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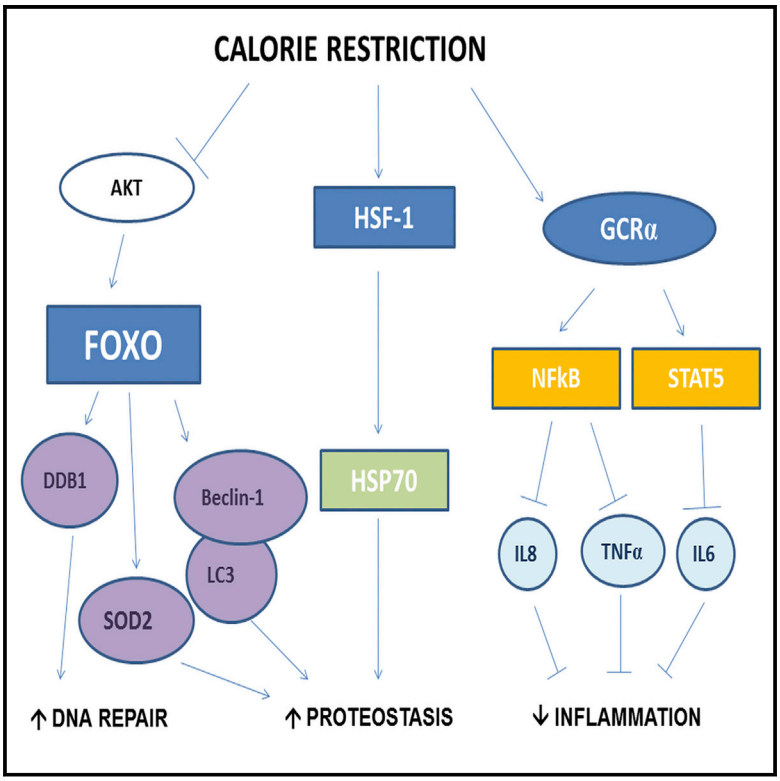
Long-Term Calorie Restriction Enhances Cellular Quality-Control Processes in Human Skeletal Muscle

Graphical Abstract



Highlights

- Calorie restriction increases health-span and lifespan in model organisms
- Little is known about the metabolic and molecular effects of CR in humans
- CR inhibits inflammation in part by increasing serum cortisol concentration
- CR elevates expression of genes and proteins that enhance protein quality control

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In Brief

Yang et al. show that calorie restriction without malnutrition in humans inhibits inflammation, at least in part by elevating serum cortisol concentration, and increases chaperone and autophagy genes and proteins involved in protein quality control and organelle homeostasis in the removal of dysfunctional proteins and organelles from cell.

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Long-Term Calorie Restriction Enhances Cellular Quality-Control Processes in Human Skeletal Muscle

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SUMMARY

Calorie restriction (CR) retards aging, acts as a hormetic intervention, and increases serum corticosterone and HSP70 expression in rodents. However, less is known regarding the effects of CR on these factors in humans. Serum cortisol and molecular chaperones and autophagic proteins were measured in the skeletal muscle of subjects on CR diets for 3–15 years and in control volunteers. Serum cortisol was higher in the CR group than in age-matched sedentary and endurance athlete groups (15.6 ± 4.6 ng/dl versus 12.3 ± 3.9 ng/dl and 11.2 ± 2.7 ng/dl, respectively; $p \leq 0.001$). HSP70, Grp78, beclin-1, and LC3 mRNA and/or protein levels were higher in the skeletal muscle of the CR group compared to controls. Our data indicate that CR in humans is associated with sustained rises in serum cortisol, reduced inflammation, and increases in key molecular chaperones and autophagic mediators involved in cellular protein quality control and removal of dysfunctional proteins and organelles.

INTRODUCTION

Calorie restriction (CR) without malnutrition increases average and maximal lifespan and prevents a range of chronic disease in model organisms (Fontana et al., 2010). The mechanisms by which CR delays aging and prevents or delays chronic diseases are still unclear. Many interrelated and overlapping neuroendocrine adaptations have been proposed to play a role, including reduction of several growth factors (e.g., insulin growth factor-1 [IGF-1] and insulin) that control the insulin/IGF-1/forkhead box O (FOXO)/mammalian target of rapamycin (mTOR) pathway and an increase in serum concentrations of glucocorticoids (stress-induced hormones secreted by the adrenal cortex) (Anderson et al., 2009; Mercken et al., 2012; de Cabo et al., 2003; Omodei et al., 2013; Csiszar et al., 2013). Cortisol, the most important human glucocorticoid, regulates important metabolic functions and activates anti-stress and anti-inflammatory pathways (Sapolsky et al., 2000; Busillo and Cidlowski, 2013).

It has been hypothesized that CR works as a mild stressor to trigger a hormetic response, resulting in reduced inflammation and increased expression of stress resistance proteins, including the heat shock protein (HSP) molecular chaperones (Mattson, 2008). In particular, CR in rodents has been shown to increase the highly conserved HSP70 family, which serves crucial roles in protein homeostasis and quality control (Heydari et al., 1996; Selsby et al., 2005). HSP70 is a molecular chaperone that coordinates several key cellular functions, including the unfolding of misfolded or denatured proteins and the maintenance of these proteins in an unfolded, folding-competent state. They also protect nascently translated proteins, promote intracellular transport of proteins, and reduce proteotoxicity by stabilizing existing proteins against aggregation (Mayer and Bukau, 2005; Stricher et al., 2013).

The purpose of the present study was to evaluate some of the metabolic and molecular effects of long-term CR on stress-induced hormones and molecular pathways in healthy lean and weight-stable men and women. Serum concentrations of cortisol and aldosterone in individuals consuming a CR diet were compared with values obtained in two comparison groups: (1) age- and sex-matched sedentary individuals consuming a Western diet (WD) and (2) age-, sex-, and body fat-matched endurance runners consuming a WD. In this study, we also examined the stress-related and anti-inflammatory molecular adaptations induced by long-term CR in the skeletal muscle of healthy lean men and women.