems to be effective in neurologic disorders. The implication of Neuroinflammation in PD has been emphasized and there is evidence show that KD may provide advantages to reduce neuroinflammatory adverse effects. Based on this surmise, it seems that KD could reverse some neuronal injuries of PD.

**Keywords:** Ketogenic diet, Neuroinflammation, Parkinson's disease

## Introduction

Parkinson's disease (PD) is a neurodegenerative disorder affects elderly older than 65 years and characterized by irreversible loss of dopaminergic (DAergic) neurons in the substantia nigra pars compacta (SNcP) and their terminal in the striatum. In PD, destruction of DAergic neurons leads to reduction of striatal dopamine levels by 70% and appearance of hypokinetic motor signs such as akinesia, tremor at rest, muscle rigidity, and postural instability (1,2). The exact mechanisms underlying of PD have not been understood, but numerous studies suggest that neuroinflammation,(3) apoptosis (4) and oxidative stress may play role in PD. There isn't

any approved treatment for delaying of PD neuronal damages and current therapies only manage its symptoms. Given this, development of novel strategies to reduction of PD insults is a high priority. Since, chronic pharmacotherapy for PD is accompanied by some adverse effects (2), hence application of non-therapeutic approaches in PD is of interest. In this paper we aimed to focus on the role of KD and neuroinflammation in PD.

## Ketogenic Diet

The ketogenic diet (KD) is a dietary regimen for producing of continuous ketonemia.

It was introduced for first time in 1920 contains high-fat, low-carbohydrate, and low-

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protein and is used to remission of drug resistance epilepsies.5 KD reduces gluconeogenesis from amino acids and activates hepatic ketogenesis through conversation of fatty acids and elevates circulating levels of major ketone bodies ( $\beta$ -hydroxybutyrate) (6,7). Under particular circumstances such as fasting, sever physical activity and hypometabolism, ketons can substitute for glucose and pyruvate as an auxiliary fuel source (8). These molecule, can penetrate the brain blood barrier (BBB) via their transporters such as monocarboxylic acids which are located on the endothelial cells of the BBB (7).

In the brain, ketone bodies (KBs) can be taken up by both neuronal (9) and non-neuronal cells, (7) then are consumed by the neurons in a concentration-dependent fashion. KBs provide nearly 70% of brain's energy expenditure (9). Within the mitochondria, succinyl-CoA: 3-ketoacid CoA transferase (SCOT) and acetyl-CoA acetyltransferase 1 (ACAT1) oxidizes KBs to the acetyl-CoA10 and then it enters to the Krebs cycle (11) to ATP production. There is evidence that show, induction of ketonemia by ketogenic diet may improve some of neurological conditions such as, cognitive deficits, (12) spinal cord injury, (6) ischemic stroke,(5) amyotrophic lateral sclerosis (13) and PD (11). Given this, present paper aims to review possible mechanisms underlying of KD anti-PD effects.

## Neuroinflammation

### A. Proinflammatory cytokines and PD

Accumulating data from epidemiological, post mortem findings and animal model of PD have demonstrated that neuroinflammation has role in pathogenesis of PD (14-16) Within the brain, neuroinflammatory responses are mediated through glial cells (17). Indeed, neuronal insults and some of some neurotoxins such as 6-hydroxydopamine (6-OHDA) drive

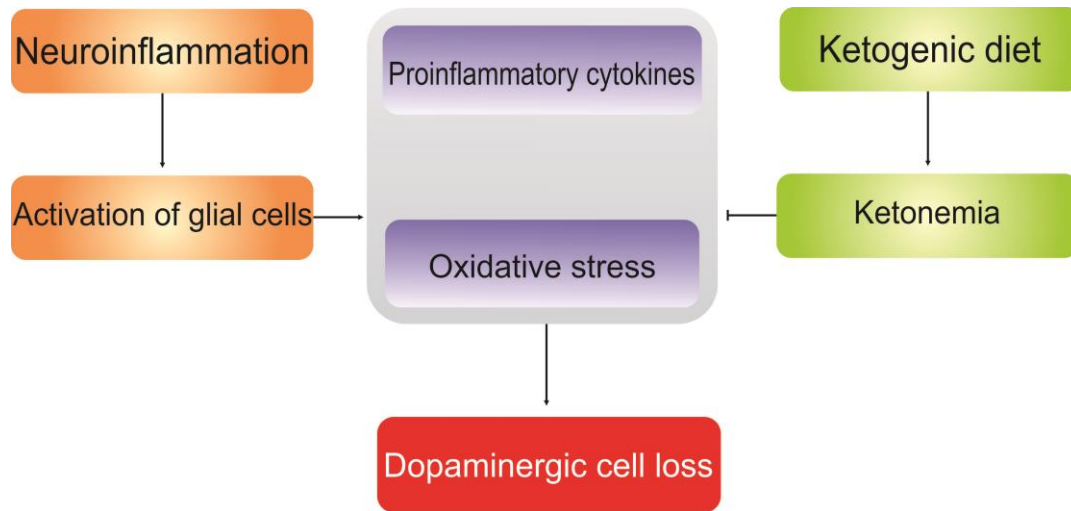
these cells from the normal form to the activated condition and activated microglia known as a biomarker of neuroinflammation (3,16). It is important to note, that 6-OHDA as neurotoxin is used to modeling of PD in rats and its able to resemble some molecular and behavioral alterations seen in PD (17). Recently, sharifi et al., described the role of neuroinflammation in development of neurological impairments in 6-OHDA-lesioned parkinsonian rats. Measuring cerebrospinal fluid levels of pro-inflammatory cytokines, they have shown that activation of microglial cells, is accompanied by increasing levels of pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6 and modulation of microglial cells activity leads to attenuation of neuroinflammation and motor signs of PD (16).

Moreover, activated glial cells release reactive oxygen species (ROS) to cope with neurotoxic injuries. However, ill control of these molecules may results in oxidative stress, mitochondrial dysfunction and apoptosis mediated neuronal cell destruction (18). In addition to 6-OHDA, 1-methyl-4-phenol-1,2,5,6-tetrahydropyridine (MPTP)-induced mice model of PD remains as a reliable tool to investigate of PD pathogenesis. Findings from MPTP- treated mice show that KD through modulation of microglial cell activation (19) mediates neuroprotective effects and improves behavioral outcomes of parkinsonian mice. Moreover, following systemic administration of MPTP, loss of tyrosine positive immunoreactive cells happens in nigrostriatal pathways. Immunohistochemical evidence also has shown that KD protects these neurons from the neurotoxic effects of MPTP (19) Beside this, Xu et al., studies on the microglia cell line, BV-2 cells, showed that,  $\beta$ -hydroxybutyrate, major component of ketone bodies, through inhibition of microglial activation prevents Lipopolysaccharide-induced inflammatory responses. They propose that, this molecule



decreases expression and releasing of TNF- $\alpha$ , IL-6 and IL-1 from the activated glial cells and increased cell viability in this invitro model of

neuroinflammation (20). As depicted in figure 1, this data shows that KD may have regulatory role on the neuroinflammation in PD brain.



**Figure 1:** The implication of neuroinflammation and the effect of KD on DAergic cell loss in PD

### B. Oxidative stress and PD

As mentioned, activated glial cells also provoke occurrence of oxidative stress in PD. It is proposed that activated microglial cells through releasing of different ROS causes destruction of vulnerable neurons. DAergic neurons in the SNpc are susceptible to oxidative stress condition. This originates from these neurons high oxygen expenditure as well as lack of adequate amount of endogenous anti-oxidants enzymes in this region (21). Given this, application of molecules to reduce both microglial activation and oxidative stress for reduction of PD signs is of interest. In vivo findings show that,  $\beta$ -Hydroxybutyrate through attenuation of H<sub>2</sub>O<sub>2</sub>, increases viability of PC12 cells (20). Notably, PC12 cell is obtained from the rat adrenal pheochromocytoma cell line (22) and widely used to assessment of some cellular and molecular aspects of neurodegenerative disorders (23). It has been suggested that, H<sub>2</sub>O<sub>2</sub> activates key enzymes of apoptotic cascades (i.e. caspase-3) and

decreases endogenous anti-oxidants content such as glutathione in PC12 cell model of PD, hence it promotes apoptotic cell death. According to Cheng et al., study, treatment of H<sub>2</sub>O<sub>2</sub> intoxicated PC12 cells by  $\beta$ -Hydroxybutyrate, ameliorate both oxidative stress and activation of apoptosis cascade, confirming that, ketogenic diet (figure 1) is able to augment anti-oxidant ability of neuronal cells (20).

### Final remark

Neuroinflammation exerts its own neuronal injuries through activation of glial cell activation, and activated glial cells release different neurotoxic molecules such as proinflammatory cytokines and ROS which result in neuronal destruction. KD guards neurons by inhibition of oxidative stress and subsequent apoptotic cell death, but its exact neuroprotective mechanisms is poorly understood and reliable investigations must be designed to reveal its anti-PD mechanisms.

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