Symposium: Calorie Restriction: Effects on Body Composition, Insulin Signaling and Aging

Introduction\textsuperscript{1,2}

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ABSTRACT At this time of increasing attention to the worldwide problem of obesity and its negative consequences for health and well being, it is timely to present a symposium on the effects of calorie restriction and the potential for calorie restriction mimetic therapies. The present symposium “Calorie Restriction: Effects on Body Composition, Insulin Signaling and Aging” was included in the Experimental Biology 2000 meeting held April 15–18, 2000 in San Diego, California. It is now recognized that calorie restriction carries with it many heretofore unrecognized consequences in addition to the life span–extending properties first described in the 1930s. This symposium addresses some of the current issues in calorie restriction and demonstrates the widespread effects of obesity and overweight are estimated to affect \textgreater50\% of American adults. Weight loss efforts have focused upon reduction in calorie intake and increase in physical activity, with pharmaceutical interventions and surgical approaches being reserved for those with more severe obesity or with complications of obesity. In those overweight persons who have successfully lost weight, increased physical activity may be of some value in sustaining weight loss or may be a marker of the highly motivated person who, after weight loss, retains a high level of commitment to continued restraint of calorie intake and increase in physical activity, with pharmaceutical interventions and surgical approaches being reserved for those with more severe obesity or with complications of obesity. In those overweight persons who have successfully lost weight, increased physical activity may be of some value in sustaining weight loss or may be a marker of the highly motivated person who, after weight loss, retains a high level of commitment to continued restraint of calorie intake (National Institutes of Health, National Heart, Lung, and Blood Institute 1998). It is, however, calorie restriction (CR)\textsuperscript{4} both during weight reduction and after weight loss in the formerly obese that is the sine qua non for sustaining reduced body weight. CR, however, has been shown to be extraordinarily difficult to sustain, despite apparently high motivation to do so in the formerly obese. Undoubtedly, this is due to the consequences of CR that accompany weight reduction.

CR has many consequences, the majority of which are unknown at this time. Neither the mechanisms by which life extension takes place (in rodents) nor the mechanisms by which the complex features associated with insulin resistance and the Metabolic Syndrome X are prevented by CR are understood (Bodkin et al. 1995). Clearly, advancements in this area will lead to better understanding of this powerful nutritional tool. The estimate of changes induced in mammals by the long-term application of CR is likely to involve thousands of alterations, only a small portion of which causally influence longevity and health. One step, the description of altered functions and the protein changes underlying those, has been advanced by several of the reports included in this symposium. The second step, identification within this changed spectrum of those that are causal or principal in the observed positive outcome, awaits a future Experimental Biology symposium.

CR produces altered pathways of nutrient disposal, including reduced plasma glucose, insulin and leptin levels (Hansen and Bodkin 1993, Hansen et al. 1996). Although glucose tolerance is retained at normal levels under CR, there is evidence to suggest alterations in the intermediary pathways of glucose metabolism. In detailed studies of weight stable reduced individuals, energy efficiency was increased, that is fewer calories per lean body mass were required to maintain stable weight (Leibel et al. 1995, DeLany et al. 1999).

Among the newest tools in molecular biology that hold promise for enhancing our understanding of the mechanisms by which CR extends life and enhances health are the application of high density oligonucleotide arrays to profile alterations in gene expression and the use of high performance liquid chromatography separations coupled with coulometric array detectors to examine simultaneous changes in serum metabolites. Each of these is featured in the present symposium.

Soon microarrays will be available to simultaneously assess the changes induced by expression of \textgreater60,000 genes. The
report here of the Wisconsin group’s application of an array of 6347 genes, as presented by Richard Weindruch, explores the efficacy of one nutritional intervention, dietary restriction (DR) in rodents, as an approach to understanding the effects of DR to retard the aging process (Weindruch et al. 2000). Weindruch et al. have reviewed their own and the work of others aimed at evaluating the effects of CR at the transcriptional level in mice, most commonly as seen in liver tissue. Possible lowering of enzyme activity related to glycolysis and increase in enzyme activity for glycogenolysis have been suggested (Dhahbi et al. 1997, Dhahbi et al. 1998, Delany et al. 1999).

Weindruch and colleagues have used oligonucleotide-based and cDNA-based arrays to examine CR effects in aging mice. They surveyed 6347 genes for increases or decreases of more than twofold with aging. They have focused attention on several genes that increased in expression related to the stress response and were possibly associated with increased production of reactive oxygen species or mitochondrial dysfunction in aging. They also identified several other genes related to energy metabolism, which are decreased in aging. Finally, they have sought to determine whether these age-related changes are affected by CR. More than 50% of those genes whose expression was increased or decreased with aging showed attenuation of these changes under CR.

One of the many challenges facing those who seek to identify the mechanisms underlying the positive effects of CR on health and aging is the undoubted fact that many aspects of metabolism are simultaneously altered by CR and that these changes do not take place as step functions but are changed progressively. Some reach asymptotes and remain at maximal or minimal values. Others show dynamic changes to which later adaptations occur, obscuring the initial shake down response to CR.

For this reason tools that permit multiple repeated measures over short periods (hours) and over long periods (years) and that permit simultaneous tracking of multiple interacting and changing steps in metabolism and endocrinology are greatly needed.

One such method is under development and testing using DR as the test experimental condition. This symposium includes the first report on the application of metabolic stereotype analysis to characterize the changes induced by or resulting from DR. The joint efforts of Kristol and colleagues are being applied to examine the effects of CR on some 1200 serum compounds with particular focus on the redox-active components of rodent serum (Vigneau-Callahan 2000). Variations in nutritional and metabolic status are being assessed by combining high performance liquid chromatography separations and coulometric array analysis to sera differing only in degree of DR. Many challenging problems have arisen including optimization of analytic validity as well as handling of biological variability. Of the 1200 compounds examined to date, ~250 appear to be sufficiently reliable for further analysis.

There is evidence that the response to CR may be genetically determined. This was particularly suggested by the finding of Ortmeyer et al. (Ortmeyer et al. 1994) that nonhuman primates maintained under constant identical conditions and held to the same stable adult body weight, nevertheless differed significantly in the way in which CR affected their glycogen metabolism, as presented in this symposium (Ortmeyer 2000).

CR of nonhuman primates has been shown to prevent or substantially delay the development of type 2 diabetes mellitus (Hansen and Bodkin 1993). Other degenerative lesions of aging, particularly in obese animal models such as the fa/fa rat, have also been shown to be substantially reduced by CR. In the present symposium, Judith Stern (Stern et al. 2000) has addressed the effects of CR specifically on glomerulonephritis that is common in obese aging rodents. End-stage renal disease has greatly increased in recent years, particularly in patients with type 2 diabetes. The rapidly increasing prevalence of obesity and of diabetes in the U.S. population and, in fact, in much of the world, heightens the concern about the human as well as economic costs of these diseases and of their complications and presents a challenge to those seeking to delay or prevent these disorders.

CR is currently the only modality that has been shown to have the power to positively alter the course of these disorders. Judith Stern has presented here a review of the work of her group as well as the work of others that clearly demonstrates the significant positive effects of CR on renal disease. Also addressed is evidence that these studies in rodents have significant relevance to humans.

CR has as one of its consequences the reduction in body fat mass. In order to specifically test the role of attenuated fat mass per se, Barzilai and Gabriely have surgically ablated fat in rodents. The results of these studies are reviewed here (Barzilai and Gabriely 2000) and suggest that many of the beneficial effects of CR are attributable to reduced fat stores.

CR carried out for 10 to 15 y in adult rhesus monkeys has been shown to result in sustained alteration in glycogen metabolism, despite apparent retention of normal insulin-stimulated glucose uptake, normal glucose tolerance and normal fasting glucose and insulin levels. Ortmeyer, in this symposium (Ortmeyer 2000), has built on previous reports of the effects of CR on insulin action on the rate-limiting enzyme of glycogen storage, glycogen synthase. CR appeared to unveil a predisposition in approximately one half of the CR monkeys toward metabolic abnormalities in response to insulin. Uniquely, CR and no other experimental manipulation or condition, has been found to produce insulin-stimulated inactivation of glycogen synthase, rather than the normally expected activation of glycogen synthase by dephosphorylation (Ortmeyer et al. 1994). Although glycogen content remained normal in all CR monkeys, we suspect that the induction of abnormal insulin action on glycogen synthase by long-term CR may represent a pointer toward the underlying defect that, under ad libitum conditions, would lead to obesity, insulin resistance and eventually type 2 diabetes in approximately one half of aging rhesus monkeys.

The power of CR to mitigate, delay or prevent this clinical development of disease, despite the presence of underlying metabolic defects in insulin action, points to the critical need for effective CR mimetic approaches to slow or halt the consequences of the underlying genetic predispositions toward obesity and type 2 diabetes in humans (and in nonhuman primates).

LITERATURE CITED


