The International Journal of Biochemistry & Cell Biology 63 (2015) 55–59

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

journal homepage: www.elsevier.com/locate/biocel

Organelles in focus

Mitochondria: The ketogenic diet—A metabolism-based therapy☆

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ARTICLE INFO

Article history:
Received 7 November 2014
Received in revised form 15 January 2015
Accepted 29 January 2015
Available online 7 February 2015

Keywords:
Mitochondria
Ketogenic diet
Metabolism
Cancer

ABSTRACT

Mitochondria are the energy-producing organelles of the cell, generating ATP via oxidative phosphorylation mainly by using pyruvate derived from glycolytic processing of glucose. Ketone bodies generated by fatty acid oxidation can serve as alternative metabolites for aerobic energy production. The ketogenic diet, which is high in fat and low in carbohydrates, mimics the metabolic state of starvation, forcing the body to utilize fat as its primary source of energy. The ketogenic diet is used therapeutically for pharmacoresistant epilepsy and for "rare diseases" of glucose metabolism (glucose transporter type 1 and pyruvate dehydrogenase deficiency). As metabolic reprogramming from oxidative phosphorylation toward increased glycolysis is a hallmark of cancer cells; there is increasing evidence that the ketogenic diet may also be beneficial as an adjuvant cancer therapy by potentiating the antitumor effect of chemotherapy and radiation treatment.

This article is part of a Directed Issue entitled: Energy Metabolism Disorders and Therapies.

Organelle facts:

- Oxidative phosphorylation (OXPHOS) in mitochondria plays a pivotal role in ATP production.
- Pyruvate generated by glycolysis is one of the major fuels of mitochondrial energy production.
- Ketone bodies are generated by fatty acid oxidation and by degradation of ketogenic amino acids.
- Ketone bodies can be used as an alternative fuel for OXPHOS.
- Aerobic energy production via OXPHOS is frequently impaired in cancer.

1. Introduction and organelle function

Mitochondria are the cell's energy-producing organelles. They are also involved in essential metabolic and catabolic pathways, calcium homeostasis, redox balance, and regulation of apoptosis. Various pathological changes in mitochondria have been linked to an array of disorders, including metabolic and neurodegenerative diseases, epilepsy, and cancer. Thus, research has increasingly focused on the molecular mechanisms of mitochondrial dysfunction in disease, and more recently on therapeutic options to target mitochondrial energy production.

Mitochondrial energy metabolism involves pyruvate oxidation, β-oxidation of fatty acids, the citric acid cycle, and the five complexes of oxidative phosphorylation (OXPHOS). Redox equivalents (NADH and $FADH_2$) produced in the first three processes are oxidized in the electron transport chain through four multiprotein complexes (I–IV) to generate a proton gradient, and culminating in the reduction of molecular oxygen to form water. The proton gradient is harnessed by complex V (ATP synthase) of the OXPHOS pathway to synthesize ATP.

2. Cell physiology

In the presence of oxygen, most cellular energy is derived from metabolism of glucose to pyruvate by glycolysis, followed by oxidation through OXPHOS inside mitochondria. In the absence of glucose, cellular energy is produced from degradation of fatty acids and proteins. Fatty acid oxidation results in the generation

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http://dx.doi.org/10.1016/j.biocel.2015.01.022
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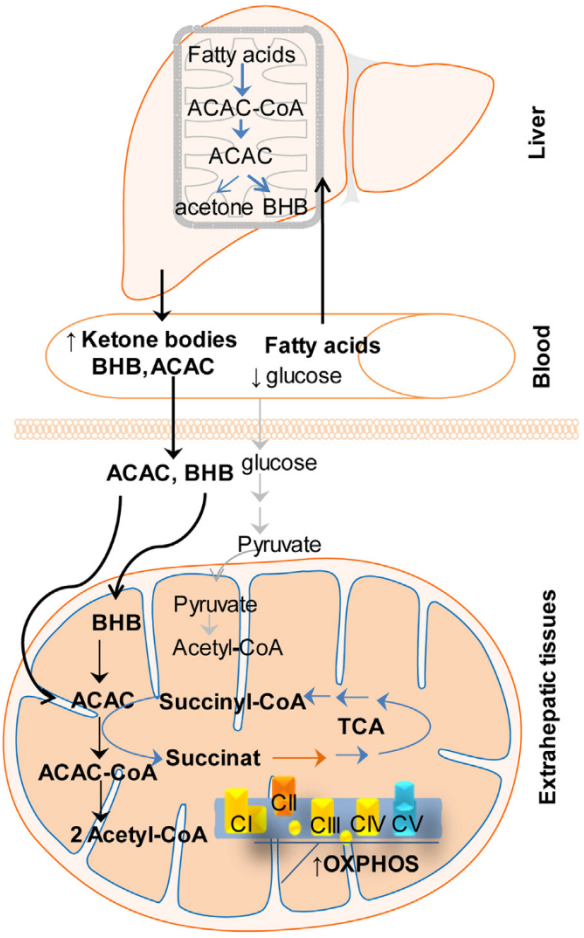

Fig. 1. The three ketone bodies acetoacetate (ACAC), β-hydroxybutyrate (BHB), and acetone are majorly produced in the mitochondrial matrix of liver cells during oxidation of fatty acids. ACAC and BHB are exported to extrahepatic tissues, where they are converted to acetyl-CoA. The acetyl-CoA is fueled into the citric acid cycle (TCA) to produce ATP via the OXPHOS. KD leads to an upregulation of fatty acid oxidation, concomitant lower blood glucose levels and subsequently lower glycolytic rate. Abbreviations: ACAC-CoA: acetoacetyl-CoA, CI: complex I, CII: complex II, CIII: complex III, CIV: complex IV, CV: complex V.

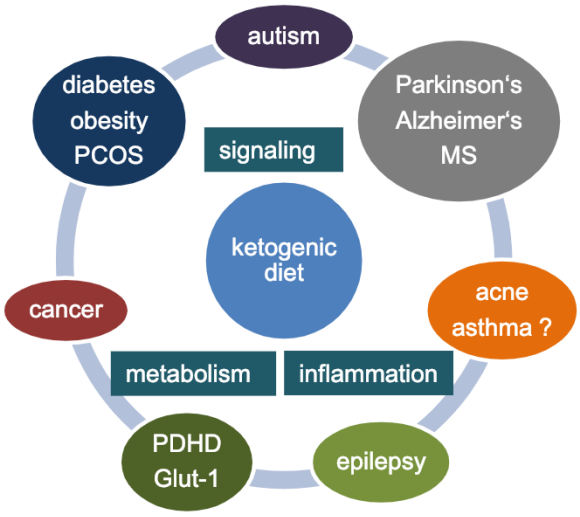

Fig. 2. Pleiotropic effects of the ketogenic diet. The therapeutic efficiency of a KD in a broad variety of diseases is mainly based on its ability to influence metabolism, cell signaling, and inflammation. A high-fat, low-carbohydrate diet causes a reorganization of metabolism. Metabolism: Parameters of metabolism and metabolites are known to correlate with disease severity (Paoli et al., 2011; Sharman et al., 2002; Volek et al., 2005; Wexler et al., 1997). Signaling: Recently, regulation of several signaling molecules including hormones and growth factors as leptin (Sumithran et al., 2013) or IGF-1 (Paoli et al., 2013) by a KD was shown. Inflammation: Several reports suggested that the KD has anti-inflammatory effects partially explaining the therapeutic efficacy in neurodegenerative disorders (Seyfried et al., 2015). References: diabetes and obesity (Nielsen and Joensson, 2008; Sumithran et al., 2013; Yancy et al., 2005) polycystic ovary syndrome, PCOS (Mavropoulos et al., 2005); autism (Stafstrom and Rho, 2012); acne (Paoli et al., 2012); asthma (Peshkin and Fineman, 1930); Alzheimer's (Van der Auwera et al., 2005); Parkinson's (Kashiwaya et al., 2000); multiple sclerosis, MS (Stafstrom and Rho, 2012); Abbreviations: Glut-1, glucose transporter 1; PDHD, pyruvate dehydrogenase complex deficiency.

of ketone bodies (3-β-hydroxybutyrate, acetoacetate, acetone) mainly produced during fasting or prolonged exercise when the supply of glucose is insufficient (Krebs, 1960; Mitchell et al., 1995). The ketogenic diet (KD) is a high-fat, low-carbohydrate diet that mimics the metabolic state of long-term fasting. Ketone bodies are generated mainly by ketogenesis in the mitochondrial matrix of liver cells and are subsequently exported via the blood to other organs to cover the energy demands of cells throughout the body (Fig. 1). Ketogenic deaminated amino acids such as leucine also feed the citric acid cycle to form ketone bodies.

3. Organelle pathology

3.1. The ketogenic diet as a therapeutic tool

Following observations in the 1920s that fasting reduced epileptic seizures, the KD was devised and used in the management of epilepsy (Barborka, 1930; Peterman, 1925; Wilder, 1921) until the 1940s, when it fell into oblivion owing to perceived compliance difficulties and the introduction of antiepileptic drugs (Neal, 2012).

Patients on the KD must consume 65–90% of their daily energy requirement as fat. This is twice that of the typical Western diet. KD meals consist predominantly of foods rich in fat—butter, cream, mayonnaise or oils with meat, fish, eggs, or cheese in quantities sufficient to ensure an adequate protein supply, and only very small portions of vegetables or salad to greatly minimize carbohydrate intake (Neal, 2012).

The KD is prescribed on an individual basis. Regular monitoring by clinicians and dietitians experienced in its use is vital to assess progress and manage side effects, which can include constipation, kidney stones, growth deficits, and poor bone health. Hyperlipidemia can manifest initially but usually resolves over time or with dietary advice on the source of fat (Neal, 2012).

Monitoring the KD is quite demanding. It requires high degree of commitment, motivation, and support to undertake and maintain the KD successfully. Actual and perceived difficulties with compliance, regime complexity, unpalatability, and difficulty with tolerance of high-fat intake, combined with a paucity of trained dietitians, have previously been barriers to the promotion of its use, especially in adults. However, innovative research and developments in the production of special medical foods specifically for the KD, resources for education, protocols, recipes, and meal planning (including patient-friendly computer programs) and the establishment of support groups and charities dedicated to raising the profile of its use are aiding and increasing the diet's acceptability, accessibility, and convenience (Neal, 2012).

The KD mainly functions via lowering blood glucose levels, however fatty acids and ketone bodies were shown to have pleiotropic effects (anticonvulsant, anti-inflammatory, modulators of mitochondrial biogenesis, antioxidative) (Hughes et al., 2014) (Fig. 2). Furthermore, by mimicking the metabolic state of fasting, KD modulates levels of hormones, neurotransmitters, and neuropeptides (Giordano et al., 2014).

Table 1
Summary of studies of the KD as adjuvant therapy for cancer in mouse models.

Cancer	Mouse strain	Diet/Outcome	PMID[a]
Malignant brain	C57BL/6J and BALBc/J-(SCID) (orthotopic)	KD 4:1; two types of brain tumors injected in mice, tumor growth retardation of 35 and 65% in KD-treated mice	17313687
Glioma	C57BL/6 (intracranial)	KD (78.8% fat); tumor growth reduction and prolonged median survival; modified expression of genes involved in oxidative stress; reduced expression of growth factor genes known to be involved in glioma growth	20831808 22019313
Glioma	Foxn1nu (orthotopic)	KD (fat:carbohydrate, protein = 2.7:1); no improvement of survival; no effect on blood glucose	21791085
Glioma	C57BL/6-cBrd/cBrd/Cr (albino C57BL/6) (orthotopic)	KD 4:1; increased ketone bodies and median survival; radiation therapy in combination with KD led to total loss of tumors	22563484
Glioma	athymic nude Foxn1nu (stereotactical implantation)	KD (56.1% fat) alone or in addition to bevacizumab. Pronounced ketosis; KD alone had no significant effect on survival; KD in combination with bevacizumab prolonged survival and showed smaller tumor size compared to bevacizumab alone	24728273
Astrocytoma	C57BL/6J (syngeneic orthotopic)	KD (fat: carbohydrate, protein = 5.48:1); 48–80% reduction in tumor weight	19032781
Malignant astrocytoma	C57BL/6J (intracerebral)	KD-CR (fat: protein and carbohydrate = 5.48:1); reduction of tumor growth by 80%	14520474
Pancreas	Athymic nude (orthopic)	Three weeks of KD (81% fat) ad libitum; reduced tumor weight and volume	25228990
Prostate	nu/nu (subcutaneous)	45% fat, 45% protein, 10% carbohydrate; significantly reduced tumor volume after 5 and 9 weeks of treatment	18042933
Prostate	SCID (subcutaneous)	no-carbohydrate KD or 40% fat Western diet; both resulted in longer survival, 33% reduction in tumor size	17999389
Prostate	CB.17 scid/scid (subcutaneous)	10% or 20% carbohydrate diets; both show no effects on survival	20716631
Prostate	Fox Chase/SCID (subcutaneous)	Low-fat high-carbohydrate diet (LFD) (12% fat, 71% carbohydrates), moderate-carbohydrate diet (MCD) (40% fat, 42.8% carbohydrate) or no-carbohydrate ketogenic diet (NCKD) (82.8% fat); no significant differences in tumor growth and survival between LFD and NCKD diet; MCD showed increased tumor growth and decreased survival	19470786
Breast	MMTV-PyMT oncomouse	KD (54.8%); tumor mass decreased by 65%; no change in mouse body weight	25304261
Colon	NMR1 (implanted)	Medium chain triglyceride (MCT)-based KD (80% of the metabolizable energy from MCTs); ketone bodies increased; blood glucose and insulin decreased; significant reduction in tumor size	3620317
Colon	NMR1 (implanted)	MCT based KD (80% fat); significantly reduced tumor weight	2736199
Colon	C57BL/6 (subcutaneous)	High-fat diet (HF) (60% fat, 20% carbohydrate), low-carbohydrate diet (LC) (60% fat, 5% carbohydrate), high-carbohydrate diet (HC) (10% fat, 70% carbohydrate), HC-calorie restricted (HC-CR) (70% average calories consumed per day of the HF group); tumor latency in HC-CR group was more than 60% longer than in the other groups and mice displayed the smallest final tumor size	18444137
Gastric	NMRI (subcutaneous)	KD (35.5% fat) enriched in MCTs and omega-3 fatty acids; larger necrotic areas; inhibition of tumor angiogenesis; inhibition of growth	18447912
Lung	nu/nu (subcutaneous)	KD 4:1; potentiation of growth inhibitory effect by combination of KD and radiation; decreased tumor volume compared to the untreated	23743570
Systemic metastatic	VM/Dk (subcutaneous)	combination of KD and hyperbaric oxygen therapy; decreased blood glucose, slowed tumor growth; increased mean survival time	23755243
Systemic metastatic	VM/Dk (subcutaneous)	Standard diet supplemented with ketone ester (KE) or 1,3-butanediol (BD). Survival prolonged by 69% and 51%, respectively	24615175

[a] PubMed-ID.

3.2. The ketogenic diet in intractable epilepsy

Worldwide, 50–60 million people have epilepsy, with 25–30% resistant to any pharmacological management. Over the past 20 years, treatment failure, concerns over side effects from medications and the negative consequences of persistent seizures on brain development and cognitive function have prompted a resurgence in the use of the KD for intractable epilepsy in children, adolescents, and adults with an accompanying focus of research interest (Neal, 2012; Neal and Cross, 2010). Efficacy studies show that after 3 months, approximately half those on a KD experience a greater than 50% reduction in seizures. Of these, about one third experience a 90% decrease, with 10–15% becoming completely seizure free comparable to the response rate to antiepileptic drugs (Hemingway et al., 2001; Neal, 2012; Neal and Cross, 2010). In addition to enhanced epileptic control, many patients report an improved quality of life and are able to reduce or discontinue medications. If successful within an initial 3-month trial period, the KD is usually followed up for 2 years to facilitate additional improvements. Even after discontinuation, benefits may be sustained without further medical or dietary intervention, although the explanation for this effect as well as for the efficacy of the KD as therapy for intractable epilepsy per se has yet to be fully elucidated (Danial et al., 2013; Patel et al., 2010).

3.3. The ketogenic diet in inherited metabolic disease

In addition to the use of the KD in intractable epilepsy, its ability to induce a shift in cellular energy supply from glucose to ketones has applications in the dietary management of specific disorders of metabolism, for example glucose transporter type 1 (Glut-1) and pyruvate dehydrogenase complex (PDH) deficiency. By a high-fat low-carbohydrate diet, the glucose metabolism and the oxidation of pyruvate in mitochondria are bypassed. The KD was also shown to have beneficial effects in a subset of patients with complex I deficiency. Reduced NAD coupling might increase the energy available for ATP synthesis and efficiency of ATP hydrolysis (Veech, 2004). Decanoic acid can increase citrate synthase and complex I activity. In addition, decanoic acid is a ligand of peroxisome proliferator-activated receptor γ (PPARγ), one master regulator of

Table 2
Summary of studies on the KD as adjuvant therapy for human cancer.

Cancer	Study group	Diet/Outcome[b]	PMID[a]
Advanced stage	Pediatric patients	MCT based KD (60% MCT, 20% protein, 10% carbohydrate, 10% other dietary fats); blood ketone levels increased 20- to 30-fold; blood glucose levels declined	7759747
Advanced metastatic	16 patients	KD (less than 70 g carbohydrates per day); patients reported improved emotional functioning and less insomnia; quality of life remained stable or worsened, reflecting the advanced disease.; five patients on diet for 3 months showed stable disease	21794124
Advanced stage malignant astrocytoma	2 pediatric patients	60% MCT oil-based diet; blood ketones elevated (20–30-fold); PET scan revealed 21.8% average decrease in glucose uptake at tumor site; one patient exhibited clinical improvements and continued with KD for 12 month remaining free of disease progression	7790697
Gastro intestinal tract	27 patients	Parental feeding with lipid-based diet (80% of total caloric requirement were fat, 20% dextrose) or glucose-based diet (100% dextrose); number of replicating cells increased in average 32.2% in the glucose-based diet group and decreased by 24.3% in the lipid-based diet but the results were not statistically significant	16839923
Glioblastoma	Single case study	CR-KD (fat:carbohydrate = 4.1), 600 kcal/day and standard therapy; increased ketone levels; reduced blood glucose; after two months of treatment no tumor was detectable; 10 weeks after suspension of KD tumor recurrence	20412570
Glioblastoma	20 patients with recurrent disease	KD (60 g carbohydrates, 500 ml of highly fermented yoghurt drinks per day, different plant oils ad libitum); urine ketosis in 92% of subjects; longer progression free survival in patients with stable ketosis ($n = 8$)	24728273
Glioblastoma multiforme	6 patients	KD (calories: 77% fat, 8% carbohydrates, 15% protein) for 3–9 months in combination with temozolomide (TMZ) or chemoradiation; four patients were alive at median follow-up of 14 month; one of the four patients was under carbohydrate-restricted KD (4.5% carbohydrates) post radiation and TMZ treatment and had no recurrence after 12 months from treatment, the other three had recurrence and started alternative chemotherapy treatments	24442482
Malignant disease	5 patients with severe weight loss	KD (70% MCT supplemented with BHB); increased body weight after 7 days (~2 kg), presence of ketosis already after 24 h in association with a reduction of blood glucose, pyruvate, and lactate levels	3122552

[a] PubMed-ID.
[b] Data of patients under KD compared to patients under normal diet.

mitochondrial biogenesis (Hughes et al., 2014). However, as the purpose of the KD in these conditions is to generate a fuel source, it requires life-long regimen adherence (Klepper, 2012).

Inherited defects in Glut-1 activity impair transfer of plasma glucose across the blood brain barrier, resulting in an 'energy crisis' for normal brain function and causing epilepsy, global cognitive delay, and a complex movement disorder. Because ketones enter the brain via a different transport mechanism from glucose use of the KD to produce these as an alternative fuel is recommended for persons with Glut-1 deficiency. If dietary compliance is maintained long term, the majority of patients who present with epilepsy become seizure free while improvements are also observed in speech, motor and mental development, and ability (De Giorgis and Veggiotti, 2013).

In the rare mitochondrial disorder PDH deficiency, glucose metabolization from pyruvate into acetyl-CoA is impaired. Instead, lactate is generated and, consequently, limited ATP is produced from the respiratory chain for cellular energy. Due to its low-carbohydrate content, the KD lowers the production of lactate from pyruvate and at the same time provides ketones as an energy fuel. However, its use is only partially able to reverse the clinical course of the neurodegenerative condition (Wexler et al., 1997).

3.4. Cancer

In cancer, many key oncogenic signaling pathways converge to adapt the cellular metabolism to support tumor cell growth and survival. Some of these alterations also seem to be required for malignant transformation; therefore, altered cellular metabolism should be considered an important hallmark of cancer (Wallace, 2005).

The major substrate for energy production in cancer cells is glucose; simultaneously, aerobic energy production through OXPHOS is frequently reduced. However, recently some cancers were described that are characterized by an increased mitochondrial capacity as found in a subset of melanomas (Vazquez et al., 2013). The shift by cancer cells from OXPHOS to glycolysis, even under normoxic conditions, is called the Warburg effect (Warburg, 1956). In cancer cells, aerobic glycolysis converts the bulk of glucose to lactate instead of metabolizing pyruvate via OXPHOS. ATP production by glycolysis can be more rapid than by OXPHOS, but it is less efficient in terms of molecules of ATP generated per unit of glucose. Therefore, tumor cells must increment the rate of glucose uptake.

Different therapies have been developed to block aerobic glycolysis in tumor cells (Chen et al., 2007; Feichtinger et al., 2010). Since tumor cells depend critically on glucose for energy production, it should be possible by means of a KD and/or calorie restriction (CR) to target the increased glucose dependence of cancer cells to selectively "starve them out" (Lv et al., 2014; Scheck et al., 2012; Zhou et al., 2007). In normal cells, the KD and/or CR lead to a decrease in blood glucose levels and an increase in ketone body utilization, thereby inducing a shift from glycolysis to respiration. In contrast, cancer cells should be unable to use ketone bodies due to their altered OXPHOS (Abdelwahab et al., 2012; Maurer et al., 2011).

In the last few years, the therapeutic potential of KD has been investigated mainly in animal models of brain tumors (Seyfried et al., 2015) (Table 1). For example, growth of malignant astrocytoma and glioblastoma xenografts in mice was inhibited significantly by a CR-KD. The KD also significantly enhanced the antitumor effect of radiation therapy in glioma patients. This suggests that cellular metabolic alterations induced through the KD may be useful as an adjuvant to the current standard of care for the treatment of human malignant gliomas (Abdelwahab et al., 2012). Table 1 summarizes published studies that have examined the KD and/or CR in the treatment of different types of tumors in animal models.

There are only a few reports on clinical studies of human cancer patients receiving adjuvant KD as part of their treatment (Table 2). KD was used for therapy in a patient with glioblastoma multiforme. Two months after starting the KD, the patient's body weight and blood glucose levels were significantly reduced and urine ketone bodies increased. At this time point no tumor was detectable (Zuccoli et al., 2010). Recently, 20 patients with glioblastoma had a longer progression-free survival under the KD (Rieger et al., 2014). Adjuvant dietary intervention in addition to classical tumor therapy could reduce either the amount of cytotoxic therapy or its duration with an improved quality of life for cancer patients.

4. Future outlook

The KD has an established place in clinical practice for the dietary management of patients with inborn errors of metabolism and pharmacoresistant epilepsy. Furthermore, high-fat, low-carbohydrate diets have been shown to prevent/alleviate cancer cachexia. Together with its potential growth-inhibiting effects in cancer, adjuvant therapeutic intervention with the KD in cancer certainly merits further investigation, especially in combination with drugs that target tumor metabolism. The KD is being resurrected as a way to support classical tumor therapy. To design a tailored adjuvant dietary intervention, a prior determination of the metabolic signature of the tumor will be necessary.

Besides the effects of the KD on the array of diseases mentioned above, recent studies indicate pleiotropic effects in inflammatory disease (e.g., arthritis, multiple sclerosis) coronary artery disease, and even diabetes (Seyfried et al., 2015) (Fig. 1). Therefore, dietary intervention using the KD might be beneficial in a much broader range of diseases than previously recognized.

Acknowledgement

This study was supported by the Mitochondrial European Educational Training (MEET), ITN MARIE CURIE PEOPLE (317433), the Austrian Research Promotion Agency (822782/THERAPEP), Research Fund of the Paracelsus Medical University (E-10/12/061-KOF) and Children's Cancer Foundation Salzburg.

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