

Metabolic Mechanisms Underlying Low Circulating Lactate and Pyruvate in Subjects With Alzheimer's Disease



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Abstract

Subjects with Alzheimer's disease (AD) may have low levels of circulating lactate and pyruvate but normal plasma ketone bodies (KBs, β -hydroxybutyrate and acetoacetate). In this paper, we point out the underlying mechanisms for the above findings. Low lactate and pyruvate may be accounted for by abnormalities in glycolytic and aerobic pathways, such as reduced glycogen store and/or decreased levels of glucose transport, decreased phosphofructokinase activity, and increases in oxidatively modified glycolytic enzymes. The fact that patients had normal levels of KBs suggests that they were not starving and that their dietary intakes were normal. There are potentially two negative practical consequences of these metabolic abnormalities: reduced residual physical performance and lower provision of energy substrates to several organs including the heart.

Keywords: Alzheimer's Disease; Plasma Lactate; Pyruvate; Ketone Bodies

Abbreviations: AD: Alzheimer's Disease; β -AP: β -Amyloid Peptide; KBs: Ketone Bodies; TCA: Tricarboxylic Chain Acid

Introduction

In a recent investigation by our group, subjects with Alzheimer's disease (AD) exhibited low plasma lactate and pyruvate concentrations, indicating altered skeletal muscle metabolic energy-generating pathways. This was particularly evident in subjects with a longer diagnosis time (> 5 years). However, the plasma concentrations of ketone bodies (KBs, β -hydroxybutyrate and acetoacetate) were normal [1]. In the present article we point out the metabolic mechanisms underlying both the deficit in circulating lactate and pyruvate, and normal KB concentrations. This could potentially be important for clinical practice in the non-pharmacological treatment of the disease.

Potential Mechanisms Underlying Altered Circulating Lactate and Pyruvate Levels

Abnormalities in glucose breakdown both through the glycolytic and aerobic pathways may account for the changes in plasma lactate and pyruvate. With respect to glycolysis, several steps might be interrupted in the muscles of AD subjects. For example, a reduction in myocyte glucose availability may occur following reduced glycogen store, as a consequence of the activation of the enzyme glycogen synthase kinase 3 β [2] in AD patients. This enzyme inhibits the enzyme glycogen synthase which normally catalyses the synthesis of glycogen. Moreover, other potential glycolytic defects may be decreased levels of glucose transport

[3], decreased phosphofructokinase activity [4] (which catalyses the irreversible phosphorylation of fructose-6-phosphate to fructose-1,6 bisphosphate), and increases in oxidatively modified glycolytic enzymes including enolase [5] (which catalyses the conversion of 2-phosphoglycerate to phosphoenolpyruvate). These enzyme defects have been described in neurons. However, in the light of the results of our previous study [1], we postulate that they might also be present in the skeletal muscle of the AD patients in our study.

Our hypothesis may be supported by two factors. Firstly, neurons and myocytes produce energy using the same enzyme activities. Secondly, the pathogenic β -AP, which is present in skeletal muscle [6], also exerts its toxicity on the production of pyruvate through glycolysis [7].

The fact that muscle hypometabolism depends on the diagnosis time of the disease suggests that the deterioration of the glycolytic pathway for energy production is progressive. The low plasma pyruvate level in subjects with a longer diagnosis time does not only mean reduced synthesis through glycolysis but also impaired utilisation of an important glucose by-product in mitochondrial reactions for aerobic energy generation. Some of the muscle pyruvate may be transaminated to the gluconeogenic amino acid alanine. We cannot exclude the possibility that impaired energy

provision to extramuscular tissues from low pyruvate may be compensated for by partial transformation of the pyruvate into alanine, one of the most important gluconeogenic amino acids. In any case, low plasma pyruvate means reduced liver availability of an important metabolite for energy production and other metabolic processes. Low/blocked mitochondrial utilisation of pyruvate impairs mitochondrial efficiency in energy production. This could be catastrophic for AD subjects, should they have intrinsic mitochondrial defects that have been reported in other body cells such as the dysregulated tricarboxylic chain acid (TCA) cycle [8] and changes in oxidative phosphorylation systems [9]. This has been experimentally demonstrated both in brain and peripheral cells such as fibroblasts [10] and platelets [11].

Plausible Explanations For Normal Circulating KBs

With respect to KBs, the normal plasma concentrations, an expression of a normal liver ketogenesis, may be due to the fact that the AD subjects were not starving and their dietary intakes, including fat ingestion and plasma glucose, were normal. We cannot exclude the possibility that skeletal muscle may partly contribute to normal plasma levels of KBs. Indeed, muscle tissue can synthesise KBs from Acetyl-CoA via direct deacylation [12]. This can occur whenever the release of free fatty acids by adipose tissue is higher than the fatty acid oxidation capacity of the muscle [12].

Potential Implications For Clinical Practice

Altered glucose metabolism might have a negative impact on the efficacy of physical rehabilitation that aims to maximise activities of daily living, function and mobility and reduce peripheral fatigue and the risk of injuries and falls. Moreover, this energy deficit can have unfavourable effects on the performance of physical activities, for example deambulation, in which the integrated metabolic work of vital visceral organs requires prompt adequate extra-energy availability. All these aspects involving the relationship between energy metabolism and complex physical activities of daily living, which have an impact on the quality of life of AD patients, should be investigated further. Another negative effect of altered glucose metabolism may be the impairment of several organs. Low plasma lactate, especially if associated with concomitant low pyruvate, reduces the rate of liver and kidney glucose production (gluconeogenesis). In this condition, the brain and the cells with obligatory anaerobic metabolism (red cells, leukocytes and kidney medulla) receive less glucose. Reduced gluconeogenesis aggravates brain glucose hypometabolism [13], which leads to a progression of synaptic dysfunction [14].

The low levels of lactate in AD patients cause its reduced utilisation as a fuel in the heart, since the myocardium normally uses circulating lactate as an important energy source. One practical consequence of our study [1] is that an adequate nutrition intake by subjects with a longer diagnosis time of AD may not be enough to ensure normal metabolic pathways of glucose breakdown. Consequently, nutrition intakes of AD subjects should be monitored in order to ensure that there is at least adequate peripheral availability of nutrients. Another potential consequence for clinical practice is that AD subjects with muscle hypometabolism may

increase muscle amino acid release from protein breakdown to ensure adequate gluconeogenesis processes. This requires a well-planned investigation.

Conclusion

The previous study [1] and the underlying metabolic alterations pointed out here suggest a need for future investigations to address whether and how to limit altered energy metabolism that could help to improve physical performance in AD subjects.

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