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Tweaking Energy Metabolism to Prevent and Treat Neurological Disorders

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Abstract

Accumulating data from epidemiological and clinical studies, and from animal models, point to pivotal roles for disordered behavioral and neuroendocrine control of energy metabolism in the pathogenesis of several major neurodegenerative disorders. Particularly troubling is the mounting evidence that excessive dietary energy intake and a sedentary lifestyle render the brain vulnerable not only to stroke, but also to Alzheimer's and Parkinson's diseases. Recent advances in understanding the molecular and cellular mechanisms by which energy intake and expenditure affect neuronal vulnerability are leading to novel therapeutic interventions that increase the durability and resiliency of the brain during aging.

Collectively, the three leading age-related neurological disorders - Alzheimer's disease (AD), stroke and Parkinson's disease (PD), are responsible for more morbidity and mortality than cardiovascular disease, cancers or diabetes. Unfortunately, and in contrast to cardiovascular disease and most cancers, there are no effective treatments for AD and PD, while thrombolytic treatment for stroke is only moderately beneficial and must be administered in such a narrow window of time that many patients cannot benefit from it. The numbers of individuals with AD, PD and stroke are rapidly rising because more people are living longer therefore reaching ages (65+ years) where these brain disease most commonly occur. Further contributing to the 'epidemic' of brain disorders is the increasing number of individuals who live with a sustained positive energy balance resulting from excessive energy (calorie) intake and/or a sedentary lifestyle. Indeed, obesity, insulin resistance and diabetes are established risk factors for stroke, and may also increase the risk of AD and PD.

During the past two decades, advances in animal models and technical innovations have lead to major progress towards understanding the events that occur in the brain in AD and PD and after a stroke. Particularly informative have been the identification of genetic mutations responsible for rare early-onset inherited forms of AD and PD, and investigations of the mechanisms by which those mutations cause neuronal dysfunction and degeneration (1). Mutations in the β -amyloid precursor protein or presenilin-1 that cause AD increase the production and self-aggregation of the β -amyloid peptide ($A\beta$), a process that results in synaptic dysfunction and neuronal degeneration in nerve cell circuits involved in cognitive functions. Mutations in a least 7 different genes cause familial PD; in each case the mutations appear to cause the degeneration of dopaminergic (and other) neurons by impairing both mitochondrial function and the ability of the neurons to degrade damaged

proteins in the proteasome (particularly α -synuclein which accumulates inside neurons to form 'Lewy bodies'). Three alterations that occur downstream of disease-specific processes and may contribute similarly to the demise of neurons in AD, PD and stroke are increased oxidative stress, perturbed cellular Ca^{2+} homeostasis and energy (ATP and NAD^+) depletion.

Overeating and a sedentary lifestyle may endanger neurons as the result of insufficient activation of adaptive stress response pathways, and by increasing oxidative damage to proteins, DNA and membrane lipids. Cells throughout the brain, including neurons, glia and vascular cells are adversely affected by excessive energy intake and diabetes. Specific perturbations that occur in neurons in the brains of obese and diabetic subjects include reduced neurotrophic factor signaling, suppression of cytoprotective gene expression and increased oxidative stress. Data suggest that hyperactivation of the hypothalamic – pituitary – adrenal axis resulting in sustained elevation of corticosteroid levels contributes to the adverse effects of diabetes on neuronal plasticity and cognition (4). It might also be the case that various early-life events increase susceptibility to these late-life metabolic changes and neurological disorders {Miller, 2008 #2757}. Nevertheless,

Studies of laboratory animals that have had their dietary energy intake decreased or increased above usual levels, and/or been allowed to exercise regularly, have unequivocally demonstrated that energy restriction and exercise protect the brain against aging, disease and even acute injury (2). When AD, PD and Huntington's disease mouse models are maintained on reduced energy diets (either a reduction in daily calorie intake or alternate day fasting) neurons become more resistant to the disease process, functional outcome is improved and death delayed. Rats and mice on reduced energy diets also have better outcomes (reduced brain damage, morbidity and mortality) in stroke models. On the other hand, energy-rich diets and diabetes accelerate the neurodegenerative processes and worsen functional outcome in animal models of stroke, AD and PD. Importantly, regular vigorous exercise can protect neurons against dysfunction and degeneration in animal models of AD, PD and stroke.

Based upon a large and ever-growing body of data from studies of human and animal subjects, and in light of the alarming increase in obesity and diabetes, it is therefore clear to us that incidences of stroke, AD and PD could be greatly reduced by reducing dietary energy intake and increasing exercise. Emerging insight into the mechanisms by which energy intake and expenditure affect the function and vulnerability of brain cells is also leading to novel pharmacological interventions aimed at mimicking the actions of energy restriction and exercise on brain cells.

Dietary energy restriction and exercise activate adaptive cellular stress response signaling pathways in neurons (Figure 1), a fundamental and evolutionarily conserved process which falls under the biological principle called 'hormesis' (3). One such neuroprotective pathway involves brain-derived neurotrophic factor (BDNF), the production of which is increased in response to exercise and dietary energy restriction. BDNF binds cell surface receptors on neurons to engage intracellular kinases such as Akt and transcription factors such as CREB, resulting in increased expression of genes that encode proteins that promote cell survival and synaptic plasticity. Other neurotrophic factors are also induced by exercise and energy restriction including fibroblast growth factor 2 and glial cell line-derived neurotrophic factor. In general, these neurotrophic factors elicit changes in gene expression that stabilize cellular Ca^{2+} and energy homeostasis and protect neurons against oxidative, metabolic and inflammatory insults. Interestingly, levels of vascular endothelial cell growth factor in the brain are increased in response to exercise which promotes angiogenesis to increase the blood supply to neurons. Two other classes of proteins that are believed to mediate

neuroprotective effects of energy restriction and exercise are protein chaperones such as heat-shock protein 70 and glucose-regulated protein 78 and mitochondrial uncoupling proteins (UCPs) such as UCP4 (Figure 1). Chaperones protect cellular proteins against oxidative damage and misfolding, while UCPs reduce mitochondrial free radical production and increase cellular energy utilization. In addition to increasing the resistance of neurons to aging and disease, the adaptive stress response signaling pathways also enhance synaptic plasticity (a process critical for learning and memory), as well as neurogenesis (the production of new neurons from stem cells) (2).

Work is in progress to translate the knowledge gained from basic research on issues surrounding energy metabolism and brain health into novel interventions to prevent and treat age-related neurodegenerative conditions. While the weight loss ‘industry’ makes multi-billion dollar profits each year, the incidences of obesity and diabetes continue to rise with our youth being most troublingly affected. And so efforts are being made by national and local governments that encourage reduced consumption of calorie-dense diets and increased exercise. However, there are several major impediments to widespread implementation of energy-conscious lifestyles including: a food industry with omnipresent and troublingly effective advertisements for unhealthy foods and drinks; declining requirements for physical fitness classes in primary (and secondary) schools; and the proliferation of technologies that discourage physical exercise with computers, the internet and auto-transportation (cars, public transit and elevators) being major examples. Perhaps the realization that, by creating a chronic state of positive energy balance, our modern societies are fostering a rising tide of mid- and late-life degenerative brain disorders will provide further impetus to governments and private foundations to treat this situation as a crisis.

Are there pharmacological interventions that can counteract the adverse effects of gluttonous and sedentary lifestyles on the brain? The answer is yes, but only with modest effectiveness in preclinical studies so far. One target in the brain is the neural circuits and signaling pathways that regulate appetite; an increasing number of neurotransmitter, intrinsic neuropeptides and peripheral hormones have been shown to act on hypothalamic neurons to either inhibit or stimulate food intake (5). For example, leptin inhibits food intake, and so leptin receptor agonists are one potential means of suppressing appetite. Unfortunately, individuals that are obese or diabetic typically suffer not only from insulin resistance, but also from leptin resistance. Four other signaling pathways that are known to inhibit food intake are those activated by BDNF and ciliary neurotrophic factor (CNTF), glucagon-like peptide 1 (GLP-1) and vasoactive intestinal polypeptide (VIP) (Table 1). Two other peptide hormones that have been shown to suppress appetite are Low molecular weight agonists of the BDNF receptor *trkB* have recently been developed, and expansion of such drug discovery approaches to target other hormone receptors is a potentially fruitful avenue of research.

Modifying neuronal energetic status is a therapeutic approach for which several agents have proven effective in animal models. One such agent is creatine which helps prevent energy depletion by increasing the phosphocreatine pool in cells, and is neuroprotective in models of PD, HD, stroke and traumatic brain injury (6). Creatine has been widely used by athletes to improve their endurance and recovery from exercise; there is considerable evidence that it is safe and effective for this application. Creatine has, and will continue to be, tested in clinical trials in human subjects with neurodegenerative disorders. Another potential treatment that increases neuronal energy pools is nicotinamide which can increase levels of the energy substrate NAD^+ in neurons. Interestingly, subtoxic doses of mitochondrial uncoupling agents such as dinitrophenol have been reported to be effective in reducing damage and improving functional outcome in animal models of stroke and head injury. Mild

mitochondrial uncoupling may protect neurons by inducing an adaptive stress response and by reducing free radical production.

Activation of adaptive cellular stress response pathways in neurons vulnerable to aging and disease is another strategy for protecting neurons against the adverse consequences of excessive energy intake and a sedentary lifestyle (Table 1). There are an increasing number of agents that can activate some of the same signaling pathways that are activated by exercise, energy restriction and cognitive challenges. The pathways include those that: activate the transcription factor Nrf2 which binds to the antioxidant response element to activate genes encoding proteins such as heme oxygenase-1, NQO1 (a quinone oxidoreductase) and multiple phase 2 enzymes; activate the transcription factor NF- κ B which induces the expression of mitochondrial manganese superoxide dismutase (SOD2) and the cell survival protein Bcl-2; activate sirtuin 1 and FOXO transcription factors; inhibit mTOR (mammalian target of rapamycin). In many cases the chemicals that have been shown to affect one or more of these adaptive stress response pathways are naturally-occurring compounds produced by plants (7). For example, sulforaphane, curcumin and plumbagin which activate the Nrf2 – ARE pathway and may thereby protect neurons against dysfunction and degeneration in experimental models of AD, PD and stroke. Resveratrol can activate sirtuin 1 which, in turn, deacetylates and activates FOXO3 resulting in increased expression of cell survival genes and inhibition of cell death genes. By inhibiting mTOR, rapamycin has been shown to be neuroprotective in multiple animal models of age-related neurological disorders.

A particularly promising group of agents in the battle against positive energy balance and its adverse effects on the brain are those that target GLP-1 signaling. GLP-1 is released into the blood by secretory intestinal epithelial cells in response to food intake. GLP-1 acts on multiple cellular targets in the periphery; it stimulates insulin production and release from pancreatic β -cells, and it increases insulin sensitivity of muscle and liver cells. GLP-1 receptors are widely expressed in neurons in the brain, and their activation has been shown to enhance synaptic plasticity and protect neurons against metabolic and oxidative insults. GLP-1 has a very short half-life in the blood (1–2 min) because it is cleaved and inactivated by a protease called DPP-IV. Therefore, preclinical and clinical efforts have led to the development of protease-resistant analogs of GLP-1 and DPP-IV inhibitors. Exendin-4 (Exenatide/Byetta), a protease-resistant GLP-1 analog is now widely used to treat patients with type 2 diabetes and, based on its effectiveness in animal models, will soon be tested in patients with neurodegenerative disorders (8).

While identification and characterization of agents that target brain cell energy metabolism and stress resistance in animal models proceeds, in most cases there are many hurdles to be crossed before the agent is used in the clinic. The vast majority of targets (receptors, kinases, transcription factors, metabolic pathways, etc.) are present in cells throughout the body which increases the probability of side effects. Drug delivery technologies that selectively target the brain should therefore be pursued so that peripheral side-effects of the drugs are minimized. Nasal administration is one such approach which has demonstrated effectiveness in delivery of peptide hormones and low molecular weight drugs. In some cases, more invasive direct administration into the brain parenchyma is being pursued, with tests of neurotrophic factors in PD being one prominent example. On the other hand, it is clear from research on exercise and dietary energy restriction that there are at least a core set of signaling and metabolic pathways that can be modulated to benefit many different organ systems including the brain (Figure 1). Behavioral modifications and pharmacological agents that tap into these pathways therefore have considerable potential to improve overall health and to protect the brain against the adversities of aging.

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Figure 1.

Promotion of brain health and resistance to disease by activation of adaptive cellular stress responses: actions on and responses to systems involved in the regulation of energy metabolism. Red font) Activators of adaptive cellular response pathways in neurons (exercise, dietary energy restriction, cognitive challenges, phytochemicals, SSRI and Exendin-4) Blue font) Effectors of adaptive stress responses. Engagement of one or more of these activators and effectors promotes neuronal survival, synaptic plasticity and neurogenesis, and improves function of the autonomic nervous system (ANS) and peripheral energy metabolism. As a result, of activation of these pathways the brain is more resistant to neurodegenerative disorders, and the body is more resistant to cardiovascular disease and diabetes. BDNF, brain-derived neurotrophic factor; FGF2, fibroblast growth factor 2; GDNF, glial cell line-derived neurotrophic factor; GRP-78, glucose-regulated protein 78; HSP-70, heat-shock protein 70; SSRI, serotonin-selective reuptake inhibitors; UCPs, mitochondrial uncoupling proteins; VEGF, vascular endothelial growth factor.

Table 1

Energy metabolism-based pharmacological approaches aimed at protecting the brain against age-related diseases.

Treatment	Target(s)	Mechanism of Action
Leptin	hypothalamus	Suppression of appetite
BDNF	hypothalamus	Suppression of appetite
CNTF	hypothalamus	Suppression of appetite
GLP-1 analogs	hypothalamus	Suppression of appetite
Cannabinoid RA	hypothalamus	Suppression of appetite
VIP agonists	hypothalamus	Suppression of appetite
SSRI	serotonergic neurons	Increased serotonin and BDNF signaling
BDNF	neurons throughout brain	Activation of adaptive stress responses
Metformin	AMPK activator	Activation of adaptive stress responses
2-deoxyglucose	glycolysis inhibitor	Activation of adaptive stress responses
Phytochemicals [*]	stress pathways	Activation of adaptive stress responses
Creatine	creatine kinase/p-creatine	maintenance of energy stores, antioxidant
Nicotinamide	NAD ⁺ metabolism	elevation of NAD ⁺ levels
Uncouplers	mitochondrial UCPs	lower oxyradicals, increased energy production
Resveratrol	Sirt1, muscle, neurons	mimics some actions of energy restriction
Rapamycin	mTOR	inhibits mTOR; energy conservation mode
GLP-1 analogs	β-cells, muscle, liver, brain	Increased insulin sensitivity, neuroprotection
DPP-IV inhibitors	GLP-1 degrading enzyme	Increased GLP-1 half-life
Anti-inflammatories ⁺	innate/humoral immune syst	suppression of pro-inflammatory pathways

^{*} Various noxious chemicals in plants that normally serve the function of dissuading insects and other organisms from eating the plants. Examples include, suforaphane, curcumin, quercetin, epicatechins and plumbagin.

⁺ Inflammation plays a role in metabolic disorders (insulin resistance, diabetes and obesity) and neurodegenerative conditions (AD, PD and stroke). AMPK, adenosine monophosphate kinase; BDNF, brain-derived neurotrophic factor; CNTF, ciliary neurotrophic factor; DPP-IV, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; mTOR, mammalian target of rapamycin; NAD, nicotinamide adenine dinucleotide; RA, receptor antagonist; SSRI, serotonin-selective reuptake inhibitors; UCP, uncoupling protein; VIP, vasoactive intestinal polypeptide.