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Metabolic regulation of aging and age-related disease

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Abstract

Inquiry into relationships between energy metabolism and brain function requires a uniquely interdisciplinary mindset, and implementation of anti-aging lifestyle strategies based on this work also involves consistent mental and physical discipline. Dr. Mark P. Mattson embodies both of these qualities, based on the breadth and depth of his work on neurobiological responses to energetic stress, and on his own diligent practice of regular exercise and caloric restriction. Dr. Mattson created a neurotrophic niche in his own laboratory, allowing trainees to grow their skills, form new connections, and eventually migrate, forming their own labs while remaining part of the extended lab family. In this historical review, we highlight Dr. Mattson's many contributions to understanding neurobiological responses to physical exercise and dietary restriction, with an emphasis on the mechanisms that may underlie neuroprotection in ageing and age-related disease. On the occasion of Dr. Mattson's retirement from the National Institute on Aging, we highlight his foundational work on metabolism and neuroplasticity by reviewing the context for these findings and considering their impact on future research on the neuroscience of aging.

Keywords

Exercise; Caloric restriction; Intermittent fasting; Mitochondria; Hippocampus; Aging

1. Introduction and historical context

Aging was historically viewed as a pathological process, with widespread reports of neuronal loss and synaptic atrophy in multiple areas of the brain (Brody, 1955; Shefer, 1973). With the advent of modern stereological methods (Pakkenberg and Gundersen, 1988), unbiased quantification of neurons and synapses revealed that in the absence of age-related pathologies, neuronal number in the medial temporal lobe is unchanged, and

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synaptic loss is either subtle or absent (Morrison and Hof, 1997; Scheff et al, 2006). Against this background, Mark Mattson's early work on selective neuronal vulnerability to excitotoxicity set the stage for subsequent refinement of hypotheses surrounding neuronal responses to aging (Figure 1). This work revealed greater vulnerability to glutamate-induced neuronal cell death in pyramidal neuron cultures, as opposed to primary cultures from the early postnatal rat dentate gyrus (Mattson and Kater, 1989). In addition to region-specific differences, pyramidal cells originating from a common progenitor also exhibited similar vulnerability to excitotoxicity *in vitro*, relative to cells arising from different progenitors (Mattson et al, 1989a). These reports set the stage for later interrogation of cell- and circuit-specific determinants of neuronal vulnerability in Huntington's disease (Pecho-Vrieseling et al, 2014), Parkinson's disease (Surmeier et al, 2017), and in tangle-bearing neurons in Alzheimer's disease (Dunckley et al, 2006).

Increasing recognition of heterogeneous cellular responses to aging occurred in parallel with widespread acceptance of individual differences in cognitive aging, as modeled using behaviorally categorized aged rats. In the absence of age-related pathologies, a subset of aged rats performs similarly to young animals (Zyzak et al, 1995), with similar variability reported in humans (Albert, 1997). The observation that healthy aging can be decoupled from widespread synaptic dysfunction led to broader inquiry into strategies to limit the negative impact of age-related diseases, such as diabetes and sarcopenia, on organismal aging. These areas of investigation were driven by observations that caloric restriction increases lifespan via evolutionarily conserved mechanisms in organisms ranging from yeast to mammals, including nonhuman primates (Osborne et al, 1917; Berg and Simms, 1965; Mitchell et al, 2016; Mattison et al, 2017). Early work on dietary regulation of longevity coincided with field observations on environmental complexity and behavior in nonhuman primates (Osborne et al, 1917; Yerkes, 1925), but the metabolic environment was considered separately from the physical and social environment for many years.

The first environmental enrichment studies increased environmental complexity by rearing rats as household pets (Hebb, 1949) and later, through the addition of toys, social conspecifics, and running wheels (Altman and Das, 1964; Volkmar and Greenough, 1972). In modern neuroscience, Altman and Das are most recognized for their early reports of ongoing neurogenesis in adulthood (1966). However, Altman and Das initially focused on postnatal gliogenesis, reporting increased glial proliferation in rats reared in enriched environments (Altman and Das, 1964). Running wheels were a component of the enrichment paradigm used by Altman and Das (1964), but the relative contributions of exercise, social stimulation, and environmental complexity to these effects went unresolved for thirty years, largely due to debates surrounding the proliferative capacity of the adult brain (Altman, 2011).

Initial attempts to distinguish between the effects of social, locomotor, and environmental complexity suggested that increased vascular density might underlie the impact of exercise on the cerebellum in adult rodents (Black et al, 1990). The effects of exercise were thought to be restricted to motor regions prior to the initial report from Carl Cotman's laboratory demonstrating increases in hippocampal BDNF with voluntary wheel-running (Neeper et al, 1995). Mark Mattson's lab would subsequently report a requirement for BDNF in the

neuroprotective effects of dietary restriction (Duan et al, 2001; Bruce-Keller et al, 1999), and additive effects of exercise and caloric restriction on hippocampal dendritic spine density and BDNF expression (Stranahan et al, 2009). After the eventual acceptance of adult neurogenesis, wheel running was identified as the primary stimulus for neurogenesis among mice housed in enriched environments (van Praag et al, 1999; Kobilo et al, 2011). Social stimulation accelerated the onset of exercise-induced neurogenesis, but was not required for these effects (Stranahan et al, 2006). Adult neurogenesis declines with increasing age, and wheel running attenuated the impact of aging and improved learning and memory (van Praag et al, 2005). Although the existence of adult neurogenesis in the human brain remains debatable (Sorrells et al, 2018), exercise and dietary restriction elicit similar increases in neurogenesis in rodents (van Praag et al, 1999; Lee et al, 2002). By contrast, adult neurogenesis was impaired in nonobese diabetic rats, and in mice with genetic obesity and insulin resistance (Stranahan et al, 2008a). In the context of positive correlations between exercise and hippocampal volume in young adults (Nauer et al, in press) and aged individuals (Varma et al, 2015; Fuss et al, 2014), Dr. Mattson's lifelong fascination with the impact of exercise and diet on brain function seems strikingly prescient, and his work in this area presents a compelling rationale for further interrogation of tissue-specific mechanisms for metabolic regulation of neuroplasticity (Figure 1).

In this review, we celebrate Mark Mattson's research on the occasion of his retirement from the National Institute on Aging. Dr. Mattson's work on metabolic regulation of aging and age-related disease recapitulates the developmental ontogeny of neural circuits, beginning with in vitro studies, and building towards ever-more-elegant in vivo studies of interactions between different tissues and cell types. Throughout his highly prolific career, the common thread in these studies is their focus on mechanisms for cellular vulnerability across the lifespan. These studies laid the foundation for more recent work on physical frailty and dementia risk in humans, and for broader investigation into determinants of 'healthspan' in addition to lifespan in aging research.

2. Regulation of intracelullar calcium in aging and AD

2.1. Calbindin-D28K and interneuronal determinants of network hyperexcitability

Mark Mattson's early in vitro work revealed that susceptibility to glutamate-induced cytotoxicity was predicted by differential elevations in intracellular calcium (Mattson et al, 1989b; Mattson, 1990). In a series of elegant studies, Dr. Mattson identified the calcium-binding protein calbindin-D28k as a cell-autonomous determinant of vulnerability to excitotoxic cell death (Mattson et al, 1991). Overexpressing calbindin prevented the effects of presenilin-1 mutation and amyloid beta application on mitochondrial calcium handling in a neuronal cell line (Guo et al, 1998), underscoring the critical role of neuronal calcium metabolism in AD pathogenesis.

Calbindin-D28k is primarily expressed by interneurons, and in the hippocampus, calbindin-positive cells represent a significant proportion of the alveus/oriens interneuronal population with lacunosum-moleculare axon arborization (O-LM cells; Sik et al, 1995; Wouterlood et al, 2001). Although numerous interneuron classification schemes exist in the literature (Maccaferri and Lacaille, 2003), the functional importance of interneurons in regulating

rhythmic firing is clearly defined (Klausberger et al, 2003). More than 20 years after his initial work on calbindin and AD-related calcium mishandling, the Mattson lab demonstrated that haploinsufficiency for the mitochondrial deacetylase protein sirtuin 3 (SIRT3) in APP/PS1 mice was associated with spontaneous epileptiform activity and age-related loss of interneurons, relative to APP/PS1 mice without the SIRT3 mutation (Cheng et al, 2020). The focus on glutamate and excitotoxicity in Dr. Mattson's early studies laid the groundwork for subsequent work by others on interneuron dysfunction and medial temporal lobe hyperexcitability as early events in the progression from mild cognitive impairment to Alzheimer's disease (Palop et al, 2007; Vossel et al, 2016). In the context of the broader literature on circuit dysfunction in aging and AD, the Mattson lab's early studies of AD-related calcium dyshomeostasis have stood the test of time and will likely generate additional insights for the field moving forward.

2.2. Growth factor regulation of CNS mitochondria

During the period in neuroscience when Mark Mattson was starting his independent career, the Nobel Prize for Physiology and Medicine had recently been awarded to Rita Levi-Montalcini and Stanley Cohen for their discovery of nerve growth factor (NGF). The NGF family members glia-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) were also identified during this time and Dr. Mattson was among the first to investigate interactions between neurotrophins and AD neuropathology (Figure 1; see Supplementary Table 1). His studies of NGF and members of the fibroblast growth factor (FGF) family identified a neuroprotective role for FGF2 against beta-amyloid toxicity in primary neurons (Cheng et al, 1991; Mattson et al, 1993a; Mark et al, 1997). These early studies also identified a parallel neuroprotective role for FGF2 in models of hypoglycemia-associated tau aggregation (Cheng and Mattson, 1992a).

Dr. Mattson's initial studies of growth factors and protection against cytotoxic stimuli in primary neurons laid the conceptual groundwork for decades of investigation into mitochondrial dysfunction and neuronal plasticity in vitro (Guo et al, 1998; Guo et al, 1999) and in vivo (Guo et al, 2008; Cheng et al, 2007). The in vivo studies carried out after his move to the National Institute on Aging in 2000 successfully scaled up the elegant mechanisms previously identified in primary neurons. Studies in leptin receptor deficient db/db mice identified JAK/STAT3-mediated mitochondrial stabilization as a determinant of cell survival after kainic acid (Guo et al, 2008). Dissociation of the anti-apoptotic mitochondrial transmembrane protein Bcl-xL also played a pivotal role in ischemia-induced cell death (Cheng et al, 2007). Conversely, intermittent fasting reduced ischemic damage and enhanced the expression of BDNF and FGF2 (Arumugam et al, 2010; Figure 1, Supplementary Table 2), consistent with the protective effects of growth factor stimulation reported in vitro (Cheng et al, 1991; Mattson et al, 1993a; Mark et al, 1997). These lines of investigation established a scalable architecture for interrogating the neuroprotective effects of exercise and diet on mitochondrial homeostasis (Cheng et al, 2016; Liu et al, 2019; see section 3.2).

2.3. Intracellular calcium, mitochondria, and membrane-associated oxidative stress

Neurons are morphologically complex and exhibit finely tuned functional specialization in different compartments. Mitochondria traffic between the soma and dendrites, and between the soma and axon terminals, allowing for compartmentalized regulation of intracellular calcium (Sheng and Cai, 2012). Mitochondrial fission and fusion are also ongoing, as is mitophagy, or targeted lysosomal degradation of dysfunctional mitochondria (Youle and van der Bliek, 2012). Given the importance of local calcium homeostasis for neuroplasticity and neuronal viability, it is logical that perturbation of mitochondrial homeostasis would have a pervasive negative impact in the CNS.

While at the University of Kentucky, Dr. Mattson's laboratory demonstrated that overexpression of mitochondrial manganese superoxide dismutase (MnSOD) maintained mitochondrial membrane potential and protected against apoptosis in primary neurons challenged with amyloid beta (Keller et al, 1998). Superoxide anions generated during mitochondrial respiration react with the gasotransmitter nitric oxide to produce peroxynitrite and other reactive oxygen species (ROS). Amyloid beta-induced mitochondrial dysfunction was associated with oxidative modification of membrane lipids and accumulation of 4-hydroxynonenal (4-HNE), an aldehyde byproduct of lipid peroxidation (Keller et al, 1997a). The cycle of mitochondrial dysfunction and membrane-associated oxidative stress likely perpetuates neuronal hyperexcitability, as exposure to 4-HNE impairs mitochondrial respiration in synaptosome preparations (Keller et al, 1997b). Calorie restriction attenuates aging-associated lipid peroxidation (Hyun et al, 2006; Figure 1, Supplementary Table 2), consistent with a potential role for metabolic preconditioning in protection against neurodegenerative disease.

The metabolic requirements of the CNS are high and the capacity for local energy storage is very low. Given these environmental constraints, it is surprising that glial mitochondrial dynamics have not received greater attention as potential regulators of cellular and circuit function (McAvoy and Kawamata, 2019). Astroglial glutamate uptake plays an essential role in limiting glutamate 'spillover' from synaptic to extrasynaptic sites. Using primary astrocytes, members of the Mattson lab demonstrated that exposure to sub-apoptotic concentrations of 4-HNE reduced glutamate uptake and impaired mitochondrial function (Blanc et al, 1998). Disruption of astroglial glutamate uptake following membrane-associated oxidative stress is another potential mechanism for excitotoxicity in aging and AD, which perturbs CNS cholesterol metabolism by promoting accumulation of long-chain ceramides and HNE adducts (Cutler et al, 2004; Figure 1). Similar membrane lipid modifications were evident in the hippocampus of rats maintained on an obesogenic high-fat diet (Stranahan et al, 2011; Figure 1, Supplementary Table 1), implicating mitochondrial dysfunction and membrane-associated oxidative stress as bidirectional determinants of neuronal function.

3. Exercise: bending the curve of cognitive and metabolic aging

3.1. Physical frailty and mental fragility: sarcopenia and dementia risk in humans

Aging is accompanied by a marked decline in muscle mass known as sarcopenia, as well as a significant decline in muscle power referred to as dynapenia (Law et al., 2012). Age-related loss of muscle mass and power is associated with significant morbidity and mortality, with risk of falling as a major factor that accompanies frailty and muscle weakness (Lavin et al., 2019). In humans, cross-sectional and longitudinal studies suggest that walking speed predicts risk of age-related cognitive impairment, with slower gaits associated with greater risk (Hoogendijk et al, 2020; Ble et al, 2005).

Sarcopenia is a primary cause of frailty and slow gait, and there are a number of potential mechanisms for sarcopenia, including increased levels of inflammatory cytokines, increased oxidative stress, and mitochondrial dysfunction (Taetsch and Valdez, 2018). Each of the above processes have been linked with senescence of muscle satellite cells, impaired protein synthesis, and degradation of neuromuscular junctions (Taetsch and Valdez, 2018). A substantial body of evidence now indicates that many of these changes can be prevented or reversed with exercise (Aguirre and Villareal, 2015; Lavin et al., 2019). A key factor in the loss of muscle power with aging is a reduction in size of type II (fast-twitch) muscle fibers. Type II fiber size declines significantly with age, and loss of type II fibers accelerates with inactivity, as observed in patients with hip fracture (Kramer et al., 2017). Exercise training in older men and women significantly increases the size of type II fibers (Leenders et al., 2013). In addition, while muscle satellite cell number has been observed to decline with aging, exercise increases satellite cell number in type II fibers in aged humans and rodent models (Verdijk et al., 2009; Liu et al., 2017).

3.2. Parallel roles for exercise in maintaining synaptic stability in the brain and periphery

Stimulation of muscle satellite cells with exercise is one strategy for combating sarcopenia in older adults, but satellite cells also play a key role in maintenance of the neuromuscular junction (NMJ). Age-related loss of muscle power is associated with fragmentation of the NMJ (Taetzsch and Valdez, 2018), and evidence from animal models suggests that depleting skeletal muscle of satellite cells drives NMJ degradation (Liu et al, 2017). Gain-of-function studies also support the interaction between satellite cells and NMJs, as satellite cell-specific overexpression of Spry1, a gene implicated in satellite cell proliferation (Chakkalakal et al, 2012), rescues age-related structural degradation of NMJs (Liu et al., 2017). In addition to the interactions with satellite cells, presynaptic enrichment of mitochondria at NMJs plays a critical role in maintenance of synaptic contacts (Wang et al, 2018). Aging is associated with atrophy of NMJs, mitochondrial fragmentation, and decreased expression of mitofusin 2 in spinal motor neurons (Wang et al, 2018). Neuronal overexpression of mitofusin 2 blocked age-related muscle loss and maintained NMJ structure in aged mice, indicating that motor neuron mitochondrial function regulates sarcopenia (Wang et al, 2018).

Recent work from the Mattson lab indicates that neuronal mitochondria may also play a role in regulating synaptic stability in the CNS. The mitochondrial deacetylase SIRT3 is upregulated in the hippocampus with exercise, and whole-body ablation of SIRT3 eliminated

the protective effects of exercise against excitotoxic stress (Cheng et al, 2016; Figure 1). Local hippocampal induction of SIRT3 was also required for the protective effects of intermittent fasting on hippocampal synaptic plasticity in AD mice, as determined by lentiviral knockdown in App^{N-L-F} transgenic mice maintained on IF for 8 months (Liu et al, 2019; Figure 1). Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) is a transcriptional coactivator that integrates cellular stress signals and mitochondrial respiration. Consistent with the high metabolic demands associated with synaptic plasticity-associated cytoskeletal rearrangement, local knockdown of PGC-1α in the hippocampal dentate gyrus reduced dendritic spine density in vivo and eliminated BDNF-stimulated synaptogenesis in vitro (Cheng et al, 2012).

While PGC-1α has received recent attention for its role in coordinating the effects of exercise in the brain (Wrann et al, 2013; Cheng et al, 2012), an extensive literature exists surrounding PGC-1α and muscle fiber adaptations to exercise in rodents and humans (Baar et al, 2002; Pilegaard et al, 2003). Muscle-specific overexpression of PGC-1α in aged mice increases mitochondrial number and promotes the expression of genes important for NMJ function (Garcia et al., 2018). This relationship is not exclusive to the NMJ, as whole-body ablation of PGC-1α blocks hippocampal induction of fibronectin type III domain containing 5 (FNDC5), the precursor protein for the peptide hormon irisin, in mice (Wrann et al, 2013). Exercise-induced mitochondrial biogenesis is also required for synaptogenesis, as whole-body UCP2 knockout mice did not exhibit wheel running-induced increases in hippocampal synaptic and mitochondrial number (Dietrich et al, 2008). Taken together, these findings strongly implicate mitochondria as a nexus for exercise- and diet-induced synaptic regulation in the brain and periphery.

3.3. Myokines and muscle-brain crosstalk with aging and exercise

Skeletal muscle adaptations to exercise impact other organ systems via the release of muscle-derived factors, termed myokines, into circulation (Pedersen, 2019). Although hormones and cytokines have received more attention with respect to the effects of exercise on the brain, recent work indicates that myokines also participate in muscle-brain crosstalk with aging (Pedersen, 2019). The cathepsin family of lysosomal proteases regulates multiple physiologic processes, including muscle biogenesis, bone formation and turnover, and amyloidosis (Andrew et al, 2016; Reiser et al, 2010). Voluntary wheel running increased levels of cathepsin B in muscle and plasma, and these increases were required for exercise-induced neurotrophic factor expression in the hippocampus of mice (Moon et al, 2016). Similar positive correlations between circulating cathepsin B and cognition were reported after exercise training in nonhuman primates and humans, suggestive of conserved mechanisms for muscle-brain interactions (Moon et al, 2016). In addition to cathepsin B, expression of FNDC5, the gene encoding the myokine irisin, was associated with exercise-induced hippocampal neurotrophic factor expression (Wrann et al, 2013). Expression of FNDC5 is reduced in brain tissue from AD patients, and in AD model mice, intrahippocampal administration of recombinant irisin normalized cognition (Lourenco et al, 2019). Lourenco et al also reported indirect evidence that a swimming exercise paradigm co-regulates FNDC5 in the brain and periphery (2019), but the question of whether peripheral irisin drives hippocampal induction of FNDC5 following exercise has

yet to be conclusively answered. Potential cellular intermediaries for such a relationship include cerebrovascular endothelial cells, pericytes, and/or astrocytes, which could respond to circulating irisin by generating alternative paracrine signals that promote FNDC5/irisin expression among neurons in the brain parenchyma. While this question is certainly important for understanding the role of FNDC5/irisin in neurobiological responses to exercise, the lack of an answer does not limit enthusiasm for further investigation of myokines and their role in regulating the CNS.

3.4. Extracellular vesicles and muscle-to-brain signaling

In addition to myokines, extracellular vesicles (EVs), including exosomes and microvesicles, have also been recognized as new players in exercise-mediated effects on cell-cell and inter-organ communication. In humans, exercise stimulates the release of EVs from skeletal muscle (Guescini et al., 2015; Whitham et al., 2018; Frühbeis et al., 2015). Transient increases in intracellular calcium are known to induce exosome secretion (Savina et al., 2003), and the release of calcium ions from the sarcoplasmic reticulum of skeletal muscle cells following motor neuron stimulation is an important mechanism driving exercise-mediated exosome release (Whitham et al. 2018). Circulating extracellular vesicles cross the blood-brain barrier and deliver their cargo to neuronal populations (Alvarez-Erviti et al. 2011; Ridder et al., 2014). While a number of studies have shown that physical activity improves executive function in the elderly (Berryman et al., 2013; Farina et al., 2016; Scherder et al., 2010), the molecular mechanisms mediating muscle-brain crosstalk with aging are not well established. Here again, Mark Mattson has been at the leading edge of work on cell-cell communication, carrying out collaborative studies of immune responses to EVs in aged humans and in patients with diabetes (Eitan et al, 2017; Freeman et al, 2018). These studies indicate that circulating EVs from aged individuals and diabetic patients plasma are internalized more readily by circulating immune cells, relative to EVs from young or nondiabetic subjects (Eitan et al, 2017; Freeman et al, 2018). Differential internalization of plasma EVs by immune cells may contribute to the pro-inflammatory systemic environment in aging, and it will be exciting to see where this line of investigation leads.

Extracellular vesicles carry both microRNA (miRNA) and full-length mRNAs that retain their biological impact on gene expression in target cells (Ying et al, 2017; Thomou et al, 2017; Pan et al, 2019). In a collaborative study, Mark Mattson reported that aging alters full-length mRNAs for pro-inflammatory cytokines in EVs from amyloid beta-stimulated macrophages (Mitsuhashi et al, 2013). Exosomes derived from different organs carry distinct signatures, with muscle-derived EVs characterized by enrichment for the transmembrane protein alpha-sarcoglycan (Guescini et al, 2015). Muscle-derived, alpha-sacroglycan positive EVs carrying the senescence-associated microRNA miR-34a are increased in the circulation with aging (Fulzele et al, 2019). This may contribute to age-related declines in multiple organ systems as the pro-survival factor Sirt1 is negatively regulated by miR-34a in cancer, non-alcoholic fatty liver disease, and age-related vascular dysfunction (Yamakuchi et al, 2008; Min et al, 2012; Guo et al, 2017).

The lipid composition of EVs also plays a role in determining their effects on target tissues. Exosomes enriched in very long chain C24:1 ceramide are elevated with age in serum of older women (Khayrullin et al., 2019), and C24:1 ceramide contributes to cell death in a variety of cell types (Hannun, 1996). Levels of very long chain C24:0 ceramide are also increased in the brains of AD patients and in CSF from patients with HIV dementia (Cutler et al, 2004; Haughey et al, 2004), with similar elevations reported in the hippocampus of rats with high-fat diet-induced elevations in serum cholesterol (Stranahan et al, 2011). Plasma EVs from patients with AD and HIV-associated neurological disorders carry distinct pathological cargoes, but have yet to be profiled with respect to lipid content (Perrotte et al, 2020; Pulliam et al, 2019; Dinkins et al, 2017). Likewise, in obesity, adipose-derived circulating EVs promote inflammation and insulin resistance, but this line of investigation focused on miRNA cargo rather than lipidomic profiles of EVs as the effector mechanism (Ying et al, 2017; Pan et al, 2019). However, given that AD, HIV dementia, and obesity are each associated with cognitive deficits and dysregulation of brain lipid metabolism (Cutler et al, 2004; Stranahan et al, 2011; Haughey et al, 2004), there may be a potential relationship between ceramide-enriched exosomes and cognitive impairment in these conditions. If these correlations were determined to be causal, modulation of exosome cargo secreted from peripheral organs and tissues may therefore serve as biomarkers and potential targets for intervention to promote brain health with aging.

3.5. Brain-to-blood efflux of extracellular vesicles in aging

Peripheral EVs have been shown to penetrate the blood-brain barrier, and emerging evidence indicates that efflux of brain-derived EVs also impacts peripheral cells and tissues (Alvarez-Erviti et al. 2011; Ridder et al., 2014; Mustapic et al., 2017). Brain-derived EVs enriched with neural cell adhesion molecule L1 have been detected in the circulation (Mustapic et al., 2017), suggesting that efflux of brain-derived EVs might influence the periphery. Neuronal-enriched extracellular vesicles (nEVs) may therefore serve as potential biomarkers for predicting cognitive decline with age and Alzheimer's disease based on relative size and nEV cargo (Kapogiannis et al., 2019). Here again, Mark Mattson engaged in collaborative studies demonstrating that nEVs in serum from older patients with decreased walking speed have increased levels of the precursor (pro) form of brain-derived neurotrophic factor (BDNF), compared to those patients with faster walking speed (Suire et al., 2017). Given that pro-BDNF exerts distinct and opposing effects on NMJ synaptogenesis, relative to mature BDNF (Yang et al, 2009), it is possible that pro-BDNF-containing nEVs might promote age-related muscle wasting. The mechanisms modulating nEV release with age or with exercise are not well known, but future studies directed at better understanding these processes will have important implications for improving healthspan and physical function with aging.

3.6. Insulin and insulin-like growth factors in aging and exercise

Aging is accompanied by reductions in insulin sensitivity and systemic glucose metabolism (Defronzo, 1981). Even within the normal physiological range, variability in systemic glucose metabolism has been correlated with working memory, such that individuals with more efficient glycemic control perform better on cognitive tests (Rolandsson et al, 2008). Here again, Mark Mattson's work on insulin-like growth factor (IGF) signaling advanced

understanding of age-related neurobiological changes (Figure 1). After observing a pivotal role for neuronal calcium handling in response to hypoglycemia in primary neurons (Cheng et al, 1991), members of the Mattson lab determined that application of insulin or insulin-like growth factors could block hypoglycemia-associated calcium dyshomeostasis (Cheng and Mattson, 1992b). This line of investigation revealed that IGF-2 stabilized mitochondrial function without preventing ATP depletion (Mattson et al, 1993b), consistent with an increase in the dynamic range of calcium buffering under conditions of metabolic stress.

At the whole-organism level, lower circulating glucose and insulin levels reflect more efficient glycemic control. Mark Mattson's in vitro studies were subsequently upheld by in vivo experiments demonstrating protection against excitotoxicity with dietary restriction (Anson et al, 2003). These studies also incorporated intermittent fasting (IF), using a paradigm in which food was available every other day (Anson et al, 2003). Under this feeding schedule, total caloric intake over a 48hr period was unchanged, relative to mice consuming chow ad libitum (Anson et al, 2003). The observation that IF and caloric restriction elicited similar protection against excitotoxicity and comparable metabolic improvements provided proof of principle for the concept of metabolic preconditioning (Anson et al, 2003).

Mark Mattson's conceptual framework for metabolic preconditioning incorporated the deleterious effects of high-fat diet and the protective effects of dietary restriction and exercise. These effects were shown to be sexually dimorphic in rats, where six months of dietary restriction enhanced cognitive performance in females, but not in males (Martin et al, 2007). High-fat diet-induced obesity had no effect on cognitive performance in males or females (Martin et al, 2007), but the 14-unit T-maze task used to assess cognition recruits different structures and circuits than classical hippocampus-dependent paradigms. Specifically, the 14-unit T-maze is sensitive to both striatal and hippocampal lesions (Jucker et al, 1990; Pistell et al, 2009), while spatial memory in the water maze is unaffected by striatal lesions (Mcdonald and White, 1994; Devan et al, 1996). Given that sex differences in recruitment of hippocampal and striatal circuits during spatial memory acquisition have yet to be fully characterized, it is possible that sexually dimorphic regulation of learning and memory by diet might be circuit-specific. This possibility is indirectly supported by the convergent regulation of hippocampal gene expression in males and females maintained on a high-fat diet (Martin et al, 2008), and by the observation that middle-aged male rats maintained on high-fat diet for longer durations exhibit memory deficits in the water maze (Stranahan et al, 2008b). Conversely, aged mice housed with a running wheel from weaning exhibit improved memory in the water maze, relative to aged sedentary mice (Stranahan et al, 2010). These datasets suggest that hippocampus-dependent tasks may be more sensitive to metabolic challenges than hippocampus- and striatum-dependent paradigms, but this possibility has yet to be directly addressed.

Mark Mattson's laboratory was among the first to use large-scale trancriptional profiling to investigate responses to energetic challenges in different brain regions. The AGEMAP (Atlas of Gene Expression in Mouse Aging Project) gene expression database included a set of anatomically comprehensive transcriptional profiling studies in males and females maintained on caloric restriction or ad libitum diets (Xu et al, 2007). The results of these

studies are consistent with circuit-specific responses to energy restriction, based on more prominent transcriptional responses to aging and CR in the hippocampus and cortex, relative to striatum (Xu et al, 2007). As a followup to the AGEMAP studies, members of the Mattson lab compared transcriptional responses to water maze learning in the hippocampus of aged male mice after lifelong running (Figure 2; Stranahan et al, 2010). These studies included mice sacrificed under basal conditions, after swimming in the water maze, or after hidden platform training (Stranahan et al, 2010). Side-by-side comparison of the two studies revealed limited overlap between the genes and pathways differentially activated at baseline in the hippocampus of aged runners, relative to the transcriptional effects of caloric restriction in the hippocampus of aged mice from the AGEMAP study (Xu et al, 2007; Stranahan et al, 2010; Figure 2). The lack of overlap between the two datasets could reflect distinct metabolic programs associated with energy expenditure in runners, relative to cellular adaptations in response to reduced energy intake in mice on CR. However, the possibility of divergent transcriptional programs associated with fluctuations in caloric intake and energy expenditure remains speculative at this point. It would certainly be beneficial to revisit these themes using newer methods that capture cellular diversity, such as single-cell RNA-seq and multiplexed FISH (Ren et al, 2019; Kishi et al, 2019), but these gene array studies upheld the principles of Dr. Mattson's early in vitro studies using large-scale in vivo approaches.

4. From primary neurons to human studies: evolution of Mark Mattson's research program

Not one to rest on his laurels, Mark Mattson subsequently began testing the translatability of these findings in human studies. These studies revealed improvements in glucose and lipid metabolism, but cognitive outcomes have yet to be evaluated (Catenacci et al, 2016; Harvie et al, 2013; Harvie et al, 2011). In young overweight females, six months of intermittent fasting or caloric restriction reduced circulating levels of leptin and C-reactive protein, markers of adiposity and obesity-induced inflammation, respectively (Harvie et al, 2011). Interestingly, alternate day feeding exerted more robust effects on glycemic control in humans (Harvie et al, 2011; Harvie et al, 2013), suggesting that pronounced temporal fluctuations in nutrient availability might have a greater impact than restricting overall calories.

The granularity of Dr. Mattson's work on dietary regulation of brain function in rodents has yet to be scaled up into human studies, and questions remain surrounding the impact of caloric intake, meal timing, and nutrient composition on brain function in genetically heterogeneous species. One step toward this future direction involves studying dietary regulation of neuroplasticity in outbred rodents, such as Diversity Outbred mice (Svenson et al, 2012) and outbred rat strains (Nadon, 2005). Using outbred rodents to study dietary regulation of brain structure and function could enable subsequent identification of homologous relationships in existing genome-wide association datasets from humans, which would in turn provide a rationale for hypothesis-driven studies using human organoids or induced pluripotent stem cells.

Translation of exercise interventions in humans lags behind studies of diet due to difficulties with adherence and standardization of exercise protocols across studies (Neufer et al, 2015). However, recent work from the Mattson laboratory has identified novel pathways through which energy intake influences exercise capacity (Marosi et al, 2018). Severe, prolonged undernutrition is associated with hypoactivity and muscle wasting (Fichter et al, 1986; Felig et al, 1970), but intermittent fasting enhances exercise endurance (Marosi et al, 2018). Data on dose-response relationships between exercise and neuroplasticity are scarce, but at the lower end of the scale, significant benefits have been reported following the transition from no exercise to minimal exercise in aged rodents and in rodent models of obesity (Barrientos et al, 2011; McGee-Lawrence et al, 2017; Erion et al, 2014). The challenge for future work in this area is to identify the dynamic range for synergistic interactions between energy intake and exercise capacity, and to determine whether these interactions differ over the lifespan.

Over the course of his career, Dr. Mattson led elegant mechanistic studies in c.elegans, primary neurons, rodent models, and humans. This trajectory recapitulates brain evolution within a timeframe of decades and has identified numerous converging mechanisms for metabolic regulation of neuronal cell biology. As Mark Mattson retires from the National Institute on Aging and transitions into his new role in medical education and scientific communication at Johns Hopkins School of Medicine, we wish Mark Mattson the best in the next phase of his highly prolific scientific career.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Exercise and diet are critical determinants of healthy aging
- Mark Mattson's research program identified growth factors, mitochondrial biogenesis, and lipid metabolism as pivot points for maintaining brain plasticity with aging
- Attentuation of age-related muscle loss may be a converging mechanism for exercise-induced extension of healthspan

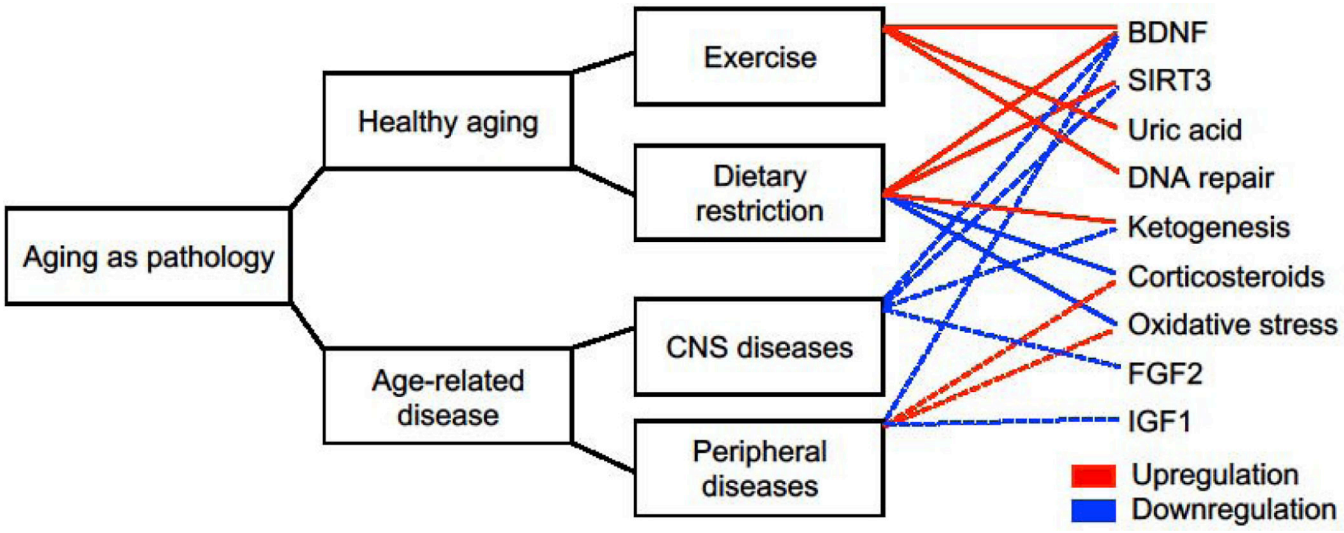

Figure 1. Mark Mattson's contributions to understanding normal and pathological aging.

As Mark Mattson was starting his career, the field of neuroscience was reinterpreting aging as a separate condition from peripheral and neurodegenerative diseases. Dr. Mattson's decades of work identified many bidirectional regulators of neuroplasticity and neurodegenerative disorders. This figure depicts a subset of these bidirectional relationships, which were extracted from (n=948) Pubmed citations of Mark Mattson's work. Bidirectional relationships were defined by published research articles demonstrating opposing regulation of a molecular target or biological process using gain- or loss-of-function approaches. For this figure, published work using in vivo or in vitro models of Alzheimer's disease, Parkinson's disease, and Huntington's disease were considered CNS diseases, while findings from animal models of diabetes and/or obesity were considered peripheral diseases. See Supplementary Tables 1–2 for supporting references.

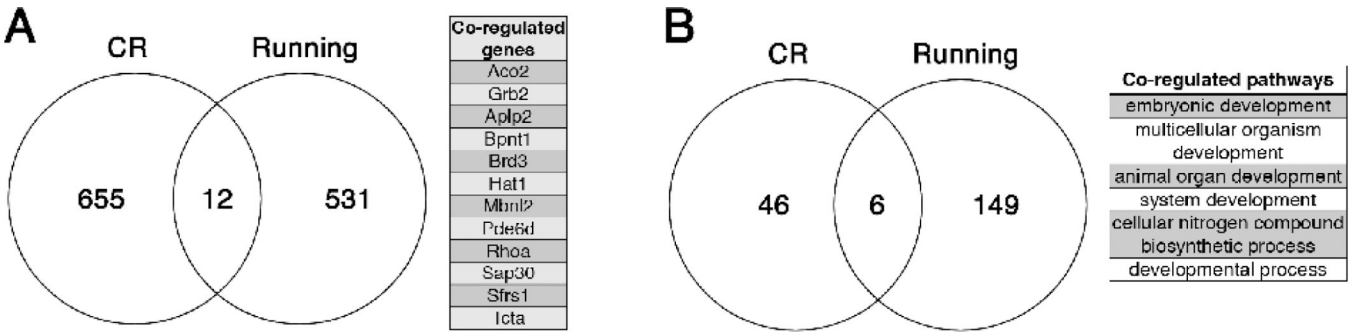

Figure 2. Distinct transcriptional programs associated with diet and exercise in the aging hippocampus.

Mining the data from Mattson lab publications investigating the impact of lifelong caloric restriction (CR) or wheel running uncovered potential evidence of distinct transcriptional programs for energy restriction and expenditure in the aged hippocampus (Xu et al, 2007; Stranahan et al, 2010). Comparing hippocampal gene expression profiles following lifelong caloric restriction in 16-month-old mice (Xu et al, 2007) with those observed after lifelong wheel running in 18–20-month-old mice (Stranahan et al, 2010) revealed limited overlap at the level of individual genes (A) and Biological Processes associated with the corresponding Gene Ontology terms (B). Mark Mattson's unique approach incorporated both breadth and depth to uncover these and other insights into metabolic regulation of brain aging.