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Review

Using positron emission tomography to study human ketone body metabolism: A review

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ABSTRACT

Ketone bodies – 3-hydroxybutyrate and acetoacetate – are important fuel substrates, which can be oxidized by most tissues in the body. They are synthesized in the liver and are derived from fatty acids released from adipose tissue. Intriguingly, under conditions of stress such as fasting, arterio-venous catheterization studies have shown that the brain switches from the use of almost 100% glucose to the use of >50–60% ketone bodies. A similar adaptive mechanism is observed in the heart, where fasting induces a shift toward ketone body uptake that provides the myocardium with an alternate fuel source and also favorably affects myocardial contractility. Within the past years there has been a renewed interest in ketone bodies and the possible beneficial effects of fasting/semi-fasting/exercising and other "ketogenic" regimens have received much attention. In this perspective, it is promising that positron emission tomography (PET) techniques with isotopically labeled ketone bodies, fatty acids and glucose offer an opportunity to study interactions between ketone body, fatty acid and glucose metabolism in tissues such as the brain and heart. PET scans are non-invasive and thus eliminates the need to place catheters in vascular territories not easily accessible. The short half-life of e.g. 11C-labeled PET tracers even allows multiple scans on the same study day and reduces the total radiation burden associated with the procedure. This short review aims to give an overview of current knowledge on ketone body metabolism obtained by PET studies and discusses the methodological challenges and perspectives involved in PET ketone body research.

Abbreviations: 3HBD, R-3HB dehydrogenase; AT, acetoacetyl thiolase; AcAc, acetoacetate; ATP, adenosine triphosphate; BBB, blood–brain barrier; CBF, cerebral blood flow; CMR, cerebral metabolic rate; CoA, coenzyme A; CPT1, carnithine pamitoyl transporter 1; FDG, fluorodeoxyglucose; FFA, free fatty acid; GLUT, glucose transporter; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; HL, HMG-CoA Lyase; LC, lumped constant; MCT, monocarboxylic acid transporter; mHS, mitochondrial HMG-CoA synthase; OHB, beta-hydroxybutyrate; PET, positron emission tomography; PDH, pyruvate dehydrogenase; SAT, succinylCoA:acetoacetate CoA transferase; SUV, standardized uptake value; TCA, tricarboxylic acid; T2, mitochondrial AcAcCoA thiolase.

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1. Introduction

Ketone bodies are produced by the liver when excess acetyl-CoA accumulates as a result of increased fatty acid oxidation and decreased glucose oxidation, and serve as important fuel sources during metabolic stress such as fasting and starvation. Ketogenesis is regulated by the supply of ketogenic precursors, primarily free fatty acids (FFAs), to the liver and by the ratio between insulin (inhibiting) and glucagon (stimulating) in the portal bed [1,2]. Ketone bodies *per se* substantially reduce circulating levels of FFAs and glycerol, compatible with a regulated feed-back inhibition of lipolysis and decreased hepatic supply of ketogenic substrate [3]. Ketone bodies are exported to the bloodstream and metabolized by extrahepatic tissues to acetyl-CoA which enters the tricarboxylic acid cycle, enabling ATP production independently of glycolysis. This results in lower oxygen consumption per mole of ATP produced, compared to glucose [4]. The principal ketone bodies in humans are beta-hydroxybutyrate (OHB), acetoacetate and acetone (the latter being largely exhaled unused), although OHB and acetoacetate technically are ketoacids. Ketone bodies have often been thought of as merely the product of a so-called spillover pathway, produced as a result of accumulation of excess acetyl-CoA in the liver in times of decreased carbohydrate availability, and which other tissues then use as an alternative fuel source. This might suggest that ketone bodies are a dispensable part of human energy metabolism, rather than an essential component. However, the fact that ketones are metabolized through biochemical pathways that are evolutionarily conserved in most animals suggests a more important role in energy metabolism. The evolutionary role of ketones in brain is also supported by the fact that in many mammals the brains of young (e.g. suckling rats) have a largely ketone-dependent metabolism to support cerebral development [5]. It is now also thought that, in addition to liver hepatocytes, brain astrocytes can synthesize ketones to be used locally by neurones [6,7].

In humans, circulating ketone bodies are always present in blood to some extent, albeit at low levels (<0.1 mmol/L) under most conditions, and increase severalfold during fasting, starvation, carbohydrate restriction and some disease states. Ketones are now known to be not only an important alternative protein-sparing and glucose-sparing fuel source for the brain and other tissues, but have also been found to exert a number of beneficial effects. There is accumulating evidence for neuroprotective effects [8–10] including anticonvulsant activity, improving cognitive function and motor performance in people with cognitive impairment [11,12], improving tolerance to insulin-induced hypoglycemia [13], protecting against oxidative stress [14] and decreasing the effects of acute brain injury and ischemic damage [15–17], as well as antitumoral effect in gliomas [18,19]. All of which has led to the suggestion that ketones could be used therapeutically for a range of diseases [4,20–23], though currently the only widely recognized therapeutic use of ketones is in the form of ketogenic diets for the treatment of epilepsy [24], and the mechanism behind their anticonvulsive activity is incompletely understood [25].

Ketones have long been studied in humans, mainly in connection with diabetic ketoacidosis and with starvation, where their primary physiological function appears to be as a protein-sparing source of energy for extrahepatic tissues. Surprisingly little is known about their role in less extreme physiological conditions, however. Increased ketogenesis resulting in moderate hyperketonemia occurs with short-term fasting regimens such as the 5:2 fast (5 days per week of ad lib eating and 2 days of consuming only 500–600 calories), low-carbohydrate diets, and, to a lesser extent, in controlled diabetes and heart failure. It is unknown to what extent states of sustained moderate hyperketonemia are metabolically equivalent to transitory or pronounced elevations in blood ketone levels, though the evidence so far suggests that the brain responds differently to hyperketonemia depending on duration and onset.

Ketones can be used by a number of organs including brain, heart and skeletal muscle, but not by the liver where they are produced. The brain in particular is a quantitatively important consumer of ketone bodies under hyperketonemia, and is the most extensively investigated organ in relation to ketone metabolism. Despite this, a great deal remains unknown about the cerebral effect of ketones, and about their interplay with other energy pathways, notably glucose and fatty acids. Due to the intrinsic methodological difficulties of studying the human brain at a molecular level, a large proportion of studies on brain ketone metabolism to date has been carried out on animals.

Early catheterization experiments on fasting humans (5–6 weeks) found that the fasting brain uses circulating ketone bodies as a major energy source [26]. Such invasive experiments are hardly reproducible nowadays, not least for ethical reasons, and less invasive methods are required to further study in vivo ketone metabolism in humans. Some evidence is derived from in vitro data on cell cultures, which may not sufficiently reflect how processes occur in the living brain, where complex intercellular trafficking and signaling pathways, particularly between neurons and astrocytes, play a central role in metabolism. It is therefore important to develop usable methods for studying such processes in vivo. Positron emission tomography (PET) has a number of advantages that make it promising as a tool to further our understanding of human ketone metabolism in a range of physiological conditions. A recent case report concerning an epileptic child treated with a ketogenic diet [27] highlights the profound shift in cerebral fuel preference away from glucose and presumably toward ketone bodies that is observed in humans with a sustained hyperketonemia. The case report also demonstrates the extent to which this reduction is apparent using 18F-FDG brain PET. The precise effect of ketones on the brain is however unclear, and experimental results are at times contradictory.

This article aims to review the contribution of PET to ketone metabolism research, first by providing a short overview of the general role of PET in human metabolic research, then discussing the experimental evidence obtained thus far in both humans and animals, with particular focus on the role of previous PET brain studies and how this modality can help to address remaining unsolved questions regarding human ketone metabolism.

1.1. *Role of PET in human metabolic research*

In recent years PET has made a significant contribution to human metabolic research, enabled by the development of an increasingly large range of targeted positron emitting tracers for in vivo visualization and measurement of metabolic activity.