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KETOGENIC PROTOCOLS FOR ENDURANCE PERFORMANCE

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Abstract

One of the objectives of athletic training is the development of energy systems in order to optimize the metabolism related to the type of effort required during the performance of the competition. An energy system is a metabolic pathway consisting of certain biochemical reactions. These reactions are based on a specific pool of enzymes that allow food derivatives (lipids, carbohydrates and proteins) to be transformed into a highly energetic molecule know as adenosine triphosphate or ATP. This molecule consists of three phosphate groups, the last of which, hydrolyzed, is able to provide the energy necessary for muscle contraction.

The main energy systems differ in power, as much energy they are able to supply in the unit of time and capacity, the longer they can provide energy. The energy metabolism systems are: the phosphagen system, which has a very high power guaranteed just for a few seconds, follows the anaerobic glycolytic system which has less power but a more extensive capacity on time (duration) and finally the oxidative phosphorylation which is based on the required power, it uses a different mixture of carbohydrates and lipids (and sometimes of proteins) and in the latter case it provides virtually infinite energy.

Recently there has been a noticeable interest in a molecule, the β-hydroxy-butyric acid, a lipid derivation that boasts characteristics very similar to glucose while technically being a lipid. b-hydroxy-butyric acid is a ketonic body produced under conditions of physiological ketosis.

The purpose of this article is to analyze the literature concerning ketone bodies with the aim of evaluating the possibility of using ketogenic protocols to maximize performance in endurance sports.

Keywords: *Ketogenic diet, b-hydroxy-butyric acid, endurance sport.*

Introduction

Ketone bodies consist of acetoacetate, D-β hydroxybutyrate (D-3-hydroxybutyrate) and acetone. They are synthesized in liver mitochondria. The overall steps involved in the formation of ketone bodies include the mobilization of fatty acids by lipolysis from adipose tissue triacylglycerol by hormone-sensitive triacylglycerol lipase, plasma fatty acid transport, fatty acid activation, fatty acid transport into mitochondria (with acylcarnitine as an intermediate), and β-oxidation. The regulatory reactions are those of lipolysis and the acyl-CoA transport across the mitochondrial membrane (CPTI). Synthesis of ketone bodies from acetyl-CoA consists in three steps: formation of acetoacetyl-CoA and acetoacetate; and reduction of acetoacetate to β-hydroxybutyrate. Nonenzymatic decarboxylation of acetoacetate yields acetone, which is eliminated via the lungs.

The major pathway of production of aceto-acetate is from β-hydroxy-β-methylglutaryl-CoA (HMG-CoA). Hydrolysis of acetoacetyl-CoA to acetoacetate by acetoacetyl-CoA hydrolase is of minor importance because the enzyme has a high K_m for acetoacetyl-CoA. HMG-CoA is also produced in the cytosol, where it is essential for the synthesis of several isoprenoid compounds and cholesterol (Chapter 17). The reduction of acetoacetyl-CoA to β-hydroxybutyrate depends on the mitochondrial $[NAD^+]/[NADH]$ ratio.

Ketogenesis in the liver

The formation of ketone bodies in the liver and their oxidation in the mitochondria of extrahepatic tissues (e.g., skeletal muscle, heart, kidney, intestines, brain) are dictated by the [substrates]/[products] ratio. The rate-controlling reactions are released of fatty acids from adipose tissue and uptake of acyl-CoA into mitochondria. Acetoacetyl-CoA may regulates ketogenesis by inhibiting the transferase and the synthase. Acetoacetyl-CoA is cleaved to two molecules of acetyl-CoA by acetyl-CoA acetyltransferase, the same enzyme involved in the synthesis of acetoacetyl-CoA. Acetyl-CoA is oxidized in the TCA cycle. β-Hydroxybutyrate is oxidized to acetoacetate by NAD^+-dependent β-hydroxybutyrate dehydrogenase by reversal of the reaction that occurred during ketogenesis. The conversion of succinyl-CoA to succinate and formation of GTP activates the process providing the transfer of coenzyme A from succinyl-CoA to acetoacetate by succinyl-CoA-acetoacetate-CoA transferase (thiophorase).

Metabolism of Ketone Bodies in Physiological and Pathological Condition

Acetoacetate and β-hydroxybutyrate are products of the normal metabolism of fatty acid oxidation and are the metabolic fuels in extrahepatic tissues. Their level in blood depends on the rates of production and utilization and the oxidation increases as their plasma levels increase. Some extrahepatic tissues (e.g., muscle) oxidize them in preference to glucose and fatty acid. Normally, ketone bodies concentration in the serum is less than 0.3 mM/L. The rate of formation of ketone bodies depends on the concentration of fatty acids derived from hydrolysis of adipose tissue triacylglycerol by hormone-sensitive lipase. Insulin, being anti-ketogenic depresses lipolysis and promotes triacylglycerol synthesis and storage, while glucagon as ketogenic has the opposite effects. Uncontrolled insulin-dependent diabetes may result in fatal ketoacidosis. Patients could be so susceptible to attacks of ketoacidosis and have the presence of persistent ketone bodies in the urine. Although ketonemia and ketonuria are generally assumed to be due to increased production of ketone bodies in the liver, studies with depancreatized rats have shown that ketosis may also arise from their diminished oxidation. Ketosis can occur in some situations as starvation and ethanol abuse. Acetone is the primary metabolite produced during isopropyl alcohol toxicity and occurs with the absence of other ketone bodies.

Also during sustained exercise ketosis can occur because of a switch in blood flow, so the blood flow to the liver, intestines, and kidneys is substantially decreased with a corresponding increase in blood flow to working muscles, following more fatty acids mobilized from adipose tissue and delivered to the

muscle. In this way the formation of ketone bodies is severely curtailed, and during the post-exercise period, with the resumption of normal blood flow to the liver, ketone bodies are generated as a result of increased mobilization of fatty acids. Reduced ketone body utilization in the extrahepatic tissues can occur instead due to deficiency of either succinyl-CoA-acetoacetate-CoA transferase or acetyl-CoA acetyltransferase.

Metabolism of Ketone Bodies and Endurance Sports

Most of the nutritional strategies recommended over the last 30 years have been based, almost exclusively, on the study of carbohydrate metabolism in order to increase the available glycogen stocks. If on the one hand a diet very rich in carbohydrates contributes to increasing the storage of glycogen, on the other hand, for a universal principle of physiological adaptation also its consumption will increase. It is obvious, in fact, that if the energy system develops in the direction of a given substrate (in this case carbohydrates) it will preferably be based on it and will go into crisis when it is lacking. On this hypothesis, some researchers have begun to investigate the possibility of an adaptation of oxidative phosphorylation to a diet rich in fat. Burke and Hawley (1) showed that 5-6 days of diet with a fat content percentage of 70%, followed by 1-2 days of diet with a carbohydrate content that is always 70% is able to increase the glycogen stocks and to move the oxidative phosphorylation towards the use of fatty acids, both in the hyperlipidic phase and during sports performance, after the carbohydrate loading. The same conclusion was reached by Yeo and collaborators (2) who subjected a group of athletes to a "dietary periodization" consisting of two weeks of hyperlipidic diet followed by 2 days of hyperglycidic diet, revealing how the adaptation induced by the two weeks of excess fat, or high fatty acid oxidation, continues despite renewed high availability of carbohydrates. It is therefore evident that a diet based predominantly on lipids is able to modify the use of preferential substrates in the energy metabolism of oxidative phosphorylation. This is a not inconsiderable result since it has always been assumed that muscle cells preferentially used glucose when it was available. According to the cited studies, on the contrary, it appears evident that a dietetic intervention is able to modify the energy metabolism for a period after the end of it. In endurance performance, very often, there are high intensity phases that need to be switched to glycolytic metabolism. What happens when the energy metabolism is adapted to a higher use of lipids? Lambert and collaborators (3) showed that a diet with a high lipid content (70% fat 7%, carbohydrates and 23% protein) allowed to have a better performance in a group of cyclists both at high and low intensity, compared to a predominantly carbohydrate diet (74% carbohydrates, 12% fat and 24% protein).

It seems that accustoming the body to using lipids does not inhibit glucose metabolism, but on instead it improves metabolic flexibility, allowing an efficient passage to carbohydrates when the intensity of the effort increases. Despite these encouraging assumptions, it is known that FFAs have the ability to re-synthesize about 0.4 mol / min of ATP against the 1-2 mol / min of glycogen, so an adaptation of energy metabolism to fatty acids could lead to a decrease in performance in tests where the demand for power is important. Moreover, as the intensity of the exercise increases there is a reduction in lipolysis in relation to the increase in lactate concentration. A study by Paoli and collaborators (4) evaluated the effect of a ketogenic diet on a group of elite athletes of artistic gymnastics. The study group consisted of 21 athletes who trained on average for 30 hours a week. The group was subjected for a month to a ketogenic diet composed of 4.5% of CHO, 54,8% of lipids and 40.7% of proteins, measuring sports performance before and after 30 days. The results show that there was no detriment to performance. The study continued with three months of free diet and subsequently with a month of carbohydrate diet (46.8% of CHO, 38.5% of fats and 14.7% of proteins) always measuring performance before and after the intervention. There was no change in performance. What changed between the two types of diet was body composition, which resulted in more lean mass after the ketogenic diet. Also in this study it is evident that a dietary intervention maintains the metabolic effects acquired for some time after the

suspension. This fact is very important because it allows to periodize targeted metabolic interventions without excessively insisting on a ketogenic protocol.

Phinney et al. (5) showed, over 30 years ago, that a ketogenic diet did not worsen performance in well-trained cyclists and reduced glucose oxidation three times. Recently Zajac and collaborators (6) conducted an interesting study on a group of cross-country cyclists, a sporting discipline that requires the intervention of all energy systems due to its performance characteristics. The aim of the study was to determine performance following a prolonged ketogenic diet.

The group underwent various blood and functional tests to monitor VO2max, lactate threshold and endurance performance. In particular, in the last test the cyclists had to pedal for about two hours: in the first 90 minutes the intensity was equal to 85% of the lactate threshold, followed by a phase of 15 'performed at 115% of the lactate threshold. The manipulated variable was the diet. One diet consisted of 50% CHO, 30% fat and 20% protein, while the other 15% carbohydrate, 70% fat and 15% protein. The biochemical analysis was aimed at detecting the levels of: insulin, cortisol, testosterone, total cholesterol, triglycerides, HDL, LDL, concentration during exercise and at rest in glucose, FFA, β-hydroxybutyrate and lactate concentration. The first significant result is the significant increase in β-hydroxybutyrate (up to 4 times compared to the traditional diet), one of the ketone bodies used for energy purposes. In terms of performance with the same effort, there was a decrease in lactate production during the 15 minutes performed at 115% of the lactate threshold. A type of ketogenic diet that has gained considerable resonance is the so-called Spanish ketogenic Mediterranean diet. This is a protocol that provides a maximum intake of carbohydrates of 30g, mainly vegetable origin, fish as the primary source of protein, minimum 30ml of extra virgin olive oil and 200-400ml of red wine. So basically it's a Mediterranean diet with the exclusion of cereals and legumes. According to Pérez-Guisado and collaborators (7) this diet would be excellent to reduce the adipose mass without causing cardiovascular problems.

Fasting, Keton body, Autophagy and Endurance

Autophagy begins with the formation of the phagophore a membrane that selectively incorporates cellular organelles. It is assumed that in mammals it derives from the endoplasmic reticulum and from the trans part of the Golgi apparatus (8,9). The closed phagophore containing the organelles takes the name of autophagosoma and merging with the lysosome it becomes autophagolysosoma starting the degradation through the lsyosomal acids containing proteases. The amino acids deriving from the degradation are reported in the cytosol to reconstitute new macromolecules or for energy metabolism (8). The selective degradation of organelles is particularly important for mitochondria, our energy production plants, which use oxygen as a comburent. Mitophagy is the process by which inadequately performing mitochondria are degraded and replaced by new ones. This process increases the efficiency of oxidative phosphorylation and limits the production of reactive oxygen species (free radicals) by containing oxidative stress (10). Autophagy can be basal, the one normally activated by our body and induced like that triggered by physical exercise, hypoxia and caloric restriction which, in addition to acting locally on active muscle, extends its action to peripheral organs and tissues. He and co-workers (11) showed how 30'of exercise can activate autophagy not only locally, but also in the brain, pancreatic cells, liver, heart and adipose tissue. The authors argue that acute autophagy may play a role in the regulation of metabolism during exercise. The same research group has shown that exercise induces autophagy in brain tissue by promoting neuronal plasticity, removing the accumulation of damaged cellular organelles and affecting neurogenesis.

The activation of autophagy originates from cellular signaling pathways that have mTOR as their main actor, which is an inhibitor of the process, mTOR is inhibited, besides fasting, also by hypoxia (12). A study by Mackenzie et al. (13) showed that the acute effect of strength exercises induces an increase in protein synthesis in conjunction with the

degradation of existing proteins. Degradation is activated by mVps34, a PI3 kinase that regulates autophagy. It would therefore seem that autophagy is necessary for muscle remodeling and is induced, among other things by high intensity exercise. Masiero and collaborators (14) have shown that defects in the autophagic process at the muscular level cause loss of muscle mass and loss of strength. Autophagy is therefore a natural mechanism of protection of our organism that is compromised with aging causing various diseases (15). Recent research has shown that caloric restriction induced by fasting and intense or long-lasting physical exercise counteract the effects of age on the involution of the autophagic process by increasing its flow (15,16, 17). This is the main action, at the cellular level, that justifies fasting and physical exercise as safeguards for longevity and disease prevention. Recently, the research has succeeded in demonstrating that autophagy is also the basis of the phenotypic development of type I and II muscle fibers necessary for increasing endurance performance. This aspect is of considerable importance for the methodological implications in the field of exercise physiology and for the explanation of some consolidated training practices that have never been completely clarified, in the biochemical aspects, until today. It has been shown that prolonged aerobic exercise (greater than 2 hours) or high intensity increases the flow of autophagy. The correct combination of these two factors makes it possible to regulate autophagy in the direction of a performance improvement. Fasting in the morning prolongs and strengthens the effects of night fasting. It is a metabolic picture that lends itself well to optimizing the production of ketogenic bodies which, as we have seen, are produced when the deficiency of oxalacetate does not allow the transformation of acetyl-CoA into citrate in the krebs cycle. The effects of fasting therefore seem to increase the production of ketone bodies and improve the activity of mitochondria, characteristics underlying the endurance performance.

Sleep slow

A protocol that is finding important feedback in the use of ketone bodies in endurance performance is known as "training low", that is training in glycogen depletion. The goal of improving both glycogen storage and lipid oxidation can be achieved by strategically combining nutrition with training (18). One of the major problems highlighted by some research (19,20) is the difficulty of performing high-intensity workouts associated with a low-carbohydrate diet. Endurance performance has many moments in which the glucose metabolism is used, which is why it is essential to be able to train in the best glucose availability conditions during the training process. This seems to contrast the development of the metabolism based on ketone bodies. An interesting pilot study carried out by Lane and collaborators (21) tried to understand if it was possible to periodize the ingestion of carbohydrates based on the type of training. They subjected a group of cyclists trained to two different experimental conditions. In the first, 8g of carbohydrates were administered per kg of body mass before performing a high-intensity workout in the late afternoon, the group then went to sleep without eating and the following morning performed a 2-hour low-intensity workout. The second experimental condition included the same workouts but 4g of carbohydrates per kg of body mass were administered before afternoon training and 4g of carbohydrates per kg of body mass before going to sleep. Although no marked development of the markers of mitochondrial biogenesis has been found, the researchers hypothesized that there may be an epigenetic adaptation in the direction of a development of the aerobic energy system detected by the PPARδ methylation, which regulates muscle metabolism and reprograms the type of fibers endurance muscles (22,23). The hypothesis behind Lane's study was liked by the research group led by Marquet (24) who also wanted to verify the increase in terms of performance. In their study they subjected 21 well-trained triathletes (VO2 max 60.1 ± 6.8 ml.min-1.kg-1) to a nutritional periodization based on training. The group was randomized and divided into two groups that followed a different diet, but the same type of training. The operation was extended for 3 weeks. A group followed a strategy called "slow sleep" in which a high intensity workout is performed with glycogen "charged" stocks followed by a carbohydrate free dinner. The

following morning the group performed another low intensity workout. The control group fed normally, before and after training, thus replenishing carbohydrates for dinner. The groups were followed for 6 weeks, the first three "baselines" in which they performed their usual training (10-15h / week divided into 40% running, 35% cycling, 25% swimming) in order to make them homogeneous. In the following 3 weeks the training scheme was the same and consisted of 6 workouts in 4 consecutive days consisting of a high intensity training in the afternoon and a low intensity one the following day. The high intensity sessions consisted of 8 x 5 min cycling at 85% of the maximum aerobic power (286 ± 26.7 W) or 6 × 5 minutes running at the speed corresponding to the intensity of 10 km with 1 recovery. The experimentally varied parameter was the diet, which included the same amount of nutrients distributed differently. The total daily carbohydrate intake was the same, 6g per kg of body weight, but distributed differently depending on the type of training. The slow sleep group did not receive carbohydrates from the end of the high intensity afternoon training until the end of low intensity training the next morning, and did not integrate during training. At the end of the morning training he reintegrated until the following afternoon training. The control group reintegrated after each workout and during training integrated with a drink containing 6% carbohydrates. Both groups supplemented the evening training with a high-protein drink. This regime was observed for the first 4 days of the week, while in the remaining 3 days the feeding was free. Several sub and maximum tests have been carried out, but the most interesting was the simulation of an Olympic triathlon in which only the slow sleep group improved the final fraction (10 km of run) on average by 73 ± 20 s.

Conclusion

The analysis of the literature highlights how adapting energy metabolism towards the use of ketone bodies can be a strategy to be adopted in order to improve endurance performance, especially in those disciplines, such as ultra-cycling, ironman triathlon and ultramarathon, where the limiting factor performance is the ability to store large amounts of muscle and liver glycogen.

The literature seems to indicate that a nutritional periodization can be the winning strategy to introduce ketogenic dietary profiles, as a matter of fact the effects after several weeks of ketogenic diet extend for some time from the ending of the same.

When we talk about nutritional strategies we should consider a broad paradigm in which not only the foods administered are to be considered, but also those that are not consumed.

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