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VIEWPOINT

Energy Intake and Amyotrophic Lateral Sclerosis

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Abstract

Roy Walford, a physician and scientist who pioneered research on the anti-aging effects of caloric restriction and subjected himself to a low-energy diet, recently died from amyotrophic lateral sclerosis (ALS). Information from his case, epidemiological findings, and recent controlled studies in mouse models of ALS suggest that low-energy diets might render motor neurons vulnerable to degeneration, whereas high-energy diets are ameliorative. This contrasts with the effects of low-energy diets on various neuronal populations in the brain that respond adaptively, activating pathways that promote plasticity and resistance to disease. One reason that motor neurons might be selectively vulnerable to low-energy diets is that they are unable to engage neuroprotective responses to energetic stress response involving the protein chaperones, such as, heat-shock protein-70.

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The improbable case of Roy Walford hints at a relationship between low-energy intake and the risk of the neurodegenerative disease, amyotrophic lateral sclerosis (ALS). ALS involves the inexorable degeneration of motor neurons in the spinal cord and motor cortex, resulting in progressive paralysis and death. Except for very rare cases of inherited ALS that result from mutations in the *Cu/Zn-superoxide dismutase* gene, the cause(s) of ALS is unknown (Majoor-Karkauer et al., 2003). Walford was a physician and scientist who made important contributions toward understanding how low-energy diets (caloric restriction) can extend the life span (Walford, 1985). Based on data showing that energy restriction improves the health and longevity of rodents, he subjected himself to a reduced-energy diet of approx 1600 calories per day combined with an exercise regimen over a period of three decades (O'Connor, 2004). In 2005, he died at the age of 79 after suffering with ALS for several years. Walford was one of eight participants in the highly publicized Biosphere 2 project in which the participants were sealed in a self-sustaining "biobubble" for 2 yr during which time they cultivated their own food, but were unable to produce sufficient food for a normal energy-level diet (Walford et al., 2002). Another Biosphere 2 participant also

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developed a motor neuron syndrome (Lassinger et al., 2004). Because the lifetime risk of ALS in industrialized countries is about 1 in 1000 (www.alsasso ciation.org), and the numbers of people on a sustained low-energy diet is also very low, Walford's case suggests that a low-energy intake might promote the development of ALS.

But Walford's case is but an anecdote among a much larger and growing body of evidence linking a negative energy balance to the pathogenesis of ALS. The tragic cases of prominent athletes, such as the baseball player Lou Gehrig who developed ALS at an early age (Kasarskis and Winslow, 1989), raised interest in a possible link between energy balance and ALS. The results of several epidemiological studies suggested that athletes and individuals with a low body mass index are at increased risk of ALS. For example, the results of a case–control study of 279 patients with motor neuron disease showed that the patients were more likely than controls to report that they had always been slim and/or had been varsity athletes (Scarmeas et al., 2003). In addition, patients with ALS were reported to have a higher metabolic rate than control subjects (Desport et al., 2001), and males (who typically expend more energy than females because of their occupations and participation in athletics) are more likely than females to develop ALS (Kurzke, 1982). Moreover, in a prospective study of patients with ALS in France there was an eightfold increased risk during a 7-mo period in patients with a low body mass index (Desport et al., 1999). However, other studies failed to find an association between levels of physical activity and risk of ALS (Veldink et al., 2005), suggesting the need for further human epidemiological studies.

Although the data from human studies is limited and inconclusive, recent findings from studies of animal models of ALS strongly suggest that energy intake can influence the pathogenesis of this disease. Cu/Zn-superoxide dismutase (SOD) mice develop ALS-like diseases involving degeneration of lower motor neurons resulting in progressive paralysis and death. An initial study showed that when such ALS mice were maintained on an intermittent-fasting dietary-restriction regimen their disease worsened, suggesting that a low-energy intake exacerbates the disease process (Pedersen and Mattson, 1999). Consistent with the disease process, it was recently reported that energy restriction (40% reduction in calorie intake) hastens the onset of clinical disease in ALS mice (Hamadeh et al., 2005). On the other hand, degeneration of motor neurons was attenuated and the survival of ALS mice was extended by administration of creatine, a compound that promotes maintenance of cellular adenosine triphosphate levels (Klivenyi et al., 1999). More recent studies have shown that ALS mice exhibited increased energy expenditure, skeletal muscle hypermetabolism, and reduced adipose tissue levels well before the appearance of symptoms (Dupuis et al., 2004). In the latter study, the course of the disease was significantly retarded and survival was extended by 20% when the ALS mice were maintained on a high-energy diet.

In our experiment, the effects of a high-fat/high-sugar "fast-food diet" (FFD) on the disease process in ALS mice were studied. Six-week-old male ALS mice were divided into two groups. One group was fed a control diet (n = 12) and the second group an FFD (n = 12). The control diet consisted of 64% carbohydrates, 17% fats, and 19% protein, whereas the FFD consisted of 38% carbohydrates, 47% fats, and 15% protein. ALS mice on the control diet developed hind limb paralysis within 100 and 140 d of age and all of these mice died by 180 d of age (Fig. 1A). The age of disease onset and the survival of ALS mice were significantly increased when they were maintained on the FFD, with all mice on this diet surviving to 220 d of age and several surviving more than 270 d. Mice maintained on the FFD gained body weight until they became symptomatic, whereas mice on the control diet either lost weight or remained at their prediet weight before the appearance of motor dysfunction (Fig. 1B). The time between disease onset and death was significantly greater in the ALS mice on the FFD compared with those on the control diet (data not shown). Thus, a high-energy diet has a clear beneficial effect in delaying the onset and slowing the disease progression in ALS mice.

The apparent vulnerability of motor neurons as negative energy balance contrasts with other types of neurons, such as those in the hippocampus, cerebral cortex, and substantia nigra, which might benefit from energy restriction. For example, energy restriction suppressed the disease process and improved functional outcome in animal models of Parkinson's (Maswood et al., 2004), Alzheimer's (Patel et al., 2005), and Huntington's (Duan et al., 2003) diseases, and stroke (Yu and Mattson, 1999).

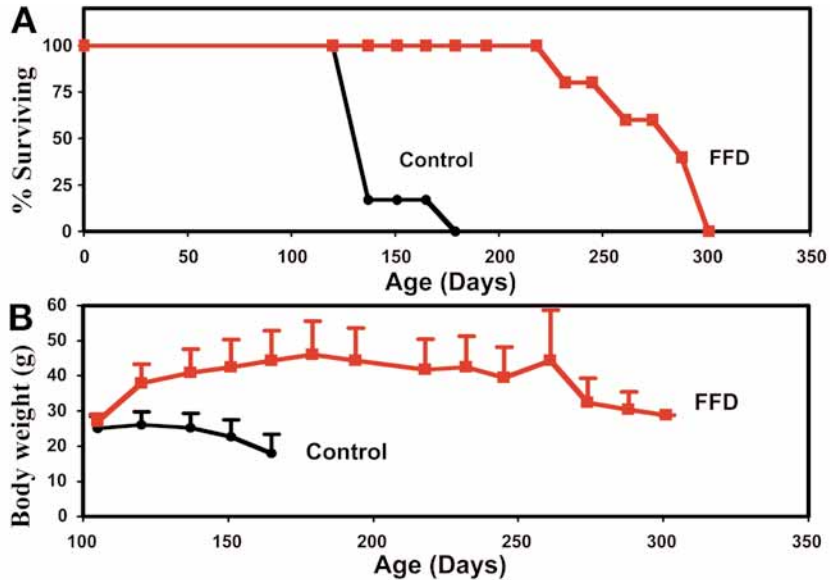

Fig. 1. A high-fat/high-sugar diet increases the survival of ALS mice. Male Cu/Zn-SOD mutant (*G93A* mutation) mice were fed either a control diet ($n = 12$) or a high-fat/high-sugar fast food diet (FFD; $n = 12$) beginning at 6 wk of age. **(A)** Gompertz plot of mortality of mice in each diet group. **(B)** Average body weights (mean and SEM) of mice in each diet group. Control and high-fat/high-sugar (FFD) diets were purchased from Dyets Inc. (Bethlehem, PA). The control diet (Dyet no. 110750) is a modified AIN-93G rodent diet that meets 1995 NRC values, which was 3720 kcal/kg containing 200 g/kg whey protein, 620 g/kg complex carbohydrates (corn starch), and 70 g/kg soybean oil. The FFD (Dyet no. 101668) was a modified AIN-93G rodent diet that meets 1995 NRC values which was 4424 kcal/kg and contained 200 g/kg whey protein, 361 g/kg complex carbohydrates (corn starch), 100 g/kg glucose, 70 g/kg soybean oil, 100 g/kg butter, and 50 g/kg egg yolk powder.

The mechanism by which low-energy diets can protect the latter neurons and other cell types in the body against age-related disease is believed to involve a conditioning response in which the cells respond to the energetic stress by increasing their production of stress resistance proteins such as Heat-shock protein (HSP)-70 (Sinclair, 2005). Although the mechanisms remain to be determined, motor neurons might not be able to respond adaptively to energetic stress and hence might be selectively vulnerable. Unlike other types of neurons, motor neurons exhibit a greatly reduced ability to upregulate HSP-70 in response to oxidative and metabolic stress (Batulan et al., 2003). Moreover, ALS-causing mutant forms of Cu/Zn-SOD sequester HSP-70 (Okado-Matsumoto and Fridovich, 2002), which would be expected to compromise the ability of motor neurons to respond adaptively to stress. Further, research aimed at understanding the effect of energy intake and expenditure on motor neuron physiology and vulnerability to disease is clearly required and might lead to novel approaches for delaying or preventing ALS in those who might be at risk.

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