Published in final edited form as:

Ageing Res Rev. 2015 March ; 20: 35–36. doi:10.1016/j.arr.2015.02.002.

Energy metabolism and the brain: A bidirectional relationship

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From an evolutionary standpoint, the efficiency of energy metabolism is one of the most critical determinants of survival and success of procreation. A complex neuroendocrine system has evolved to regulate energy metabolism under different environmental and behavioral contingencies, including absence or abundance of food, cold or hot weather, exertion or rest, fighting infection, repairing trauma, ovulating, or supporting pregnancy or lactation, to name but a few. Each one of these conditions strikes a different balance between energy supply and demand. The human brain, which provides flexible behavioral responses that help adapt to an ever-changing environment, has evolutionarily acquired greater control over energy intake and expenditure, partially at the expense of the simple logic of endocrine feedback loops, but always in close coordination with them (for a review of recent insights, see Karatsoreos et al., 2013).

In addition, the brain is not only a major regulator of metabolism, but also the organ that consumes the most energy per unit weight in the human body. Therefore, its healthy function, and its malfunction in brain diseases is intricately connected with energy metabolism. Emerging evidence suggests that impaired energy metabolism is a modifier or even proximate cause of brain aging and the pathogenesis of neurodegenerative diseases, such as Alzheimer's disease (Kapogiannis and Mattson, 2011; Mattson et al., 2010; Pathak et al., 2013).

This special issue of ARR is composed of systematic reviews written by leading scientists who cast light on key aspects of the bidirectional relationship between brain and energy metabolism and the roles of alterations in the underlying cellular and molecular regulatory pathways in aging and aging-associated disorders.

Food intake is modulated by the phylogenetically ancient hypothalamus, which also regulates sleep/wake cycles. However, the connection between food intake and sleep is more complex than previously imagined as illustrated by the discovery of orexins (or hypocretins), neuropeptides produced by a distinct neuronal population in the lateral-posterior hypothalamus, which have been identified as key regulator of both feeding and sleeping behaviors. Nixon et al. review animal model studies where modulation of the orexin system has an impact on the aging process and the development of obesity and sleep disorders. Next, they turn their attention on clinical studies examining orexin-mediated effects on obesity, sleep disorders and cognitive aging. Finally, they examine recent evidence

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implicating sleep disorders in Alzheimer's disease and other neurodegenerative diseases, an avenue of research that raises novel tantalizing possibilities for prevention and treatment of these conditions.

The most prevalent metabolic abnormality for all age-groups, including older individuals, is obesity, but the factors that drive this epidemic are still not fully known. Murray et al. review recent evidence from clinical and animal studies addressing the 'Food Addiction Hypothesis' (Volkow et al., 2012). They conclude that behaviors, brain changes and molecular mechanisms implicated in classic addiction disorders at least partly account for the development of obesity in people, including an expanding portion of aged individuals.

Calorie restriction beyond what is generally considered normal amount of energy intake (without corresponding nutrient deficiency) is perhaps the most obvious and potentially effective solution to the problem of obesity. Calorie restriction creates a unique metabolic state impacting the aging process resulting in increased healthspan and lifespan, and, perhaps, an added tantalizing possibility, resistance to brain aging and neurodegenerative diseases. Unfortunately, calorie restriction demands such a dramatic behavioral transformation in what is considered "normal" human behavior that remains unpalatable to most people. This conundrum gave rise to the search for calorie restriction mimetics – drugs targeting the molecular pathways favorably modulated by calorie restriction and, therefore, being able to recapitulate its health benefits. Ingram et al. provide us with an authoritative review of the current state of the science. Specifically, they discuss several viable candidate strategies, both upstream to digestion, such as bariatric surgery and inhibitors of digestion, as well as downstream to it, such as inhibitors of glycolysis, modulators of insulin receptors, IGF-1 receptors, sirtuin activators, and inhibitors of mTOR.

Whereas calorie restriction proponents focus mainly on the total amount of calories consumed, the notion that not all energy sources are created equal appeals to many experts and the wider public. But how strong is the evidence that calories consumed in the form of olive oil, vegetables, and fish have beneficial effects on brain health during aging compared to calories consumed as red meat? Are there specific nutrients contained in the former that may account for any health benefits? Or are any pervasive lifestyle and social factors implicated? A prominent proponent of the Mediterranean diet, Nikolaos Scarmeas, takes a critical look at the literature (including his own original research) to conclude that present evidence generally supports a positive recommendation for the Mediterranean diet – although further research is needed to elucidate the relevant mechanisms.

A chronic positive energy balance is reflected in excessive deposition of adipose tissue and higher body weight. Given the suggestion of earlier neuroimaging studies that obesity is associated with brain atrophy, Ariel Willette and I critically reviewed recent studies for evidence on the impact of obesity in different age groups on gray and white matter volume. We found that the most replicable and reliable finding in this literature is that obesity has a negative association with hippocampus and frontal lobe grey matter.

Regarding the effects of energy metabolism on the aging brain, Mark Mattson is a prominent proponent of the idea that a chronic positive energy balance is detrimental to brain health

and to neurons during aging, rendering them vulnerable to neurodegenerative disease processes. In his present review, rich in evolutionary perspectives, he highlights the benefits of diet and exercise on brain function, examines recent findings on the molecular mechanisms underlying the beneficial effects of diet and exercise (chief among which is neurotrophin signaling), and, finally, considers the socioeconomic causes and sequelae of pro- and anti-obesity behaviors.

From these contributions, the field appears in a state of creative flux, increased sophistication and refinement. We hope that the present issue will add clarity and stimulate research in a field where interventions with potential major impact on the aging process are within grasp.

Acknowledgments

I would like to thank Mark Mattson, the Editor-in-Chief of Ageing Research Reviews, for the opportunity to edit this Special Issue and also for his personal contribution to it. Finally, I would like to thank all authors who contributed to this Issue for the zest with which they approached their topics, their diligence and excellent scholarship.

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