Preface

The Alzheimer's Disease-Diabetes Angle: Inevitable Fate of Aging or Metabolic Imbalance Limiting Successful Aging

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Modern societies face the increasing burden of age-related diseases, in particular Alzheimer's disease (AD) and type 2 diabetes (T2D). While numerous epidemiological studies have described the incidence of both diseases in the Western world and extensively defined common environmental risk factors, only little is known on the pathomechanisms linking both diseases [1–3]. Thus, it is not yet clear whether both diseases represent the endpoint of aged, exhausted, and dysfunctional cells having reached their maximal life expectancy or whether AD and T2D are the consequences of living in superabundance including excessive food supply, work demands, psychosocial stress, and an excessive sedentary life style [4–9]. Evidence for the latter is provided by the fact that high adiposity increases the risk of AD [10–12] and T2D [10,13] and implies that the progressive loss of energy balance is one underlying pathomechanism of both diseases.

Interestingly, mammalian hibernators such as ground squirrels and hamsters demonstrate comparable and annual recurrent periods of obesity with concomitant insulin resistance and key features of AD such as tau phosphorylation [14,15]. These pathologies, however, are reversed by a time-dependent metabolic shift between carbohydrate- and fat-based metabolism, a delicate balance of kinases and phosphatases and changes in gene expression [15–17]. While massive fat depots serve as the main source of metabolic fuel throughout the winter [18], phosphorylation of tau during obligate hibernation seems to be a reversible consequence of hypothermia [19,20]. These changes gradually decrease over a period of months until the animals emerge from hibernation each spring [18]. Thus, fat storage and tau phosphorylation occur predictably on an annual basis, but subsequent fasting depletes fat during the course of winter and ensures that each spring the obese hibernator emerges lean [18]. Another example for a phylogenetic conserved adaptive response to energetic stress is provided by hummingbirds [21], which consume a high sugar diet and seasonally develop hyperglycemia and obesity, which is normalized during the breeding season [21]. Thus, hibernating mammals and hummingbirds provide an extreme example of the utility of accumulating body resources in nutrient-rich times for later use during times of fasting.

These observations, however, indicate that mechanisms have to exist that enable cells to re-program their metabolism and maintain accurate energy balance despite repeated situations of excessive energy surplus. Fasting periods might also change and/or normalize gene expression patterns and activate cellular defense mechanisms that protect cells from being impaired by subsequent nutrition supply [18]. Noteworthy, centenarians seem to be equipped with gene variants that

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allow them to optimize the energy balance and to minimize the effects of exposure to environmental stressors [22].

Features of the metabolism in starvation, hibernation, and various conditions of energy deprivation have led to the definition of the deprivation syndrome as a phylogenetically conserved adaptive response to energetic stress, which is characterized by hypometabolism, oxidative stress, and adjustments of the glucose-fatty acid cycle [23].

Several pathological features have been identified as common denominators of AD and T2D including impaired glucose/energy metabolism, altered insulin-signaling pathways, mitochondrial dysfunction, oxidative stress, and inflammation. There is also increasing evidence that posttranslational modifications such as sumoylation and glycation might contribute to gene expression changes and the loss of cellular function in situations, in which energy balance cannot be restored. In this context it is of particular interest that amyloid-β peptides, causing neurodegeneration and cognitive decline in AD [24], and advanced glycation end products (AGEs), accumulating in T2D [25,26], are ligands of the receptor for AGEs (RAGE) [27–31], known to perpetuate inflammation, to increase oxidative stress and to mediate downregulation of protective cellular mechanisms in situations of ligand excess [29]. Thus, RAGE might play a central role in converting the reversible obesity, accompanying insulin resistance and Alzheimer-like pathologies of natural hibernation into the pandemic of human obesity, metabolic syndrome, AD, and T2D.

The identification and functional characterization of these checkpoints in model organisms and their confirmation in prospective clinical studies holds great promise, that understanding the common pathways of AD and T2D will provide progress in both fields of research. This special issue summarizes the current knowledge on pathways triggered by oxidative stress, reactive metabolites, inflammation, and RAGE in AD and T2D and addresses common features of both in model organisms such as *C. elegans*, in experimental rodent models, and from the clinical perspective.

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