[Frontiers in Bioscience 3, d125-135, January 15, 1998]

DOES CALORIC RESTRICTION ALTER IL-2 TRANSCRIPTION?

Mohammad A. Pahlavani

Geriatric Research, Education and Clinical Center, South Texas Veterans Health Care System and Department of Physiology, University of Texas Health Science Center, San Antonio, Texas 78284

Received 1/5/98 Accepted 1/9/98

TABLE OF CONTENTS

1. ABSTRACT

Caloric restriction has been the subject of intensive research and is known to be the most efficacious means of increasing longevity and reducing pathology. Caloric restriction has been found to influence a wide variety of age-sensitive immunological parameters such as interleukin-2 (IL-2) gene expression, and overall, the immunological status of rodents fed a caloric restriction diet is superior to the immunological status of the non-restricted animals. IL-2 is a growth promoting cytokine that plays a critical role in immune function. The expression of IL-2 has been shown to decrease with age, and the decrease in IL-2 expression parallels the age-related decrease in immune function. The focus of this review article is to discuss the studies on the influence of caloric restriction on IL-2 expression and the recent findings on the mechanisms by which caloric restriction enhances IL-2 gene expression. A number of studies have demonstrated that caloric restriction alters the expression of the IL-2 gene at the level of transcription. The increase in IL-2 expression correlates with an increase in binding activity of the transcription factor NFAT which plays a predominant role in IL-2 transcription. In addition, preliminary results suggest that activation of the upstream signaling molecules, the mitogen-activated protein kinase (MAPK) signaling cascade, may play a role in the enhancement of IL-2 transcription.

2. INTRODUCTION

The initial experiments in the 1930's by McCay *et al.* (1) showed that severe reduction of food intake in rats increased their life spans dramatically. Subsequent studies in the 1950s and 1960s demonstrated that dietary restriction (i.e., undernutrition, not malnutrition) significantly prolonged the survival of rodents. This prolongation has been observed with a variety of different techniques that reduce the amount of food consumed by rodents (reviewed in 2-4). Over the past decade, it has become apparent that the reduction in total calories is the component of the dietary restriction regimen responsible for the increase in survival (5,6). In other words, reducing the caloric intake of the rodents through any nutritional modification increases survival compared to that of rodents fed the normal calories in the laboratory chow diet (*ad libitum*). All evidence currently suggests that caloric restriction increases the survival of rodents by retarding the aging process (2-6). Therefore, caloric restriction has become a powerful technique for studying the process of aging.

Although it is well established that caloric restriction increases survival of rodents and reduces the pathology of diseases associated with aging, the physiological and biochemical basis for this effect have not been estabilished. The view that caloric restriction alters the aging process at the level of gene expression was first suggested by Barrows (7) in 1972. He proposed that protein synthesis was reduced in tissues of rats fed caloric restricted diets, and that the reduction in protein synthesis resulted in a reduced use of the genetic code. Barrows (7) suggested that caloric restriction increased longevity because the genetic code was used less by cells. The view that caloric restriction alters gene expression was expanded further in 1979 when Young (8) introduced the concept that nutrition might alter the aging process(es) by interacting at the structural and functional level of the gene by specifically altering translation and/or posttranslational processes. In 1982, Lindell (9) suggested that caloric restriction was a "physiological stress" that enhanced gene expression and that the enhancement in gene expression was a significant factor in maintaining cellular homeostasis in the caloric restricted rodents. In 1985, Richardson (10) proposed that caloric restriction retards the age-related decline in gene expression. Thus, over the