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Review

How increased oxidative stress promotes longevity and metabolic health: The concept of mitochondrial hormesis (mitohormesis)

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ABSTRACT

Recent evidence suggests that calorie restriction and specifically reduced glucose metabolism induces mitochondrial metabolism to extend life span in various model organisms, including *Saccharomyces cerevisiae*, *Drosophila melanogaster*, *Caenorhabditis elegans* and possibly mice. In conflict with Harman's free radical theory of aging (FRTA), these effects may be due to increased formation of reactive oxygen species (ROS) within the mitochondria causing an adaptive response that culminates in subsequently increased stress resistance assumed to ultimately cause a long-term reduction of oxidative stress. This type of retrograde response has been named mitochondrial hormesis or mitohormesis, and may in addition be applicable to the health-promoting effects of physical exercise in humans and, hypothetically, impaired insulin/IGF-1-signaling in model organisms. Consistently, abrogation of this mitochondrial ROS signal by antioxidants impairs the lifespan-extending and health-promoting capabilities of glucose restriction and physical exercise, respectively. In summary, the findings discussed in this review indicate that ROS are essential signaling molecules which are required to promote health and longevity. Hence, the concept of mitohormesis provides a common mechanistic denominator for the physiological effects of physical exercise, reduced calorie uptake, glucose restriction, and possibly beyond.

1. Calorie restriction

A limited reduction of nutritional calorie uptake, so-called calorie restriction (CR), has been shown to extend life span in multiple species and model organisms, as initially observed by McCay et al. (1935). It is beyond the scope of this review to summarize the multiple findings on CR, since excellent reviews on this topic have been published in the past (Weindruch and Walford, 1988; Masoro, 2000; Speakman et al., 2002; Heilbronn and Ravussin, 2003; Ingram et al., 2004; Anson et al., 2005; Gredilla and Barja, 2005; Sinclair, 2005; Wolff and Dillin, 2006; Bishop and Guarente, 2007; Piper and Bartke, 2008). It should be emphasized, however, that unequivocal evidence for the effectiveness of CR in primates and especially humans is missing. A recent publication on an ongoing study in *Macaca mulatta* shows that CR has no statistically significant effect on overall mortality (Colman et al., 2009). However, since about half of the study group was still alive at the time of manuscript preparation, future findings from this ongoing study may show whether CR in rhesus monkeys significantly affects mortality. Nevertheless, so-called "age-related mortality" was significantly decreased in *M. mulatta.* It should be noted, though, that age-related mortality (as defined in this study) accounted for only 54% of deaths during the study period. In contrast and quite strikingly, age-related gluco-regulatory impairment was completely abolished in calorically restricted monkeys. Hence and due to additional findings (Fontana et al., 2004; Heilbronn et al., 2006; Ingram et al., 2006a; Weindruch, 2006; Fontana and Klein, 2007) it appears possible that CR extends life span in primates and/or humans.

The initial conceptual background for restricting dietary calories is based on the assumption that reducing nutritive calorie availability would reduce the metabolic rate of an organism. Accordingly, it was proposed more than a century ago that maximum life span is inversely proportional to the amount of nutritive energy metabolized (Rubner, 1908). Subsequently, the rate-of-living hypothesis evolved, suggesting that an increased metabolic rate would decrease life span in eukaryotes (Pearl, 1928). Several decades later it was proposed that increased metabolic rate would promote increased formation of reactive oxygen species (ROS) to cause cumulative damage to the cell, and hence the organism (Harman, 1956). Notably, respiratory enzymes using oxygen to generate readily available energy were explicitly proposed to be the most relevant culprit in this regard (Harman, 1956). This concept was named free radical theory of aging (FRTA).

Based on these assumptions, considerable experimental effort has been made to elucidate the underlying mechanistic principles.

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On the one hand, it has repeatedly been shown that CR is capable of delaying a number of age-related diseases, including obesity, type 2 diabetes, hypercholesterolemia, atherosclerosis, different cancers, as well as neurodegeneration and cardiomyopathy. This has been attributed to specific and diverse effects of CR on the respective molecular processes assumed to cause these disorders. According to some of these approaches, delayed aging would simply reflect a cumulative reduction of age-associated and mortality-promoting medical conditions as a consequence of CR. On the other hand, it was shown that CR *per se* promotes increased stress defense, and specifically induces endogenous defense mechanisms against ROS (Koizumi et al., 1987; Semsei et al., 1989; Rao et al., 1990; Pieri et al., 1992; Youngman et al., 1992; Xia et al., 1995; Masoro, 1998a; Barros et al., 2004). In most cases, this was interpreted as a consequence of reduced metabolic rate, and hence reduced ROS production. More recently, a different perspective has emerged, suggesting that CR causes an adaptive response to specific metabolic alterations in states of reduced food uptake.

2. Reduction of specific macronutrients

Nutritional, *i.e.* metabolizable calories are derived from carbohydrates, triacylglycerols (fat) and proteins. These contain a few different monosaccharides (including glucose), and significant numbers of fatty acids and amino acids, respectively. Limited evidence exists whether the generally accepted effects of calorie restriction can be attributed to specific macronutrients, *i.e.* whether restriction of a single macronutrient may exert the same effects than overall CR does. This topic has been reviewed in detail elsewhere (Piper and Bartke, 2008), hence the following paragraphs will focus on specific aspects of macronutrient choice only.

In invertebrate model organisms, restriction of proteins as well as carbohydrates, mostly glucose, has been studied with different and sometimes opposing outcomes, whereas studies on triacylglycerols are lacking for invertebrates. While the effects of glucose restriction will be discussed below, in *Drosophila melanogaster*, restriction of casein extends life span (Min and Tatar, 2006). Moreover, it has been proposed that restriction of both yeast as well as sugar may extend *Drosophila* lifespan despite unaltered calorie uptake (Mair et al., 2005). Very recently, it was shown that increased abundance of essential amino acids, and particularly methionine counteracts the lifespan-extending effects of CR in *D. melanogaster* (Grandison et al., 2009). Notably, restriction of methionine in rodents similarly delays ageing (Zimmerman et al., 2003; Miller et al., 2005) and increasing protein content impairs antioxidant defense in rats (De et al., 1983). For *Caenorhabditis elegans*, impaired activity of peptide transport similarly extends life span (Meissner et al., 2004). However, selective depletion of nutritive amino acids is difficult to achieve in *C. elegans*, and hence to our best knowledge has not been studied.

In mammals and especially humans, increasing evidence suggests that a number of health-promoting metabolic effects can by more easily achieved by a selective reduction of dietary carbohydrates: Whereas efficacy of long-term weight reduction appears to be comparable between low-carbohydrate and low-energy diets (mainly depleted in triacylglycerols) (Nordmann et al., 2006; Hession et al., 2009), several serum parameters seem to be favourably affected by a specific reduction of carbohydrate uptake, whereas total energy uptake was, in most studies, not significantly affected by the type of diet (Nordmann et al., 2006; Hession et al., 2009). Hence, it appears feasible that a depletion of carbohydrates and/or glucose only exerts specific effects beyond those observed with general CR. In anticipation of mechanisms outlined below, it should be noted that metabolism of glucose can yield ATP even in the absence of mitochondrial organelles or even oxygen, while conversion of fatty acids and/or (most) amino acids into ATP depends on oxidative phosphorylation (OxPhos) and hence oxygen.

3. Glucose restriction

A specific restriction of nutritive glucose is, with the exception of yeast and *D. melanogaster*, difficult to achieve in eukaryotic model organisms. In *Saccharomyces cerevisiae*, it was shown that reduced glucose availability significantly extends chronological life span, and this extension depends on induction of respiration (Lin et al., 2002) as well as sirtuins (Lin et al., 2000). While the dependence on sirtuins is a matter of debate (Kaeberlein et al., 2004; Agarwal et al., 2005; Guarente, 2006; Smith et al., 2007), alternative mechanisms independent of sirtuins have been proposed (Barros et al., 2004; Roux et al., 2009).

In *C. elegans* and mammals, a specific restriction of intracellular glucose availability is commonly achieved by application of a competitive inhibitor of glycolysis, 2-deoxy-glucose (DOG) (Wick et al., 1957). In *C. elegans*, it was shown that application of DOG induces respiration and extends life span (Schulz et al., 2007), in this regard reflecting previous findings in yeast (Lin et al., 2002). However and in conflict with these aforementioned findings in yeast, this process was independent of sirtuins, but rather required activation of AMP-activated kinase (AMPK) (Schulz et al., 2007). This kinase was previously established as a sensor of cellular energy depletion in both mammals (Hardie et al., 2006) and specifically *C. elegans* (Apfeld et al., 2004; Greer et al., 2007), and has been found to induce a health-promoting metabolic state particularly by inducing mitochondrial metabolism (Hardie et al., 2006). Accordingly, application of DOG to rodents efficiently mimics features of the metabolic state of CR (Lane, 1998) as well as carbohydrate restriction (Garriga-Canut et al., 2006), suggesting that DOG acts as a CR mimetic (Duan and Mattson, 1999; Sinclair, 2005; Zhu et al., 2005; Ingram et al., 2006b).

Accordingly and as an alternate route to modulate intracellular glucose availability, combined disruption of insulin-dependent glucose transporter GLUT4 in adipose and muscle tissues of mice causes adult hyperglycemia as well as a metabolic switch to increased fatty acid turnover and utilization, while lifespan was studied up to 18 months of age only, and found to be unaltered (Kotani et al., 2004). Conversely, transgenic over-expression of GLUT4 in mice efficiently lowers blood glucose by increasing cellular glucose uptake, but does not extend life span (McCarter et al., 2007). Moreover, it was shown that increased glucose availability reduces *C. elegans* lifespan (Schulz et al., 2007) while potentially underlying mechanisms have been subsequently proposed (Lee et al., 2009; Schlotterer et al., 2009). Altogether, these findings suggest that increased intracellular glucose availability exerts detrimental effects on longevity, whereas decreased glucose availability promotes oxidative metabolism and extends life span.

4. Impaired insulin/IGF-1 signaling and glucose availability

Insulin and insulin-like growth factor 1 (IGF-1) are peptide hormones. Insulin is produced in and secreted from the pancreatic beta-cells, while IGF-1 is produced in the liver. IGF-1 production and release depends on a third hormone named somatotropin (STH) a.k.a. growth hormone (GH) which stems from the anterior pituitary gland. Insulin, GH and IGF-1 are hormones that bind to specific and, at least in mammals, distinct receptors. However, GH exerts some of its effects indirectly by regulating the abundance of IGF-1. Moreover, it should be noted that most of the IGF-1-independent, *i.e.* direct and receptor-mediated effects of GH commonly counteract insulin action.

Impaired availability and/or activity of GH and/or IGF-1 starting in early life causes reduced growth or dwarfism. Mice with the corresponding mutations are called Ames, Snell, and *little*, and have been described in more detail elsewhere (Quarrie and Riabowol, 2004). Interestingly, such growth-impaired mice have increased lifespan (Brown-Borg et al., 1996), while increased GH signaling impairs lifespan (Pendergrass et al., 1993; Steger et al., 1993).

Accordingly, heterozygous global disruption of the IFG-1 receptor (Holzenberger et al., 2003) as well as impaired neuronal IFG-1 receptor function (Kappeler et al., 2008) extend murine lifespan, and prevents proteotoxicity and neurodegeneration (Cohen et al., 2009).

Impaired activation of the insulin receptor has been linked to a state called insulin resistance, defined as an inappropriately reduced intracellular response to an extracellular insulin stimulus (Kahn, 1994). The key intracellular response towards extracellular activation of the insulin receptor is increased glucose uptake as mediated by translocation of the glucose transporter GLUT4. Hence it appears generally accepted that insulin resistance causes type 2 diabetes leading to reduced intracellular glucose availability (Biddinger and Kahn, 2006). This notion is supported by observations from humans in regards to increased prevalence of hyperglycemia, insulin resistance and lastly type 2 diabetes with increasing age (DeFronzo, 1981).

Conversely, targeted whole-body disruption of the insulin receptor in mice causes embryonic lethality, but when disruption is restricted to the (in regards to glucose metabolism) most relevant tissue, skeletal muscle, neither hyperglycemia nor diabetes was observed, but rather a striking increase in fatty acid turnover occurred (Brüning et al., 1998). Life span analyses in these mice have not been published. In addition, adipocyte-specific disruption of the insulin receptor extends murine life span (Blüher et al., 2003) and so does global heterozygous disruption of the downstream insulin receptor substrate 1 (IRS-1) (Selman et al., 2008a) which interestingly also is located downstream of the of IGF-1 receptor. Similarly, neuronal disruption of IRS-2 was shown to promote longevity (Taguchi et al., 2007), and so did heterozygous global disruption of IRS-2 (Taguchi et al., 2007) while others could not confirm the latter evidence using the same model (Selman et al., 2008b). Taken together, these findings suggest that a limited impairment of insulin and/or IGF-1 signaling may actually extend murine life span due to widely unresolved reasons. Of note, mutations of insulin/IGF-1 signaling have been shown to be associated with human longevity (van Heemst et al., 2005; Pawlikowska et al., 2009).

In invertebrates, long-standing evidence exists in this regard: In both *C. elegans* and *D. melanogaster*, mutations in the respective orthologues of the insulin/IGF-1 receptor or proteins located downstream of these receptors significantly extend life span (Friedman and Johnson, 1988; Kenyon et al., 1993; Kimura et al., 1997; Clancy et al., 2001; Tatar et al., 2001). However, there is little evidence in invertebrates whether and to which extent impaired insulin/IGF-1 signaling affects glucose availability.

While some authors propose that impaired insulin/IGF-1/GH signaling extends life span independently of pathways activated by CR (Lakowski and Hekimi, 1998; Bartke et al., 2001; Houthoofd et al., 2003; Min et al., 2008; Bonkowski et al., 2009), others have suggested that impaired insulin/IGF-1 signaling may share mechanistic features of caloric restriction and hence decreased energy availability, at least to some extent (Brown-Borg et al., 2002; Clancy et al., 2002; Al-Regaiey et al., 2005; Bonkowski et al., 2006; Greer et al., 2007; Narasimhan et al., 2009; Yen and Mobbs, in press). Independently, it appears likely that impaired insulin/IGF-1 signaling causes an intracellular glucose depletion in most model organisms, hypothetically mimicking the metabolic state of glucose restriction, hence contributing to lifespan extension by impaired insulin/IGF-1 signaling. While experimental evidence for this hypothesis is missing, some findings from rodents support the assumption that impaired insulin/IGF-1 signaling induces mitochondrial metabolism, whereas lifespan in most cases has not been studied (Yechoor et al., 2004; Brooks et al., 2007; Katic et al., 2007; Russell and Kahn, 2007; Westbrook et al., 2009).

5. Induction of mitochondrial metabolism by calorie/glucose restriction

While some papers suggest that the net uptake of calories is not reduced over life time in states of CR (Masoro et al., 1982; Mair et al., 2005), it is by definition agreed upon that during the actual CR intervention a relative depletion of available energy occurs.

Mitochondria convert nutritional energy more effectively into readily available energy, *i.e.* ATP, than non-oxidative metabolism of carbohydrates and some amino acids does. E.g., while glycolytic metabolism of one mol of glucose generates 4 mols of ATP only, its oxidative metabolism generates 30 mols of ATP. Hence, and as indicated by findings in yeast (Lin et al., 2002) and *C. elegans* (Schulz et al., 2007), decreased glucose availability would induce mitochondrial metabolism to increase OxPhos, aiming to maintain intracellular ATP supply. Similarly, however analyzing global CR (and not specifically glucose restriction), it was shown that food deprivation promotes mitochondrial biogenesis and OxPhos in rodents (Nisoli et al., 2005). Additionally, it has been suggested that mass-specific energy expenditure in CR rats is higher than expected (Selman et al., 2005) and that cultured mammalian cells induce their respiratory capacity in states of CR (Lopez-Lluch et al., 2006). Moreover, impaired insulin/IGF-1/GH signaling causes an induction of mitochondrial metabolism in rodents (Yechoor et al., 2004; Katic et al., 2007; Russell and Kahn, 2007; Westbrook et al., 2009). In addition, induction of mitochondrial metabolism by various pharmacological measures (Ames, 2005) and specifically physical exercise (Warburton et al., 2006; Lanza et al., 2008) has been proposed to extend lifespan. In contrast, mitochondrial dysfunction has been proposed as a key cause of aging (Trifunovic and Larsson, 2008; Bratic and Trifunovic, 2010), diabetes (Wiederkehr and Wollheim, 2006), cancer (Ristow, 2006), as well as neurodegeneration (Fukui and Moraes, 2008; Tatsuta and Langer, 2008). Moreover, impaired mitochondrial capacity decreases life span in yeast (Bonawitz et al., 2006), *C. elegans* (Zarse et al., 2007) and rodents (Thierbach et al., 2005). Mechanistically, sirtuins (see above) as well as AMPK signaling (see above) may be involved. Moreover, disruption of the target-of-rapamycin protein mTOR (Wullschleger et al., 2006) has been shown to extend *S. cerevisae* lifespan (Powers et al., 2006) interestingly by inducing mitochondrial metabolism (Bonawitz et al., 2007). Consistently and as to be anticipated from states of glucose restriction (Schulz et al., 2007) as well as TOR disruption (Bonawitz et al., 2007), the TOR target and translational repressor 4E-BP has subsequently been shown to modulate mitochondria metabolism in states of CR (Zid et al., 2009). Moreover, TOR/TORC1 activity appears to be controlled by AMPK (Gwinn et al., 2008), altogether suggesting that both TOR and AMPK may be upstream regulators of mitochondrial metabolism and OxPhos.

While all these aforementioned findings suggest that increased mitochondrial metabolism is instrumental and possibly required for the extension of lifespan, it should be noted that, in conflict with the findings mentioned above, CR has been shown to increase life span in the absence of increased respiration (Houthoofd et al., 2002; Kaeberlein et al., 2004), or even in the absence of respiration at all (Kaeberlein et al., 2005).

6. Oxidative stress and mitochondrial hormesis (mitohormesis)

About five decades ago and as stated above, increased formation of ROS as a consequence of increased metabolic rate was pro-

posed to be the major culprit for the ageing process and decreased life span (Harman, 1956). Mitochondria are the main source of ROS. For a long time, these were considered exclusively unwanted by-products of OxPhos. In support of this view, a significant number of studies in various model organisms suggests that amelioration of oxidative stress contributes to an increase of lifespan (Harrington and Harley, 1988; Phillips et al., 1989; Orr and Sohal, 1994; Parkes et al., 1998; Melov et al., 1999; Adachi and Ishii, 2000; Melov et al., 2000; Moskovitz et al., 2001; Bakaev and Lyudmila, 2002; Ruan et al., 2002; Ishii et al., 2004; Huang et al., 2006; Zou et al., 2007; Kim et al., 2008; Quick et al., 2008; Dai et al., 2009; Shibamura et al., 2009). Consistently, significant effort has been made to reduce ROS formation due to the assumption that such interventions may block or at least ameliorate aging processes in humans.

Accordingly, both synthetic as well as naturally occurring compounds that physically interact with ROS to inactivate the latter, so-called antioxidants, have been extensively been investigated. Unexpectedly, many prospective clinical trials aiming to find any health-promoting effects of antioxidants failed, in the best case showing no health-promoting effects of these compounds (Greenberg et al., 1994; Liu et al., 1999; Rautalahti et al., 1999; Virtamo et al., 2000; Heart Protection Study Collaborative Group, 2002; Sacco et al., 2003; Zureik et al., 2004; Czernichow et al., 2005, 2006; Cook et al., 2007; Kataja-Tuomola et al., 2008; Sesso et al., 2008; Katsiki and Manes, 2009; Lin et al., 2009; Song et al., 2009). More importantly, a number of studies suggests that antioxidants may promote cancer in humans (Bjelakovic et al., 2004; Bairati et al., 2005; Hercberg et al., 2007; Bardia et al., 2008; Lawenda et al., 2008; Myung et al., 2010). Accordingly, other studies show that antioxidant supplements may be disease-promoting and/or may even reduce lifespan in humans (Albanes et al., 1996; Omenn et al., 1996; Vivekananthan et al., 2003; Lonn et al., 2005; Bjelakovic et al., 2007; Ward et al., 2007; Lippman et al., 2009).

Consistently and in conflict with Harman's hypothesis, evidence has emerged in recent years that ROS may actually work as essential, and potentially lifespan-promoting, signaling molecules which transduce signals from the mitochondrial compartment to other compartments of the cell (Barja, 1993; Rhee et al., 2003; Kaelin, 2005; Connor et al., 2005; Guzy et al., 2005; Guzy and Schumacker, 2006; Chandel and Budinger, 2007; Schulz et al., 2007; Veal et al., 2007; Owusu-Ansah et al., 2008; Finley and Haigis, 2009; Ristow et al., 2009; Loh et al., 2009). Independently, it has been suggested that CR acts by inducing low-level stress that culminates in increased stress resistance and ultimately longevity (Masoro, 1998b,a). This would reflect an adaptive response commonly defined as hormesis (Southam and Ehrlich, 1943) (for a current definition see (Calabrese et al., 2007)), and was later named mitochondrial hormesis or mitohormesis, referring to ROS-related stress emanating from the mitochondria (Tapia, 2006).

Consistent with these hypotheses, it was shown in rodents that calorie restriction induces antioxidant defense capacities (Koizumi et al., 1987; Semsei et al., 1989; Rao et al., 1990; Pieri et al., 1992; Youngman et al., 1992; Xia et al., 1995; Sreekumar et al., 2002). In yeast, glucose restriction decreases ROS production despite in increased respiratory activity (Barros et al., 2004). In contrast and while using the same model organism, others showed that glucose restriction increases ROS production (Agarwal et al., 2005; Kharade et al., 2005; Piper et al., 2006). Interestingly, an induction of ROS defense enzymes was also observed (Agarwal et al., 2005; Kharade et al., 2005; Piper et al., 2006), tentatively suggesting a mechanistic link between increased respiration, elevated ROS production and adaptive induction of ROS defense.

Accordingly, in *D. melanogaster* CR was unable to primarily decrease ROS production, and genetically decreased ROS production was unable to extend life span (Miwa et al., 2004). Consistently, altering ROS production or antioxidant defense in various model organisms has similarly failed to reciprocally modulate life span (Huang et al., 2000; Bayne and Sohal, 2002; Keaney and Gems, 2003; Andziak et al., 2006; Selman et al., 2006; Ran et al., 2007; Doonan et al., 2008; Heidler et al., 2009; Jang and van Remmen, 2009; Jang et al., 2009; Lapointe et al., 2009; Van Raamsdonk and Hekimi, 2009; Yen et al., 2009; Zhang et al., 2009; Pun et al., 2010). Moreover, long-lived mutants of *C. elegans* unambiguously show increased stress resistance which in some studies is paralleled by increased metabolic activity (Lithgow et al., 1995; Vanfleteren and De Vreese, 1995; Honda and Honda, 1999; Murphy et al., 2003; Houthoofd et al., 2005; Dong et al., 2007). Of note, similar results in regards to neuroprotective mechanisms of CR and specifically DOG application have been described in rodents (Arumugam et al., 2006). Lastly, humans on a ketogenic, *i.e.* carbohydrate-depleted diet show increased antioxidant defense presumably following increased oxidative metabolism due to increased rates of beta-oxidation (Nazarewicz et al., 2007).

While all these aforementioned publications support the possibility that ROS itself induce ROS defense and ultimately increase life span, it remained to be shown that prevention of ROS formation would reduce the life-extending capabilities of CR. These experiments were undertaken by showing that DOG reduces glucose availability, increases respiration and ROS formation, promotes activity of ROS defense enzymes, and extends life span in *C. elegans* (Schulz et al., 2007). Notably, co-treatment of nematodes with several different antioxidants which inactivate ROS fully abolished the life-extending effects of CR and DOG, providing direct evidence for an essential role of increased ROS formation in extension of life span (Schulz et al., 2007).

7. Physical exercise

As summarized above, CR and specifically glucose restriction induce mitochondrial respiration and ROS formation in various model organisms. The ROS signal appears to induce ROS defense mechanisms, culminating in extended lifespan, which reflects a typical adaptive response, consistent with the mitohormesis hypothesis. Antioxidants prevent this adaptive response, and extension of lifespan is abolished. It remains to be resolved, in which time-resolved order these processes occur, and specifically whether increased ROS defense counteracts respiration-derived ROS formation.

Moreover, these findings indicate that approaches to induce mitochondrial metabolism are likely to promote metabolic health and may potentially extended lifespan. This notion is supported by the fact that not only calorie and/or glucose (and possibly amino acid) restriction, but also longevity-promoting physical exercise induces mitochondrial metabolism and ROS formation (Davies et al., 1982; Chevion et al., 2003; Powers and Jackson, 2008). Notably, supplementation with ROS-reducing antioxidants inhibits (Gomez-Cabrera et al., 2008; Ristow et al., 2009) the health-promoting effects (Higuchi et al., 1985; Lindsted et al., 1991; Manini et al., 2006; Warburton et al., 2006; Lanza et al., 2008) of physical exercise. This suggests that CR, glucose restriction and physical exercise share, at least in part, a common metabolic denominator (Fig. 1), *i.e.* increased mitochondrial metabolism and ROS formation inducing a adaptive response that culminates in increased stress resistance, antioxidant defense and extended life span.

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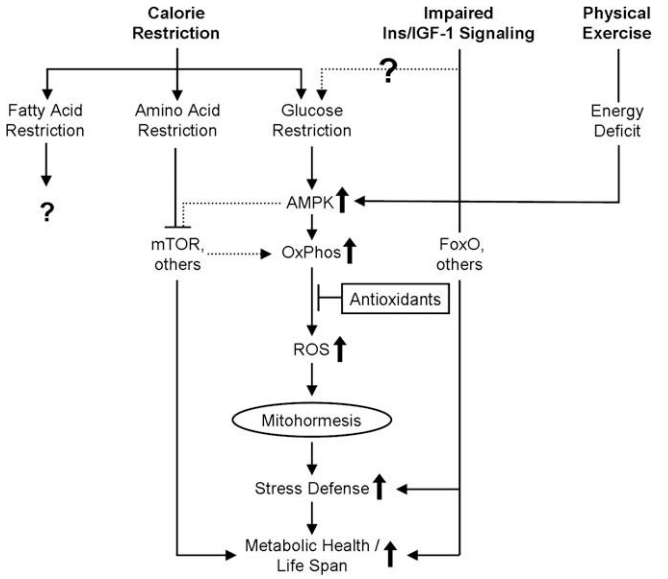

Fig. 1. Mitohormesis and lifespan extension: For both calorie restriction as well as physical exercise, experimental evidence suggests that induction of mitochondrial metabolism is required for the lifespan-extending and/or health-promoting effects of these interventions. This increase in mitochondrial metabolism generates a ROS signal that is required to induce an adaptive response to culminate in increased lifespan. For impaired insulin-IGF-1 signaling however, this links remains to be experimentally shown.

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