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EDITORIAL

The therapeutic potential of ketone bodies in Parkinson's disease

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1. Introduction

While most instances of Parkinson's disease (PD) are idiopathic, multiple lines of evidence implicate a role for mitochondrial dysfunction in its etiology or progression. Deficits in bioenergetics, increased reactive oxygen species (ROS), calcium dysregulation, mitochondrial DNA mutations, dysfunctional dynamics (e.g. fission, fusion and transport) and impaired mitophagy have been identified, however efforts to improve mitochondrial function in clinical trials have been mostly disappointing [1]. Meanwhile, a class of endogenous functional metabolites, ketone bodies, which have properties seemingly suited to rescuing mitochondrial function, have been largely overlooked.

2. Ketone bodies and their mechanisms

Ketone bodies are endogenous four-carbon acids produced hepatically from free fatty acids during periods of dietary carbohydrate restriction or energy restriction/demand that are readily transported (facilitated diffusion via. monocarboxylate transporters) into the brain where they can partly substitute for glucose as a metabolite, and potentially trigger beneficial signaling pathways. The two primary ketones are beta-hydroxybutyrate (BHB) and aceto-acetate (AcAc). The third ketone (acetone), which is a spontaneous breakdown product of AcAc, is mostly eliminated by respiration or in urine. As AcAc is relatively short-lived, the main circulating ketone that crosses the blood-brain barrier is BHB. In cells, BHB is converted to AcAc which is then broken down to acetyl-CoA to enter the Krebs cycle, which in turn feeds the electron transport chain (ETC) that resynthesizes most cellular adenosine triphosphate (ATP).

The Krebs cycle and the ETC are linked by the redox state, whereby certain dinucleotides are reduced in the Krebs cycle and become electron donors to the ETC. The ETC consists of five enzyme complexes (CI-CV) in the inner mitochondrial membrane (IMM) that ferry electrons from CI to CIV, where the chain terminates with the delivery of electrons to molecular oxygen and the production of water. In the process, protons are pumped from the mitochondrial matrix into the intermembrane space, creating a potential difference across the IMM that provides the driving force for the resynthesis of ATP by CV. A natural by-product of electron transport is the generation of ROS, which cells normally have the capacity to regulate or that might drive a beneficial mitohormesis. Dysfunction along the ETC could see a reduction in ATP and an increase in ROS. Neurons most at risk may be those with particularly high energy demand, which is the case for dopaminergic neurons in the substantia nigra pars compacta that have complex unmyelinated axonal arbors, substantial total length, high levels of synaptic connectivity and a canonical role in PD [2].

There are multiple lines of evidence that CI is dysfunctional in PD. This comes from studies of the neurotoxin 1-methyl-4-phenylpyridinium (MPP+) in human and animal models and certain pesticides (e.g. rotenone), which accumulate in nigrostriatal neurons through the dopaminergic reuptake system and result in a clinical syndrome essentially indistinguishable from PD. Further support comes from human autopsy [3].

The relevance is that BHB has the potential to improve suboptimally functioning CI, as well as to bypass more severe CI dysfunction [4]. The conversion of BHB to AcAc modifies the redox state of CI and increases its drive, thus potentially up-regulating CI that are still partially functioning. Furthermore, the Krebs cycle is substantially up-regulated because of an abundance of BHB-derived acetyl-CoA. This increases the production of other metabolic intermediates by the Krebs cycle, such as succinate, which increases the drive of CII, in essence bypassing CI to restart the ETC. The combination of these factors would be expected increase ATP resynthesis and cellular bioenergetics.

As well, BHB is a signaling metabolite with epigenetic properties [5]. It is a histone deacetylase (HDAC) inhibitor, altering the transcription of genes encoding endogenous antioxidants, among others, and is itself an anti-oxidant. BHB induces brain-derived neurotrophic factor (BDNF) expression in cerebral cortical neurons. A major inflammasome of the innate immune system (NLRP3) is inhibited by BHB, and BHB has been shown to be anti-inflammatory in models of PD [6].

3. PD models

In a murine model of PD using the neurotoxin MPP+ (or its precursor), it was shown that BHB protected against cell death, increased mitochondrial oxygen consumption, substantially increased ATP resynthesis, and improved motor function [7].

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While there was an increase in ROS, this may have been secondary to the increased ATP resynthesis and be tolerated if there was an increase in endogenous antioxidants, or contribute to beneficial mitohormetic effects. The mechanism was shown to be acting through CII rather than an upregulation of CI, perhaps attesting to the severity of the damage to CI in this model. In a comparable PD mouse model, ketones were shown to alleviate motor dysfunction, reduce neuronal loss in the substantia nigra, decrease microglia activation and down-regulate proinflammatory cytokines [8].

4. Endogenous ketones

Ketosis is a natural metabolic state for the human, ancestrally important in times of food crises but uncommon in the modern era. However, a diet low in natural and refined sugars and starches that limits dietary glucose can shift human metabolism to beta-oxidation of fatty acids and hepatic ketogenesis. This ketogenic diet (KD) can be augmented with foods rich in medium-chain triglycerides (MCTs, such as coconut oil), periods of fasting, time-restricted eating, regular exercise, or some combination thereof.

There have been three preliminary trials of a KD in PD. In a small feasibility study, five participants with PD were able to follow a KD for 1 month, and all saw an improvement in their Unified Parkinson Disease Rating Scale [9]. However, the investigators were unable to rule out a placebo effect. A proof of concept trial that recruited 14 people with PD and mild cognitive impairment, randomized to a standard western diet or a KD (8 weeks in duration, n = 7 in each group), reported a between-group improvement in aspects of cognitive performance in the KD group, without a difference in motor function [10]. Mean serum BHB concentration was 0.31 mmol/L vs. 0.08 mmol/L (KD and controls respectively). A further pilot randomized control trial compared a low-fat diet with a KD in 38 people with PD and a wide range of disease severity [11]. Mean serum BHB concentration after 8 weeks was 1.2 mmol/L vs. 0.2 mmol/L (KD vs. low-fat respectively). Motor and non-motor symptoms improved in both groups, however the KD group saw a greater improvement in non-motor symptoms, including cognitive performance. An adverse effect for some in the KD group was a transient increase in tremor and/or rigidity, which led 2 participants to withdraw over the first week of the study and that requires monitoring.

It is difficult to draw conclusions from these pilot studies, as acknowledged by the investigators themselves. The duration of the studies may not have been sufficient to allow for full keto-adaptation (e.g. for epigenetic effects to manifest). Most of the participants had a large range of disease duration and severity, whereas the potential benefits of ketones are more likely in early PD before substantial neuronal loss. The BHB concentrations achieved were either below the 0.5 mmol/L threshold operationally used to define physiological ketosis, or not greatly above that. It is difficult to design a dietary intervention that is blinded.

5. Exogenous ketones

Exogenous ketone supplements may augment dietary interventions, or substitute for them. Supplement formulations include mineral salts of BHB, BHB monoesters, AcAc diesters and purified MCT oils, some of which can be formulated in combination. MCT oils, that are metabolized in the liver to ketones, produce only mild ketonemia, a limiting factor being gastro-intestinal distress (GID). The most widely available and affordable ketone supplements are BHB mineral salts, for example of sodium, potassium, magnesium or calcium, which can be combined to limit overload from any one mineral (e.g. sodium). These salts also produce only mild-moderate ketosis and can be accompanied by GID. The chemical synthesis of BHB yields two enantiomers of BHB (D- and L- forms), however only the D-form is physiological, potentially reducing the effective dose unless a D-enantiomer formulation is specified. Esters of BHB or AcAc, typically with 1,3-butanediol (BD), can more substantially increase blood ketone concentration. The BD is metabolized in the liver to ketone bodies [12], thus doubling the yield. The two main formulations are a BD-D-BHB monoester [13], which is commercially available, and a BD-AcAc diester, which is under development for seizure disorders [14]. A recent study in early-stage PD (n = 14) reported that administration of the BHB monoester transiently increased BHB > 3 mmol/L and improved endurance exercise performance [15].

6. Conclusion

Ketone supplementation combined with a regular carbohydrate-rich diet creates an unphysiological metabolic state that could undermine efficacy. A more promising approach may be to maintain a steady state of ketosis with a KD, while periodically boosting ketone concentration with supplementation. Progress will need to be made in developing a regimen that can be sustained for years, identifying individuals most likely to respond to ketone therapy, determining the threshold concentration for therapeutic ketosis, and managing other pharmacological treatments and social constraints. However, the bioenergetic potential of ketones and their wide-ranging pleiotropic effects indicate that ketone therapy holds considerable promise in PD and warrants further investigation.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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References

1. Camilleri A, Vassallo N. The centrality of mitochondria in the pathogenesis and treatment of Parkinson's disease. CNS Neurosci Ther. 2014;20:591–602.
2. Pissadaki EK, Bolam JP. The energy cost of action potential propagation in dopamine neurons: clues to susceptibility in Parkinson's disease. Front Comput Neurosci. 2013;7:13.
3. Schapira AHV, Cooper JM, Dexter D, et al. Mitochondrial Complex I deficiency in Parkinson's disease. J Neurochem. 1990;54:823–827.
4. Veech RL, Todd King M, Pawlosky R, et al. The "Great" controlling nucleotide coenzymes. IUBMB Life. 2019;71:565–579.
5. Newman JC, Verdin E. β-Hydroxybutyrate: a signalling metabolite. Annu Rev Nutr. 2017;37:51–76.
6. Fu SP, Wang JF, Xue WJ, et al. Anti-inflammatory effects of BHBA in both in vivo and in vitro Parkinson's disease models are mediated by GPR109A-dependent mechanisms. J Neuroinflammation. 2015;12:1–14.
7. Tieu K, Ramasamy R, Przedborski S, et al. D-b-Hydroxybutyrate rescues mitochondrial respiration and mitigates features of Parkinson disease. J Clin Investig. 2003;112:892–901.
8. Yang X, Cheng B. Neuroprotective and anti-inflammatory activities of ketogenic diet on MPTP-induced neurotoxicity. J Mol Neurosci. 2010;42:145–153.
9. van Itallie TB, Nonas C, Rocco A, et al. Treatment of Parkinson disease with diet-induced hyperketonemia: a feasibility study. Neurology. 2005;64:728–730.
10. Krikorian R, Shidler MD, Summer SS, et al. Nutritional ketosis for mild cognitive impairment in Parkinson's disease: a controlled pilot trial. Clin Parkinsonism Relat Disord. 2019;1:41–47.
11. Phillips MCL, Murtagh DKJ, Gilbertson LJ, et al. Low-fat versus ketogenic diet in Parkinson's disease: a pilot randomized controlled trial. Mov Disord. 2018;33:1306–1314.
12. Desrochers S, David F, Garneau M, et al. Metabolism of R- and S-1,3-butanediol in perfused livers from meal-fed and starved rats. Biochem J. 1992;285:647–653.
13. Soto-mota A, Norwitz NG, Clarke K. Why a D-β-hydroxybutyrate monoester? Biochem Soc Trans. 2020;48:51–59.
14. D'Agostino DP, Pilla R, Held HE, et al. Therapeutic ketosis with ketone ester delays central nervous system oxygen toxicity seizures in rats. Am J Physiol. 2013;304:829–836.
15. Norwitz NG, Dearlove DJ, Lu M, et al. A ketone ester drink enhances endurance exercise performance in Parkinson's disease. Front Neurosci. 2020;14:584130.