Available online at www.sciencedirect.com
SCIENCE DIRECT®
Prostaglandins, Leukotrienes and Essential Fatty Acids 70 (2004) 233–234
Prostaglandins Leukotrienes and Essential Fatty Acids
www.elsevier.com/locate/plefa

Preface

Metabolic and health implications of moderate ketosis and the ketogenic diet

Why ketones in a journal on PUFA and eicosanoids?

Over the past 10 years, the tantalizing link between β-oxidation of PUFA and ketogenesis has been interesting, fundamentally valid, and yet still somewhat overlooked; in short, just the sort of topic that this journal's founder and former editor, David Horrobin, and the current Editors, would be interested in. The authors of this thematic issue are all experts in one or more aspects of ketone metabolism. Serving as editor of this issue meets two important goals for me—it opens up the readership of this journal to an emerging frontier in fatty acid research area that I hope will lead to further research, and it raises the subject of preferential long-chain fatty acid substrates for ketogenesis for the specialists in ketone metabolism.

There are two basic observations that form the rationale both for this paper and for this issue of the journal. Further details and references are provided in the following article, entitled 'Metabolism of polyunsaturated fatty acids and ketogenesis: an emerging connection'. First, amongst common dietary long-chain fatty acids, two PUFA—linoleate (18:2ω6) and α-linolenate (18:3ω3)—appear to be preferentially utilized for ketogenesis. Empirically, this is somewhat puzzling because linoleate and α-linolenate are vitamin-like precursors to two series of long-chain PUFA, several of which have important functions as membrane constituents. At least three 20 carbon PUFA also give rise to the large and diverse family of signaling molecules, the eicosanoids (prostaglandins, leukotrienes, hepoxylins, HETES, etc.). Linoleate or α-linolenate are vitamin-like because their absence from the diet leads to defined symptoms of deficiency that have been well studied since the 1930s. So, why does the body also β-oxidize linoleate and α-linolenate and use part of the oxidized carbon for ketogenesis?

Second, a mild-to-moderate state of ketosis induced while consuming a very high fat, low carbohydrate ketogenic diet has long been known to be protective against seizures [1]. Ketosis is rightfully feared in uncontrolled diabetes but the low-to-moderate plasma ketone levels that are produced while on the high-fat ketogenic diet and which are protective against seizures

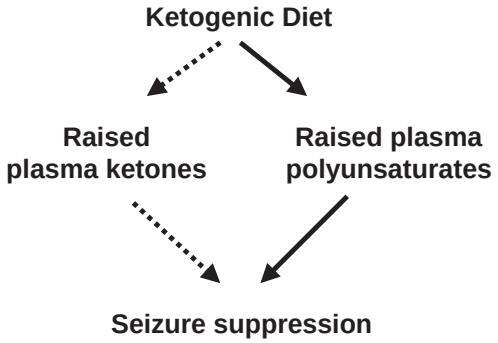

Fig. 1. Recent reports suggest that the ketogenic diet can achieve seizure suppression without necessarily raising plasma ketone bodies (ketones) [1,2]. This is shown in the figure as the dotted line connecting the ketogenic diet to seizure suppression via plasma ketones. Animal studies reviewed elsewhere [3] as well as recent human data [1] indicate that raised plasma polyunsaturated fatty acids suppress seizures directly, which is shown as the solid line. Hence, it is important clinically and experimentally to study how exactly ketosis suppresses seizures and whether the mechanism involves raised plasma polyunsaturates.

are an order of magnitude lower than in diabetic ketoacidosis and can be sustained without long-term harm for more than 2 years.

It has naturally been assumed that ketosis itself is beneficial to seizure control. Under some circumstances this is true in animal models. However, many animal experiments using the ketogenic diet have not shown improved control of experimental seizures despite significant ketosis. A positive link between ketosis and seizure control in children has been reported in some studies but, again, just as many disagree [2]. Children on the ketogenic diet can have highly variable plasma ketone levels and those with high or low levels may still be in good seizure control. Plasma β-hydroxybutyrate at even 10 mM is not necessarily sufficient for seizure control in either humans or animal models.

This impasse brings PUFA into the picture because the ketogenic diet raises plasma levels of free fatty acids released from adipose tissue (see Fig. 1) [3]. Whether the raised content of PUFA in plasma is in further support of ketogenesis in the liver or whether the released PUFA (including arachidonate [20:4ω6] and

0952-3278/$ - see front matter
doi:10.1016/j.plefa.2003.11.007

docosahexaenoate [22:6ω3]) are directly protective against seizures independently of ketosis is currently under investigation. At the moment, both mechanisms appear plausible.

References

[1] D.D. Fraser, S. Whiting, R.D. Andrew, E.A. Macdonald, K. Musa-Veloso, S.C. Cunnane, Elevated polyunsaturated fatty acids in blood serum obtained from children on the ketogenic diet, Neurology 60 (2003) 1026–1029.

[2] K. Musa-Veloso, Breath acetone as a measure of systemic ketosis in children with refractory seizures on a ketogenic diet, Ph.D. Thesis, University of Toronto, 2003.

[3] S.C. Cunnane, K. Musa, S. Whiting, D.D. Fraser, Potential role of polyunsaturates in seizure protection achieved with the ketogenic diet, Prostagl. Leukot. Essent. Fatty Acids 67 (2002) 131–135.

S.C. Cunnane
Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Canada, ON MSS 3E2
E-mail address: stephen.cunnane@usherbrooke.ca