Obesity is one of the most serious problems of public health and the fifth leading cause of death. It is estimated that 44% of diabetic load, 23% of heart ischemic load and 7-41% of all cancers load are related to obesity. Approximately 80% of older adults (+65 years) have at least one of the above mentioned chronic diseases, and 50% have at least two chronic disease (1). Along with other organs, brain is also affected with aging and high calorie intake as Fitzpatrik and colleagues suggested in a review article that obese people have problems on decision-making, planning and solving skill, with fewer difficulties on the tasks of verbal fluency, learning and memory (2). In contrast, a reduction of calorie intake without malnutrition called “calorie restriction” (CR) has a wide range of benefits. Moderate CR can prevent or reverse the damaging effects of overweight/obesity, type 2 diabetes, hypertension, chronic inflammation and other age-associated metabolic diseases (1).

As the first groups who worked on CR, Osborne et al. in 1917 showed that reducing calorie intake in rats increased their length of life. Since then, large amount of time and research efforts have been and continued to be devoted to the study of anti-aging and anti-cancer mechanisms underlying CR in yeasts, worms, insects, rodents and humans (3). Significant increase in life span has been reported when the nutrient availability drops between 30% and 75% of normal calorie provision, according to the species. Not only calorie restricted rodents lived longer than the adlibitum-fed counterparts but a significant part of them (about 30%) died without any apparent pathology, raising the striking possibility that aging is not necessarily tightly linked with costly pathologies (4).

Preliminary results from human studies are reproducing many of the metabolic and physiological responses observed in rodents and monkeys. Short term CR (6-24 months) induces reduction of body weight, subcutaneous and visceral fat, lean body mass, insulin, energy expenditure, and core body temperature (5). Core body temperature, levels of dehydro-eiandrosterone sulfate (DHEAS) and insulin are biomarkers of CR and longevity in human similar to rodents and monkeys. In a 6-month CR related study on overweight individuals, a significant reduction of fasting insulin levels and core body temperature in CR and CR with exercise group has been reported; however, DHEAS and fasting glucose remained unchanged, as DHEAS falls 2-4% per year in humans. The other hypothesis to explain the anti-aging effects of CR is reduced energy expenditure with a consequent reduction in the production of reactive oxygen species (ROS). In this study, a metabolic adaptation over 24 hours following 6 months of CR has also occurred (6). CR decreases serum insulin-like growth factor1 (IGF-1) concentration by approximately 40% in rodents. This is a key role in protection against cancer and slowing age; as IGF-1 promotes tumor development and inhibits apoptosis (3).

**Cognitive impairment and calorie restriction**

Evidence from clinical and basic researches points to a deep connection between brain function decline and metabolic dysregulation during senescence. Excess nutrient availability may be detrimental to brain function. Conversely, a 30% reduction in
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Calorie intake for a period of 3 months was found to improve memory performance in elderly individuals (7). Aside from these observations, the results three ongoing CR studies on rhesus monkeys till now have demonstrated that CR-treated monkeys suffer less severe brain atrophy (a hallmark of aging brain) compared to the control fed ad libitum (8).

Alzheimer's disease: Alzheimer's disease (AD) is a high prevalent neurodegenerative disorder characterized by progressive loss of memory and executive function resulting from synaptic dysfunction and neurodegeneration within vulnerable brain regions (9). Aggregation and accumulation of beta amyloid peptide (Aβ), derived from the amyloid precursor protein (APP) holoprotein, induce synaptic dysfunction, oxidative damage, tau aggregation, and other types of cellular injury that ultimately drive neuropathology associated with the AD disease (10). A study in 1997 showed the scatter plot of AD prevalence versus total food supply for countries; it further indicated that for every per capita additional grams of fat or calorie consumed per day, there is an average increase of 0.03% and 0.003%, respectively, in AD prevalence in the adult population of 65 years age or older (7). On the other hand, it has been shown that sustained CR reduces Aβ neuropathology compared with ad libitum feeding in several AD mouse models (11). Previous studies in which CR started in relatively young mice (<7months age) with transgenic APP mutations and relatively light amyloid loads demonstrated that CR blocks the mutation of Aβ-containing amyloid plaques (12).

Parkinson's disease: Parkinson disease (PD) is the second leading age related disorder after AD with an average onset age of 60 years (13). PD results from the dysfunction and degeneration of dopamine (DA) neurons in the substantia nigra (SN) and DA axon terminals, resulting in progressive motor dysfunction (14). Two findings profoundly influence our science about PD: one mitochondrial dysfunction, oxidative stress and neurodegeneration, and second discovering the genetic cause of PD (15). CR in caenorhabditiselegans whose dopaminergic neurons were degenerated by 6-hydroxy dopamin showed preventive effect on dopaminergic degeneration by increasing the content of neurotransmitter dopamine (16). Also a study on rhesus monkeys with hemi Parkinson condition treated by 30%CR exhibited higher levels of dopamine and dopamine metabolites in spatial pathway compared with the control group. Also it significantly increased the level of dopamine neurons and glial cell line derived neurotrophic factor, which is known to promote the survival of DA neurons (17).

Huntington: Huntington’s disease (HD) is a fatal neurodegenerative disorder caused by an expanded polyglutamine repeat in Huntington protein (18); it is an inherited neurodegenerative disorder with a distinct phenotype, including dystonia, incoordination, cognitive decline, and behavioral difficulties (19). Several studies have suggested that excite toxicity and mitochondrial dysfunction play roles in the pathogenesis of HD (18). It is suggested that higher levels of cellular energy may have a role on disease progression. Because administration of creatine, a ATP-depletion delays the disease onset, and improves neuronal survival (20). CR in Huntington mutant mice increased the level of Brain-derived neurotrophic factor (BDNF) and the protein chaperone heat-shock-protein-70 in the stratum and cortex, which were depleted in HD mice fed a normal diet. CR promotes neuronal degeneration by impairing cellular resistance (21).

Underlying mechanisms: There is ample evidence that the mechanisms involve significant alterations in energy metabolism; response to oxidative damage, insulin sensitivity, inflammation, and changes in the neuroendocrine, paracrine and reproductive systems (22). CR induces a down-regulation of

Figure 1. Alzheimer's disease prevalence in +65 years population vs. total food supply.
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