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Adaptive Responses of Neuronal Mitochondria to Bioenergetic Challenges: Roles in Neuroplasticity and Disease Resistance

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Abstract

An important concept in neurobiology is “neurons that fire together, wire together” which means that the formation and maintenance of synapses is promoted by activation of those synapses. Very similar to the effects of the stress of exercise on muscle cells, emerging findings suggest that neurons respond to activity by activating signaling pathways (e.g., Ca^{2+}, CREB, PGC-1α, NF-κB) that stimulate mitochondrial biogenesis and cellular stress resistance. These pathways are also activated by aerobic exercise and food deprivation, two bioenergetic challenges of fundamental importance in the evolution of the brains of all mammals, including humans. The metabolic ‘switch’ in fuel source from liver glycogen store-derived glucose to adipose cell-derived fatty acids and their ketone metabolites during fasting and sustained exercise, appears to be a pivotal trigger of both brain-intrinsic and peripheral organ-derived signals that enhance learning and memory and underlying synaptic plasticity and neurogenesis. Brain-intrinsic extracellular signals include the excitatory neurotransmitter glutamate and the neurotrophic factor BDNF, and peripheral signals may include the liver-derived ketone 3-hydroxybutyrate and the muscle cell-derived protein irisin. Emerging findings suggest that fasting, exercise and an intellectually challenging lifestyle can protect neurons against the dysfunction and degeneration that they would otherwise suffer in acute brain injuries (stroke and head trauma) and neurodegenerative disorders including Alzheimer’s, Parkinson’s and Huntington’s disease. Among the prominent intracellular responses of neurons to these bioenergetic challenges are up-regulation of antioxidant defenses, autophagy/mitophagy and DNA repair. A better understanding of such fundamental hormesis-based adaptive neuronal response mechanisms is expected to result in the development and implementation of novel interventions to promote optimal brain function and healthy brain aging.

Keywords

3-hydroxybutyrate; aerobic exercise; autophagy; CREB; hormesis; intermittent fasting; mitochondrial biogenesis; PGC-1α

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Bioenergetic Challenges as Fundamental ‘Drivers’ of Brain Evolution

In order to survive and reproduce, organisms must obtain sufficient energy from their environment. Be they herbivores, carnivores or omnivores, mammals have evolved to be highly efficient in obtaining food and storing the molecular energy substrates in the food in forms that are readily mobilized to sustain high levels of physical and mental exertion. In the case of carnivorous predators living in environments where prey are limited, it is intuitively obvious and an established fact that the brain and body must function well when the animal has not eaten for extended time periods of many days to weeks or even months [1, 2]. For example, the availability of food for gray wolves varies considerably within and between years such that the wolves may locate and kill a prey species only once every 10 – 20 days [3]. In the case of herbivores, there are very large seasonal fluctuations in food availability such that, similar to many carnivores, the animals must endure extended periods of food deprivation. For example, the deer that live in regions of the Northern hemisphere with harsh winters experience a drastic reduction in food availability and lose considerable weight during the winter months [4]. The success of any individual in obtaining the energy (calories) required to survive and reproduce depends critically upon their cognitive abilities, which for many species involves cooperation with other members of their species. Thus, by hunting in ‘packs’ wolves can surround and collectively kill animals, such as buffalo, that could not be killed by an individual wolf. Our human ancestors responded to limited food resources by evolving the extraordinary abilities of imagination and creativity [5] to: invent tools to kill prey at a distance (spears, bow and arrows, firearms); domesticate large animals solely for the purpose of their consumption; develop machines and agricultural processes for large-scale production of grains, fruits and vegetables; and create methods for the processing of foodstuffs into inexpensive high energy-density products such as high-fructose corn syrup, and saturated and trans fats [2].

As with other species, human brain evolution was influenced greatly by the ‘pressure’ of limited food resources. The brain regions that expanded most during the evolution of non-human primates and the different species of their human descendants play fundamental roles in the processing of visual and auditory patterns (occipital and parietal lobes) and decision making (prefrontal cortex) [5]. Neuronal networks in these and associated brain regions (e.g., hippocampus, frontal cortex) mediate the mental ‘fabrication’ of new patterns (images and sounds) in the processes of imagination and creativity. The flexibility of mental ‘manipulation’ of patterns is the basis all aspects of the advanced capabilities of the human brain including: spoken and written languages; the invention of tools, machines, drugs, etc.; efficient decision-making; and the ability to understand the world and universe using the tools of science [5]. A major expansion of the prefrontal cortex occurred in arboreal primates who were foragers that subsisted on the fruits and nuts in the canopy; individuals that were able to make accurate decisions as to where and when those foods were available (mediated by the prefrontal cortex) were selected for [6]. The archeological record suggests that during an extended time period during early evolution of bipedal ground-dwelling human species, the only tools developed were for the purpose of obtaining food [7]. The invention of methods for the cultivation of crops and animal husbandry led to a rapid decrease in hunter-gatherer lifestyles and fostered the evolution of large societies (cities,

states and countries) of individuals who then devoted their time and energy to learning and teaching specialized skills, and to the development of new technologies.

In this Perspective Article we posit that, via evolutionarily conserved cellular and molecular signaling mechanisms that converge on brain cell mitochondria, fasting and vigorous exercise enhance cognitive performance and increase resistance of neurons to injury, aging and disease. It has been known for decades that, in response to the bioenergetic challenge of intermittent vigorous exercise, signaling pathways are activated in muscle cells that result in an increase in the number of healthy mitochondria (mitochondrial biogenesis) and so increase resistance of muscle cells to fatigue [8, 9]. Moderate energy restriction/intermittent fasting can also improve skeletal and cardiac muscle health and stress resistance [10]. Elevated ketone levels, such as occurs during fasting, may enhance endurance exercise performance [11]. Emerging evidence suggests that, similar to the effects of exercise on muscle cells, exercise and energy restriction activate signaling pathways in neurons that bolster mitochondrial function and cellular stress resistance. Moreover, by brain autonomous and non-autonomous mechanisms described below, mitochondrial responses to bioenergetics challenges can enhance synaptic plasticity, learning and memory and neurogenesis. Because both exercise and intermittent fasting have robust neuroprotective and neuroplasticity-promoting effects in animal models of many different brain disorders in which mitochondrial dysfunction is implicated [12, 13], we will also consider how bioenergetic challenge-based improvements in mitochondrial health could be applied to the prevention and treatment of a range of human brain disorders.

Overview of Mitochondrial Functions and Dynamics in Neurons

Mitochondria are essential for cell viability and proper cell function, including their prominent roles in the production of ATP, metabolism of reactive oxygen species, regulation of Ca^{2+} dynamics, and apoptosis [13, 14]. In neurons, mitochondria are critical for maintenance of membrane ion (Na^+ and Ca^{2+}) gradients, and for neurotransmission and synaptic plasticity [15]. Most of the ATP produced in neurons is generated by the mitochondrial membrane-associated ATP synthase which is the final enzyme complex in the electron transport chain. Neurons have a limited glycolytic capacity such that only approximately 10% of their ATP is produced by glycolysis [16]. Therefore, mitochondrial bioenergetics is pivotal for the many different ATP-dependent processes that enable neurons to function and respond adaptively to environmental challenges. Examples include fueling of: membrane ion-motive ATPases; kinases involved in the intracellular transduction of extracellular signals including neurotransmitters and neurotrophic factors; proteins involved in cytoskeletal remodeling; the movement of organelles within the neuron; and the release and recycling of neurotransmitters [13, 17–21].

Neuronal mitochondria are especially susceptible to oxidative stress because their electron transport chain is very active in these excitable cells and therefore generates large amounts of superoxide anion radical [13]. The mitochondrial antioxidant enzyme superoxide dismutase 2 (SOD2), and proteins such as sirtuin 3 (SIRT3) that increase SOD2 activity, are very important in the removal of superoxide [22]. Another feature of mitochondria is that they contain high amounts of polyunsaturated fatty acids which are especially vulnerable to

reactive oxygen species (ROS) [23]. When polyunsaturated fatty acids are oxidized, one of the byproducts is the aldehyde 4-hydroxynonenal (HNE), which, through the non-enzymatic process of Michael addition, can covalently modify cysteine, lysine, and histidine residues of proteins, which can impair the function of the proteins [24]. Some of the proteins that are modified by HNE are mitochondrial electron transport chain proteins, ion and nutrient transporters, growth factor and neurotransmitter receptors, protein chaperones, proteasomal proteins, and cytoskeletal proteins [24–26]. Mitochondrial DNA is particularly susceptible to oxidative stress because of its proximity to the respiratory chain and absence of protective histones [21]. Because the mitochondrial DNA encodes 13 protein components of the electron transport chain, oxidative damage to DNA can impair ATP production and elicit a destructive cycle in which ROS damage DNA resulting in increased ROS generation [24].

The numbers of mitochondria in a cell and the size of individual mitochondria are malleable, and are regulated by the processes of mitochondrial fission and fusion. Fission plays a role in mitochondrial biogenesis, and is also fundamental to the elimination of dysfunctional mitochondria in a process called mitophagy [14, 27–30]. Proteins that mediate mitochondrial fission include dynamin-related protein 1 (Drp 1) and fission 1 (Fis1), and proteins involved in mitochondrial fusion include mitofusins 1 and 2 (Mfn1/2) and optic atrophy type 1 (Opa1) [31, 32]. The processes of fission and fusion are associated with the movement of mitochondria to specific subcellular locations, and can also influence the ability of the cell to repair damaged mitochondrial DNA [21]. The process of mitochondrial biogenesis involves not only the fission of mitochondria, but also an increase in the size of mitochondria prior to and after fission. The protein peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) is a transcriptional regulator that promotes the expression or transcriptional activity of proteins critical for mitochondrial biogenesis including transcription factor A of mitochondria (TFAM) and nuclear respiratory factors 1 and 2 [33]. PGC-1α can be induced by metabolic challenges such as exercise, by ROS and by cyclic AMP response element binding protein (CREB).

Mitophagy is a term used to describe the process by which mitochondria are chaperoned through an autophagy pathway that ends in destruction of the mitochondrial components in lysosomes. Mitophagy is an ongoing process in healthy cells that selectively removes damaged or dysfunctional mitochondria that could harm the cell by generating excessive amounts of ROS and by the release of pro-apoptotic signals such as cytochrome C [34]. Mitophagy can be stimulated by moderate levels of metabolic and oxidative stress and by inhibition of the mTOR (mammalian target of rapamycin) pathway. Dietary energy restriction and exercise, which are known to improve brain function and increase resistance of neurons to oxidative, metabolic and excitatory stress, inhibit the mTOR pathway and stimulate both mitophagy and mitochondrial biogenesis [35, 36].

Roles for Mitochondria in Neuroplasticity

During development of the nervous system, neural stem cells proliferate and can cease dividing and differentiate into neurons that grow dendrites and an axon, which then form synapses with other neurons [37]. As neuronal circuits are established, some neurons undergo programmed cell death (apoptosis) as a result of being ‘outcompeted’ by other

neurons for activity-dependent neurotropic factor support [38]. Sensory inputs (sights, sounds, smells, tastes, touches) and motor outputs (body movements, vocalizations) refine synaptic connections in ways that enable all behavioral capabilities of the adult organisms. Neuronal circuits continually undergo refinement throughout life, as new synapses form, and existing synapses may enlarge or retract, often in response to environmental demands (e.g., intellectual challenges, stressful situations) [39, 40].

Studies in which changes in the subcellular location and number of mitochondria are monitored as newly generated neurons extend neurites, establish axonal polarity and form synapses suggest important roles for mitochondrial biogenesis and motility in the formation of neuronal circuits. For example, when neurites first begin to grow in embryonic hippocampal neurons the mitochondria remain in the cell body with the majority of mitochondria located at the base of only one of the short neurites (Figure 1). The neurite with mitochondria at its base then begins to grow rapidly and differentiates into the axon, while the other more slowly growing neurites become dendrites [41]. When mitochondria are rendered dysfunctional, and the neurons are supplied with an alternative energy source, an axon will not differentiate. Additional findings suggest that mitochondria enable axon initiation and growth, in part, by reducing local cytoplasmic Ca^{2+} concentrations to levels optimal for microtubule polymerization [41]. Presumably, mitochondrial biogenesis and movement into the axon is particularly important because the axon grows much faster and longer than the dendrites and so requires more energy to support its rapid growth. As synapses form the number of mitochondria increases and they become distributed along the length of the dendrites and axon, in presynaptic terminals, and at the base of dendritic spines [35]. Synaptic activity causes mitochondria to be positioned at the base of dendritic spines, where they play important roles in the structural plasticity of the spines [42]. When mitochondrial biogenesis is inhibited by RNA interference-mediated reduction of PGC-1α levels, the formation of synapses in developing hippocampal neuronal circuits is significantly reduced, and established synapses in the adult hippocampus are lost [35]. Knocking down PGC-1α levels also inhibits the ability of pituitary adenylate cyclase-activating peptide to stimulate neurite outgrowth [43], and prevents synaptogenesis [35] in cultured hippocampal neurons.

Brain-derived neurotrophic factor (BDNF) plays very important roles in learning and memory, and in adaptive responses of neurons to bioenergetic challenges [44]. BDNF can stimulate mitochondrial biogenesis in cultured embryonic hippocampal neurons [35]. In hippocampal neurons that have formed synapses, BDNF causes a relatively rapid inhibitory effect on mitochondrial motility resulting in increased numbers of mitochondria in presynaptic terminals; this response to BDNF is mediated by the Ca^{2+}-responsive mitochondrial Rho GTPase Miro1 [45]. Interestingly, Miro1 also controls mitochondria positioning and Ca^{2+} dynamics in astrocytes that are closely associated with synapses, suggesting roles for astrocyte mitochondria in synaptic plasticity [46]. Analyses of mitochondrial dynamics in neurons in which the mitochondrial motility-regulating protein syntaphilin is manipulated demonstrated that axons in which mitochondria are highly mobile exhibit greater pulse-to-pulse variability in neurotransmitter release [47]. Together with data showing that BDNF reduces presynaptic mitochondrial motility, the latter findings suggest the possibility that BDNF might reduce variability of glutamate release from presynaptic

terminals, although this remains to be determined. In any case, the emerging findings suggest that reciprocal interactions between the cytoskeleton and mitochondria play important roles in the regulation of presynaptic function, and that BDNF influences these processes.

Several mitochondrial proteins that are responsive to neuronal activity and bioenergetic challenges may play particularly important roles in synaptic plasticity. Cultured neurons in which the mitochondrial uncoupling protein UCP4 is genetically knocked down exhibit alterations in Ca^{2+} dynamics and hypersensitivity to stimuli such as the neurotransmitter glutamate that induce Ca^{2+} influx or release from endoplasmic reticulum stores [48, 49]. Moreover, UCP2-deficient mice exhibit heightened anxiety and impaired cognitive function that are associated with altered neuronal network activity [50]. Both dietary energy restriction and exercise can increase UCP expression in brain neurons, suggesting roles for UCPs in beneficial adaptive responses of neurons to bioenergetic challenges [49, 51]. Indeed, whereas exercise normally increases synapse density in the hippocampus, it fails to increase synapse density in mice lacking UCP2 in neurons [51]. The contributions of UCP4 to the enhancement of neuroplasticity in response to exercise and energy restriction remain to be explored. Another example of a mitochondrial protein that has recently been found to play important roles in adaptive neuroplasticity is sirtuin 3 (SIRT3) an enzyme that removes acetyl groups from lysine residues of substrate proteins. Exercise and excitatory glutamatergic neurotransmission induce the expression of SIRT3 in hippocampal neurons, and neurons lacking SIRT3 exhibit exaggerated Ca^{2+} responses to glutamate and increased susceptibility to epileptic seizures [22]. Effects of SIRT3 on synaptic plasticity may be mediated, in part, by mitochondrial superoxide dismutase 2 (SOD2). SIRT3 deacetylates SOD2 which increases its dismutase activity and so decreases levels of superoxide anion radical [22]. SOD2 can counteract impairment of learning and memory in a mouse model of AD [52], consistent with a role for SOD2 in sustaining synaptic plasticity. Altogether, the emerging evidence suggests that mitochondria play important roles in synaptic plasticity during normal brain function, and in conditions in which neurons are subjected to oxidative and metabolic stress. Future studies should clarify how signaling pathways involved in neuroplasticity influence mitochondrial dynamics and function, as well as how mitochondria enable and modulate structural and functional aspects of synaptic plasticity.

Roles for Mitochondria in Bioenergetic Challenge-Mediated Neuroplasticity and Stress Resistance

Three bioenergetic challenges that stimulate adaptive responses of mitochondria in neurons are exercise, dietary energy restriction/fasting and activity in neuronal circuits (Figure 2). In contrast, a typical western diet, particularly when combined with a sedentary and intellectually unchallenging lifestyle, down-regulates the same adaptive responses and may thereby result in the accumulation of dysfunctional/damaged mitochondria in neurons [52, 53]. When rats or mice exercise voluntarily on a running wheel, are maintained on an intermittent fasting diet or are housed in an enriched environment, there is increased neuronal network activity in several different brain regions including circuits in the hippocampus that play fundamental roles in learning and memory [54–56]. The excitatory

synapses activated under such conditions deploy the neurotransmitter glutamate which binds to receptors on the postsynaptic membrane resulting in membrane depolarization and Ca^{2+} influx through glutamate receptor channels (principally the NMDA receptor) and voltage-dependent channels. Ca^{2+} activates kinases such as Ca^{2+}/calmodulin-dependent protein kinases II and IV, and mitogen-activated protein (MAP) kinases. The kinases then phosphorylate and activate transcription factors including cyclic AMP response element-binding protein (CREB), nuclear factor kappa B (NF-κB), and activator protein-1 (AP-1). Gene targets of these transcription factors include those encoding BDNF, fibroblast growth factor 2 (FGF2), SOD2 and DNA repair enzymes [12, 53]. As described below, the activation of these signaling pathways enhances neuroplasticity (the formation and 'strengthening' of synapses, and the production of new neurons from stem cells) and the resistance of the neurons to various types of stress.

Exercise

Physical exercise improves general health and brain health, and is also recognized as a non-pharmacological strategy to counteract age-related brain dysfunction and neurodegenerative diseases [57]. In rats and mice, exercise can enhance synapse formation and synaptic plasticity/long-term potentiation [51, 58, 59], and can stimulate neurogenesis [60] and angiogenesis [61]. Contributing to these changes in neural and vascular cells are the production and secretion of BDNF, insulin like growth factor (IGF-1), and vascular endothelial cell growth factor (VEGF) [62, 63].

With exercise, alterations in mitochondria and energy metabolism occur in the brain. Adaptations of brain cells to exercise include increased mitochondrial biogenesis and function and improvements in antioxidant networks, thus improving the ability to decrease ROS damage [21, 64–67]. When evaluated after 4 weeks of voluntary wheel running, levels of creatine kinase, fructose-bisphosphate aldolase C, phosphoglycerate kinase 1 and ATP synthase were elevated in the hippocampus of rats, suggesting that glycolytic and oxidative metabolism were increased [68]. Similarly, both voluntary wheel running and treadmill exercise training resulted in increases in levels and enzymatic activities of multiple proteins involved in mitochondrial energy metabolism including malate dehydrogenase, isocitrate dehydrogenase (NAD) subunit alpha, and ubiquinol-cytochrome-c reductase complex core protein I [69]. Voluntary exercise in mice induced UCP2 mRNA expression and increased mitochondrial oxygen consumption in coupled and uncoupled respiratory states in the hippocampus [51]. These changes occurred in association with an increase in mitochondrial number and dendritic spines in wild type mice, but did not occur in UCP2 knockout mice. One month of voluntary wheel running resulted in increased expression of the mitochondrial protein deacetylase SIRT3 in the hippocampus and cerebral cortex of mice [22]. The exercise-induced expression of SIRT3 is mediated by excitatory synaptic activity because an NMDA receptor antagonist abolished exercise-induced up-regulation of SIRT3. Two mitochondrial proteins deacetylated by SIRT3 are SOD2 and cyclophilin D, which likely contribute to exercise-induced neuronal stress resistance [22]. The synaptic activity-induced expression of BDNF may further contribute to the beneficial effects of exercise on synaptic plasticity and neuronal stress resistance because activation of the BDNF receptor trkB can stimulate mitochondrial biogenesis and the expression of proteins involved in mitochondrial

stress resistance including Bcl2 and antioxidant enzymes [35, 44]. Altogether, the emerging data suggest that exercise can elicit adaptations of neuronal mitochondria in the brain to sustain increased metabolic demands as well as promote improvements in brain function (Figure 2).

Dietary Energy Restriction and Ketogenesis

Dietary energy restriction (DER) entails a reduction in daily calorie intake and/or intermittent fasting (IF) in which little or no energy is consumed for extended time periods of 16 hours or more on an intermittent basis (e.g., fasting every other day or two days/week) [70]. DER can increase the average lifespan of mice, rats and monkeys [1]. DER reduces oxidative stress in many tissues and can enhance mitochondrial biogenesis and mitochondrial efficiency, and reduce oxidative cellular damage [71–73]. DER has also been shown to enhance neurogenesis and synaptic plasticity [12] and can protect neurons in the brain and improve functional outcome in animal models of stroke, Parkinson's disease and Alzheimer's disease [74–80].

The cellular and molecular mechanisms by which DER can improve brain function and resistance of neurons to injury and neurodegenerative disorders are being revealed by studies of mice. IF engages signaling pathways that lead to increased levels of several different proteins that are known to play important roles in neuroplasticity and/or neuronal stress resistance. For example, mice maintained on an alternate day fasting diet for 3 months exhibited significant elevations of BDNF, FGF2, heat-shock protein 70, glucose-regulated protein 78, and heme oxygenase 1 in their cerebral cortex and striatum [79]. Each of the latter proteins has been reported to protect neurons against degeneration by mitochondrial dysfunction [35, 74, 81, 82]. Another mechanism by which DER may protect neuronal mitochondria is by up-regulating SIRT3. Thus: Qiu et al. (2010) showed that SIRT3 decreases levels of ROS in non-neuronal cells by deacetylating and thereby activating SOD2: Cheng et al. (2016) found that neurons lacking SIRT3 are highly sensitive to metabolic, oxidative and excitotoxic stress; and Amigo et al. (2016) showed that caloric restriction up-regulates SIRT3 in brain mitochondria [22, 83, 84]. In addition to decreasing mitochondrial oxidative stress, SIRT3 may protect neurons against apoptosis by deacetylating and thereby inhibiting cyclophilin D, a protein that mediates opening of the mitochondrial membrane permeability transition pores that trigger apoptosis [22].

Peripheral metabolic adaptations in response to fasting may result in beneficial effects on the brain. One major metabolic consequence of fasting is a switch of fuel source from liver glycogen to adipose-derived fatty acids which are metabolized to the ketone bodies 3-hydroxybutyrate (3OHB) and acetoacetate. As a result, circulating glucose levels are maintained at a low level and ketone levels are elevated. 3OHB is transported into the brain and into neurons where it is metabolized to acetyl coenzyme A which can be used to generate ATP in the tricarboxylic acid cycle. When glucose supply is limited, fats are converted to ketones which become the major energy source for brain cells [85, 86]. Mitochondria isolated from brain tissue of animals fed a ketogenic diet exhibit reduced ROS production [87]. Similarly, direct exposure of cultured rat cortical neurons to 3OHB resulted in a decreased production of ROS by complex I of the mitochondrial respiratory chain [88].

These kinds of findings suggest that the metabolic shift to ketogenesis fuels the brain's energy demands and may also lessen the amount of oxidative stress neurons experience.

Interestingly, 3OHB can also affect signaling pathways involved in neuronal plasticity and cellular stress resistance. The ability of 3OHB to constrain neuronal excitability may underlie the anti-seizure effects of fasting and ketogenic diets [89]. Suppression of seizures by 3OHB may result, in part, from increased GABAergic tone perhaps secondary to increased production of GABA from glutamine [90]. In addition, 3OHB can induce the expression of BDNF in neurons by a mechanism involving activation of the transcription factor NF-κB [91]. 3OHB has also been reported to function as a ligand for one or more membrane receptors, and to inhibit some protein deacetylases [92]. Moreover, neurons treated with ketones exhibit increased SIRT1 activity, which may result from increased levels of NAD^+ (a cofactor for SIRT1 activation) and stimulation of autophagy [93]. The relative contributions of 3OHB as an energy supply for neurons and its signaling functions to beneficial effects of fasting on the brain remain to be determined.

Sedentary Lifestyle and Excessive Caloric Intake

Lack of exercise and excessive calorie intake alters brain physiology and increases the risk of stroke [94]. Such metabolically morbid lifestyles may also predispose to Alzheimer's and Parkinson's diseases [95, 96]. Many westernized societies have diets that are rich in saturated fatty acids and refined sugars, which can damage the cardiovascular system, but may also adversely affect the brain [97]. Indeed, since the traditional Japanese diet was 'complemented' with consumption of processed 'Western foods' the prevalence of Alzheimer's disease in Japan has risen from 1% to 7% [98].

A sedentary over-nourished lifestyle may adversely affect the brain by impairing cellular stress resistance and neuroplasticity. For example, rats fed a high fat diet for 2 months had reduced levels of BDNF in the hippocampus, and reduced expression of several proteins involved in synaptic function and plasticity including synapsin I, CREB, and growth-associated protein 43 [99]. Rats fed a diet with high levels of fat and sugar had impaired hippocampal plasticity and cognitive performance [20]. Elderly human subjects with metabolic syndrome or diabetes performed worse on cognitive tests involving information processing speed, attention, and executive function compared to age-matched healthy subjects [100]. Measurements of relative levels of metabolites in the brains of human subjects revealed that those with a high body mass index had reduced levels of N-acetylaspartate, an indicator of metabolic health of neurons, in frontal, parietal, and temporal white matter and frontal gray matter [101]. Furthermore, compared to rats that were sedentary, those that exercised had increased levels of mitochondrial enzymes in their hippocampus including ubiquinol-cytochrome-c reductase complex core protein 1 (Uqcrc1), malate dehydrogenase and isocitrate dehydrogenase compared to sedentary rats [69]. These findings suggest that high energy diets and a sedentary lifestyle can have detrimental effects on neurons, including on the bioenergetic processes that take place in the mitochondria.

Involvement of Neuronal Mitochondria in Acute Brain Injuries and Neurodegenerative Disorders

In this section we provide brief summaries of findings that have elucidated roles for mitochondrial alterations in the pathogenesis of neuronal dysfunction and degeneration in acute brain insults (stroke and traumatic brain injury) and three major neurodegenerative disorders (Alzheimer's, Parkinson's and Huntington's diseases). This information sets the stage for subsequent descriptions of studies of the impact of bioenergetic challenges (exercise and dietary energy restriction) and pharmacological interventions that can bolster mitochondrial function and stress resistance, thereby increasing the resistance of neurons to degeneration and promoting neuroplasticity.

Stroke

An ischemic stroke occurs when blood flow to part of the brain is greatly reduced, usually as a result of formation of a clot in an atherosclerotic cerebral vessel. Many survivors of a stroke have physical and/or mental disabilities, making stroke a major cause of morbidity [102]. During ischemia neurons are subjected to hypoxia and glucose deprivation, leading to diminished electron transport chain activity and ATP depletion, and uncontrolled Ca^{2+} influx through glutamate receptor channels [13]. When blood flow is returned after ischemia, the energy-deprived neurons are exposed to oxygen resulting in oxidative damage and may die by excitotoxic necrosis and apoptosis [103]. Neurons located in the region of the brain supplied completely by the affected artery (the ischemic core) will usually die rapidly by necrosis, whereas neurons located in the surrounding penumbra often die by apoptosis [104]. The degree of mitochondrial damage plays a determining factor in the amount of neuronal injury that can occur [105]. Complex I of the electron transport chain is particularly sensitive to ischemia/reperfusion injuries, resulting in impaired oxidative phosphorylation [106–108]. At the same time, mitochondria accumulate Ca^{2+} which can trigger opening of mitochondrial permeability transition pores through which cytochrome c enters the cytoplasm resulting in activation of caspase 3 which executes the apoptotic cell death process.

Traumatic Brain Injury

Traumatic brain injury (TBI) is a common cause of mortality and morbidity in the United States, and can come with a large economic burden resulting from motor and cognitive disabilities [109–111]. A TBI can compromise brain metabolism and cause mitochondrial dysfunction. Studies have shown that after TBI pyruvate dehydrogenase activity is decreased and there is reduced cytochrome c content [112, 113]. There are many consequences to mitochondrial dysfunction, including oxidative stress, dysregulated Ca^{2+} handling and metabolic failure [113]. Furthermore, oxidative stress from mitochondrial dysfunction can cause oxidative modification of proteins, lipids, or DNA and cause more metabolic impairment [103]. Damage to mitochondrial respiratory capacity reduces a neuron's ability to respond to changes in energy demand, impairing cerebral energy metabolism, which contributes to neuronal death seen after trauma to the brain [103, 114].

Mitochondrial Alterations and Age-Related Neurodegenerative Disorders

Neuronal mitochondria are particularly prone to the accumulation of molecular damage and dysfunction during aging. With greater exposure to high levels of ROS and diminished DNA repair capabilities, mutations of mitochondrial DNA accumulate during aging which can promote dysfunction of the electron transport chain [21, 115]. In a cross-amplifying reciprocal manner, mitochondrial dysfunction promotes damage to proteins and lipids throughout the neuron, dysregulation of cellular ion homeostasis and impaired autophagy/mitophagy (Figure 3). Moreover, nuclear DNA damage can trigger cell death by mechanisms involving activation of poly (ADP ribose) polymerase (PARP) and NAD^+ depletion [116]. Such general age-related alterations in neuronal mitochondria are greatly accelerated in neurodegenerative disorders. In this section of our article we summarize findings that suggest disease-specific mechanisms of neuronal dysfunction and death, both upstream and downstream of mitochondrial abnormalities, in Alzheimer's, Parkinson's and Huntington's diseases.

Alzheimer's Disease—Alzheimer's disease (AD) is the leading cause of dementia and is characterized by the degeneration of neurons in the hippocampus, entorhinal cortex, frontal cortex, and associated structures that are involved with cognition. Also affected are brain regions involved in emotional behaviors including the amygdala, prefrontal cortex, hypothalamus and other areas which are involved with emotional behaviors [117, 118]. AD is defined by the aggregation and extracellular accumulation of neurotoxic forms of amyloid β-peptide (Aβ) plaques and by the intracellular aggregation of hyperphosphorylated forms of the microtubule-associated protein Tau in neurons. Studies of postmortem brain tissue from AD patients, and of cell culture and animal models have shown that the aggregation and accumulation of Aβ and Tau can cause synaptic dysfunction, oxidative stress, calcium dysregulation, and neurodegeneration [119–121]. The vast majority of AD cases are diagnosed in people in their seventh or eighth decades of life and are sporadic with no clear genetic cause. However, somewhat less than 5% of AD cases result from dominantly inherited mutations in the β-amyloid precursor protein (APP), presenilin 1 (PS1) or presenilin 2 [117]. The APP mutations are located very close to or within the Aβ sequence of APP, where they cause increased generation of a neurotoxic form(s) of Aβ (Aβ1-42). PS1 is an integral membrane protease that is a component of the γ-secretase complex that cuts APP at its C terminus. PS1 mutations tend to enhance production of Aβ1–42, and may also perturb cellular Ca^{2+} homeostasis by causing excessive accumulation of Ca^{2+} in the endoplasmic reticulum [122]. Tau mutations are responsible for some cases of frontotemporal lobe dementias, which are characterized by extensive Tau pathology (neurofibrillary tangles) with little or no Aβ pathology [123]. However, it has become clear that in contrast to such 'pure' inherited dementias, the brains of subjects with late-onset dementia exhibit considerable variability in Aβ, Tau, and other histopathological features [2].

Studies of both animal models of AD and brains from AD patients suggest that brain cell ATP levels are reduced and complex IV of the electron transport chain is dysfunctional [124]. Many mitochondrial enzymes that are related to metabolism are altered in AD including cytochrome *c* oxidase, α-ketoglutarate dehydrogenase complex, and pyruvate

dehydrogenase complex [125–127]. In addition, data suggest that mitochondrial biogenesis is reduced in neurons in AD and that damaged mitochondria accumulate as a consequence of lysosome dysfunction and impaired mitophagy [128]. It remains unclear whether mitochondrial alterations are early and pivotal events in the neurodegenerative process in AD, or occurs in later stages as neurons die.

Because aging is the major risk factor for sporadic AD, we presume that aging-related molecular and cellular alterations can promote aberrant APP and Tau metabolism and thereby initiate neurodegenerative cascades that result in the neuropathology and associated cognitive deficits in AD. Oxidative modification of proteins involved in APP and Tau metabolism, and perturbed neuronal Ca^{2+} handling may be two such upstream factors [120]. Emerging evidence suggests that aging-related decrements in mitochondrial function also occur early on the pathway to AD, and may even be central to the oxidative and ionic cellular stress that can trigger Aβ and Tau pathologies. Longitudinal positron emission tomography-based imaging of regional cerebral glucose uptake have shown that reduced energy metabolism occurs in cells of vulnerable brain regions well prior to the clinical manifestations of AD [129]. The impaired glucose utilization may result, in part, from an adverse effect of Aβ on glucose transport into neurons because the oxidative stress caused by Aβ can impair function of the neuronal glucose transporter GLUT3 [130]. On the other hand, impaired mitochondrial function can accelerate the latter age-related alterations in neurons, and may also cause amyloidogenic processing of APP [131] and accumulation of hyperphosphorylated Tau in neurons [132]. Membrane lipid peroxidation resulting from mitochondria- and Aβ-derived ROS generates the aldehyde 4-hydroxynonenal which can promote amyloidogenic APP processing and the accumulation of pTau either by direct modification of APP secretase complex proteins and Tau or, indirectly by disrupting cellular Ca^{2+} regulation and mitochondrial function [13, 122, 133, 134].

Finally, it is important to consider that age-related deficiencies in adaptive cellular stress response pathways (e.g., decrements in neurotrophic factor signaling, DNA repair, antioxidant enzymes, autophagy and proteasome systems) may occur early and compromise mitochondrial function in AD [13]. Evidence in support of this possibility includes that: 1) the expression of BDNF and nerve growth factor, two neurotrophic factors known to support the survival and plasticity of neurons affected in AD, are decreased in the brains of AD patients [135]; 2) levels of the DNA repair enzyme polymerase β are decreased in the brain during normal aging and reductions of polymerase β levels are sufficient to render neurons vulnerable to the toxicity of Aβ and pTau [22, 136]; 3) lysosome dysfunction is associated with Aβ and pTau pathologies in AD, and 4) stimulation of autophagy ameliorates Aβ pathology and cognitive deficits in a mouse model of AD [128, 137]. These kinds of findings suggest a potential role for therapeutic interventions that bolster adaptive cellular stress responses in AD treatment and risk reduction.

Parkinson's Disease—Parkinson's Disease (PD) is the second most common neurodegenerative disease, and involves the progressive accumulation of α-synuclein and the degeneration of neurons. Degeneration may begin in peripheral autonomic neurons and progress trans-neuronally in a retrograde manner to the brainstem and midbrain resulting in the loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc) [138,

139]. The loss of dopaminergic (DA) neurons in the SNpc results in the motor symptoms seen with PD including rigidity, gait difficulty, resting tremors, bradykinesia, and dyskinesia [140]. Neurons affected in PD often exhibit massive accumulations of oxidized and nitrated proteins including α-synuclein, tyrosine hydroxylase, heme oxygenase, neurofilament and Tau proteins that are resistant to proteasomal degradation [141, 142].

Evidence strongly suggests that mitochondrial abnormalities occur early in PD, and are both necessary and sufficient to cause the disease. A small percentage of PD cases are caused by either dominant or recessive mutations in genes that encode proteins intimately involved in mitochondrial function and quality control. Briefly, autosomal recessive mutations in DJ-1, PINK1 and Parkin all result in impaired mitophagy; DJ-1 interacts directly with mitochondria where it functions as a redox sensor of mitochondrial stress, while PINK1 and Parkin play critical roles in mitophagy [143]. PINK1 associates with mitochondria where, in response to prolonged membrane depolarization, PINK1 is cleaved and then recruits Parkin. Parkin is an E3 ubiquitin ligase that ubiquitinates multiple proteins involved in mitochondrial transport, fission and mitophagy including Miro, Drp-1 and mitofusins. Parkin also ubiquitinates α-synuclein, thereby targeting α-synuclein for degradation. Some cases of dominantly inherited PD are caused by mutations in α-synuclein or by increased expression of wild-type α-synuclein; these mutations result in the intracellular accumulation of α-synuclein as a result of overloading α-synuclein clearance pathways (proteasomal and autophagic) and impaired mitophagy. Finally, dominantly inherited mutations in LRRK2 (leucine-rich repeat kinase 2) result in abnormal mitochondrial fragmentation [143].

A second line of evidence that strongly implicates mitochondrial dysfunction in PD is the fact that toxins that selectively inhibit mitochondrial complex I cause selective loss of dopaminergic neurons and motor dysfunction in mice, rats, monkeys and humans [144]. These neurotoxins include MPTP, rotenone, and 6-hydroxydopamine. The reason(s) that dopaminergic neurons are exquisitely sensitive to these toxins is not fully established but may include selective transport of the toxin into the dopaminergic neurons and the rapid and continuous firing of these neurons. Although not believed to be a major cause of sporadic late-onset PD, there is evidence that environmental exposures to such neurotoxins can increase the risk of PD [145].

Huntington's Disease—Huntington's disease (HD) is the most common inherited neurodegenerative disorder. It is caused by expansions of CAG repeats in the *huntingtin* gene, resulting in polyglutamine repeats in the huntingtin protein [13, 146]. The brain regions that are most severely affected are the striatum and cerebral cortex. Similar to HD patients, mutant mice exhibit accumulation of huntingtin aggregates in neurons and selective damage to striatal medium spiny neurons resulting in progressive motor dysfunction and early death. Studies of isolated mitochondria from different transgenic strains of HD mice (R6/2, YAC12, and *Hdh*150 knock-in) revealed that there is an increase in Ca^{2+} loading capacity of forebrain mitochondria from the R6/2 and YAC12 mice, but not in the homozygous or heterozygous *Hdh150* knock-in mice. However, when *Hdh*150 neurons were challenged with high Ca^{2+} influx by transient NMDAR activation, more striatal neurons failed to re-establish Ca^{2+} homeostasis, possibly due to defects in ATP synthesis or transport [147]. These results show that mitochondrial protein function is impaired in HD.

HD-like neuropathology and behavioral symptoms can be induced by exposure of mice or rats to the mitochondrial complex II inhibitor 2-nitropropionic acid (3NPA). In a study by Cheng et al. (2016) it was shown that mice with reduced SIRT3 levels exhibit increased vulnerability of striatal neurons to 3NPA and worsened motor performance on a rotarod test [22]. Additional findings in the latter study suggested that hyperacetylation of mitochondrial SOD2 and cyclophilin D contributed to the increased vulnerability of SIRT3 deficient mice to 3NPA. It will therefore be of interest to determine whether interventions that increase SIRT3 expression and/or activity exhibit neuroprotective effects in animal models of HD.

Roles for Mitochondria in Bioenergetic Challenge-Induced Neuroprotection

This section presents examples of evidence supporting the possibility that interventions that bolster mitochondrial function and stress resistance hold considerable promise for the treatment and/or risk reduction in a wide range of neurological disorders that involve neuronal degeneration.

Stroke

Rats that underwent a 30-minute cerebral four-vessel occlusion, a model relevant to cardiac arrest, had reduced neuronal loss in their neocortex, hippocampus, and striatum when calorie restricted [148]. Similarly, alternate day fasting prior to middle cerebral artery occlusion and reperfusion protected neurons in the cerebral cortex and improved functional outcome in rats and mice [74, 79]. The latter studies showed that intermittent fasting stimulates increased production of multiple neuroprotective proteins including BDNF, FGF2, HSP-70, GRP-78 and HO-1. Rats exercised for 5 days starting 24 hours after focal cerebral ischemia exhibited increased expression of genes encoding PGC-1α and NRF-1, had smaller infarct volumes, and reduced neurological deficits compared to sedentary rats [149]. Treadmill training after experimental stroke resulted in increased levels of mtDNA, NRF-1, TFAM, COXIV and HSP60 suggesting stimulation of mitochondrial biogenesis [150]. In another study, rats exercised after ischemia, had improved motor performance and elevated levels of BDNF and TrkB [151]. It was also recently reported that running wheel exercise induces the expression of SIRT3 in hippocampal and cortical neurons, and protects neurons against excitotoxic injury [22].

Pharmacological interventions that target mitochondria have proven effective in reducing brain damage and improving functional outcome in animal models of stroke. For example, the mitochondrial uncoupling agent 2, 4-dinitrophenol (DNP) reduced cerebral infarct volume by 40% and improved functional outcome in a rat model of focal ischemic stroke [152]. This neuroprotective effect of mild mitochondrial uncoupling was associated with improved mitochondrial function and reduced mitochondrial calcium uptake and cytochrome c release. Analyses of the effects of a neuroprotective dose of DNP on cerebral gene expression revealed up-regulation of BDNF and CREB signaling pathways as well as autophagy [153]. Interestingly, once daily administration of the non-metabolizable glucose analog 2-deoxyglucose increased the resistance of cerebral cortical neurons to degeneration in a rat stroke model [154]. Levels of the neuroprotective protein chaperone HSP-70 in brain neurons were increased in response to 2-deoxyglucose consistent with a hormesis-based

mechanism [154]. Elevating levels of ketone bodies and NAD levels are additional approaches that have been reported to be beneficial in animal models of stroke. For example, administration of 3OHB prior to experimental stroke up-regulated HIF-1α and Bcl-2 and resulted in a 55% reduction in infarct volume [155]. Treatment of mice with the NAD^+ precursor nicotinamide protected cerebral neurons and improved functional outcome in a mouse model of focal ischemic stroke [156].

Traumatic brain injury

Davis et al. (2008) found that rats fasted for 24 hours, but not 48 hours, after a moderate controlled cortical impact had increased tissue sparing, decreased biomarkers of oxidative stress, less calcium loading, and increased oxidative phosphorylation in mitochondria isolated from the brain [111]. They then administered ketones to the rats after the injury, and these rats had increased tissue sparing. Therefore, it was concluded that the mechanism by which fasting induces neuroprotection is through ketosis. More evidence that ketones are neuroprotective comes from another study where a ketogenic diet following head trauma reduced contusion volume [157]. A potential reason for the protective effects seen with ketones is that glucose transport may be compromised after TBI, whereas ketone uptake into neurons is less affected. Inducing a mild metabolic challenge to neurons by treatment with the mitochondrial uncoupling agent DNP can also reduce brain damage and improve functional outcome in rats [158]. Interestingly, a ketogenic diet increased the expression of mitochondrial UCPs including UCP2 and UCP4 in brain cells [87], suggesting a potential role for a hormesis-based mechanism of neuroprotection by ketones. Consistent with the latter possibility it was recently reported that 3OHB induces BDNF expression in neurons by a mechanism involving a mild mitochondrial stress response and activation of the transcription factor NF-κB [91]. Increasing mitochondrial energy substrates relatively directly by administration of creatine or nicotinamide was also reported beneficial in animal models of TBI [159, 160].

Alzheimer's disease

Daily caloric restriction and alternate day fasting were reported to ameliorate cognitive deficits in mouse models of AD [76, 78]. Caloric restriction also lessened brain Aβ pathology in old monkeys [75]. Interestingly, whereas daily caloric restriction also reduced the amount of Aβ deposits in the brain, intermittent fasting did not, suggesting that intermittent fasting preserves synaptic function even when Aβ accumulation occurs [78]. It will be of considerable interest to determine whether the cellular and molecular mechanisms by which intermittent fasting protects neurons against Aβ in mouse models, are engaged in human subjects who exhibit high amounts of Aβ pathology with little or no consequences for their cognition [161].

Running wheel exercise attenuates the development of Aβ pathology, and preserves synaptic plasticity and cognitive function in several different mouse models of AD, including APP mutant transgenic mice [162, 163] and 3xTgAD mice [164]. Exercise may suppress AD pathology by reducing oxidative stress and inducing the activity-dependent expression of BDNF [44, 57, 59]. In APP/PS1 mice, 20 weeks of treadmill exercise improved cognitive function, and reduced brain tissue levels of Aβ42, ROS, and mitochondrial DNA damage,

and increased levels of mitochondrial complex I, IV, and ATP synthase activities [165]. Increased expression and activity of SOD2 may play an important role in the maintenance of neuronal function and suppression of disease pathogenesis in AD mouse models [22, 166–168]. Epidemiological data suggest that humans who maintain a moderate level of aerobic physical activity during their life are at reduced risk of AD [2, 169]. Moreover, it was reported that the amount of cerebral Aβ is inversely correlated with the amount of exercise of the subjects, implying that physical activity reduces Aβ deposition or increases Aβ clearance rates [170].

Administration of 3OHB or fatty acid ketone precursors ameliorated behavioral deficits in mouse models of AD [171]. A study by Yin et al. (2016) showed that APP mice fed ketones had improved memory in Morris water maze and novel object recognition tests and had improved mitochondrial function through restoration of mitochondrial complex I activity and reducing Aβ-42 levels [172]. A ketogenic diet also improved cognitive function in patients with AD [173]. Pharmacological treatments that induce mild metabolic cellular stress have also been reported to have beneficial effects in AD mouse models. These include 2-deoxyglucose [174], the mitochondrial uncoupling agent DNP, [175] and the potassium channel opener diazoxide [176].

Parkinson's disease

Older adults that performed moderate to vigorous exercise during their mid-life had a 33% lower risk of developing PD [177]. Moreover, exercise programs improve mobility and balance in PD patients [178, 179]. Studies using neurotoxin-based rodent PD models have shown that mild intermittent metabolic challenges, including wheel running and intermittent fasting, protect dopaminergic neurons and improve functional outcome. In mouse models of PD, mice that exercised on a treadmill 5 days/week (40 min/day) for a total of 18 weeks beginning 1 week before a 5 week treatment with a low-dose of MPTP administered twice each week exhibited improvements in mitochondrial function, elevated BDNF and GDNF levels in their striatum, and reduced behavioral deficits compared to sedentary control mice exposed to MPTP [180]. In another study, two weeks of exercise increased the survival of dopaminergic neurons in the substantia nigra and maintained dopaminergic projections to the striatum in mice administered 6-hydroxydopamine [181]. Similarly, 8 weeks of treadmill training increased levels of antioxidant enzymes in the striatum, and reduced levels of oxidative damage to lipids and proteins in the 6-hydroxydopamine rat model [182]. Rhesus monkeys maintained for 6 months on a caloric restriction diet exhibited significantly reduced striatal dopamine depletion, lessened motor deficits, and increased striatal BDNF and GDNF levels after unilateral intra-carotid artery administration of MPTP [183]. Mice overexpressing a familial PD mutant form of α-synuclein in neurons exhibit impaired brainstem parasympathetic neuron function prior to developing motor symptoms, and this abnormality in the autonomic nervous system can be reversed by IF [80]. Thus, dietary energy restriction is neuroprotective in both neurotoxin-based and genetic mutation-based animal models of PD.

Inducing an intermittent bioenergetic stress in mice by once daily administration of 2-deoxyglucose, resulted in resistance of midbrain dopaminergic neurons to degeneration and

superior performance on a rotarod test in the MPTP model of PD [77]. Furthermore, 2-deoxyglucose preserved mitochondrial function and reduced oxidative stress, and in cultured dopaminergic cells increased cell viability when the cells were exposed to rotenone, a complex I inhibitor or Fe^{2+} to induce oxidative stress [77]. These findings suggest that 2-deoxyglucose and other agents that induce mild metabolic stress might eventually be used in PD patients.

Elevating ketone levels might also prove beneficial in PD. PD patients on a ketogenic diet for 1 month had a 43% improvement in scores on the Unified Parkinson's Disease Rating Scale [184]. In both animal models and in dopaminergic neurons exposed to mitochondrial complex I inhibitor MPP^+, 3OHB protected dopaminergic neurons against degeneration [185–187]. 3OHB rescued mitochondrial respiration in a MPTP-induced PD mouse model through a mitochondrial complex II-dependent mechanism leading to increased ATP production and survival of dopaminergic neurons [185]. 3OHB also induces the expression of BDNF in neurons [91] which may contribute to neuroprotection in PD models because BDNF is known to promote survival of dopaminergic neurons [188].

A final example of a novel approach for impacting the neurodegenerative process in PD is to enhance glucagon-like peptide 1 (GLP1) signaling. GLP-1 is a gut peptide that is released into the blood in response to the consumption of food, particularly sugars. GLP-1 stimulates insulin release from the pancreas and also increases the sensitivity of muscle and liver cells to insulin [189]. GLP-1 crosses the blood-brain barrier and GLP-1 receptors, which are coupled to the GTP-binding protein Gs and downstream cyclic AMP and CREB signaling, are widely expressed in neurons [190]. GLP-1 has a short half-life in the blood of only a few minutes because it is cleaved by the circulating protease DPP-IV. Non-cleavable analogs of GLP-1, including exendin-4 and liraglutide have been developed for the treatment of type 2 diabetes. Studies of two different neurotoxin-based animal models of PD, MPTP in mice and 6-hydroxydopamine in rats, showed that exendin-4 treatment protects nigral dopaminergic neurons and improves functional outcome [191, 192]. Liraglutide was also shown to be beneficial in the MPTP mouse model of PD [193]. A small open-label trial, treatment of PD patients with exendin-4 resulted in improvements in motor and non-motor PD symptoms [194]. Because GLP-1 signals via cyclic AMP and CREB, it would be predicted that GLP-1 agonists will stimulate mitochondrial biogenesis and bolster mitochondrial stress resistance (e.g., by increasing SIRT3 expression), although this remains to be determined. Altogether, the evidence suggests clear beneficial effects of regular exercise in bolstering the resistance of dopaminergic and autonomic neurons to mitochondrial stress, and support the widespread application of exercise programs to people with or at risk for PD.

Huntington's disease

Intermittent fasting was reported to protect striatal neurons and improve functional outcome in the 3-nitropropionic acid model of HD [195] and in mutant huntingtin transgenic mice [196]. Huntingtin mutant mice have reduced levels of BDNF in their striatum and cortex and intermittent fasting increased BDNF levels in these brain regions, as well as increasing levels of HSP70. Interestingly, however, running wheel exercise had no discernable beneficial effects in the same line of HD mice [197], perhaps because the mice exhibit a

progressive wasting phenotype. In the R6/2 1J mouse model of HD, a ketogenic diet improved working memory in the female mice, but not male mice [198]. Treatment of huntingtin mutant mice with the GLP-1 analog exendin-4 ameliorates brain neuropathology, improves motor function and extends survival [199], findings that provide a rationale for clinical trials of GLP-1 receptor agonists in HD patients.

‘Strengthening’ Neuronal Mitochondria to Optimize Brain Function and Forestall Neurodegeneration

As described above, emerging findings suggest that neurons respond to the three most common and evolutionarily meaningful physiological bioenergetic challenges –food deprivation/fasting, physical exertion, and intellectual challenges – by increasing both the number of healthy mitochondria they contain and the stress resistance of individual mitochondria. The intercellular signals that mediate these mitochondria-centered adaptive responses include brain cell-intrinsic neurotransmitters (particularly glutamate) and neurotrophic factors (BDNF, FGF2), and signaling molecules emanating from peripheral organs (particularly liver and muscle) including the ketone 3OHB, irisin [200] and cathepsin B [201]. Interestingly, all three of the latter peripheral organ-derived factors have been shown to increase BDNF expression in brain cells [91, 200, 201]. Because BDNF has been shown to stimulate mitochondrial biogenesis in neurons [35] and to increase resistance of neurons to metabolic and excitotoxic stress [44], BDNF signaling may be particularly important in the beneficial effects of exercise on neuroplasticity and neuronal stress resistance. Studies of animal models have shown that intermittent fasting is highly effective in protecting the brain against a range of stressors that are known to cause neuronal degeneration by impairing mitochondrial function [1, 12]. The underlying cellular and molecular mechanisms appear to be generally similar to those of exercise, and involve both increases in neuronal network activity and signals from the periphery, most notably 3OHB.

While the data from studies of animal models are compelling, and evidence from epidemiological studies and some intervention trials are consistent with beneficial effects of fasting, exercise, and intellectual engagement on brain function and resilience, studies aimed at determining the optimal ‘doses’ and timing of these interventions in specific neurological disorders is lacking. Because of the safety and robustness of health benefits these lifestyle interventions, it is very important that medical education and health care delivery systems develop and incorporate specific prescriptions for brain-bolstering intermittent fasting and exercise routines. However, there are major hurdles [12] that would have to be overcome to implement such brain-healthy prescriptions including: the lack of emphasis on disease prevention in medical school curricula; the expectation of patients that modern medicine (i.e., drugs and surgery) will “cure” any disease they develop because of their ‘couch potato’ lifestyle; the tremendous influence of the food and pharmaceutical industries in instigating and perpetuating poor health habits with no remorse for the fact that they are a major factor in the recent ‘epidemics’ of obesity and diabetes in many developed countries throughout the world [202]. Obesity and diabetes can be cured by energy restriction and exercise, and the risk for cardiovascular disease, stroke and Alzheimer’s disease (e.g., hypertension, insulin resistance) may also be reduced by intermittent fasting and exercise. Unfortunately, there has

been no major effort to apply this knowledge, particularly in countries where a profit motive drives the health care system. Should not the goal of health care systems be to prevent or delay the onset of chronic diseases, rather than encouraging poor health by largely ignoring what works, letting people become sick, and then prescribing expensive drugs?

Lacking the implementation of prescriptions for brain-healthy energy restriction and exercise regimens into general medical practice, it will be of interest and importance to develop and apply pharmacological interventions that trigger some of the same adaptive stress response pathways that are activated by exercise and fasting. Examples include DNP [175], diazoxide [176], 2-deoxyglucose [77, 203] and rapamycin [204]. Such agents exhibit classical biphasic dose responses with regards to their induction of cellular metabolic stress, with neuroprotection occurring with low to moderate doses that do not exhibit significant side-effects. As most drugs are toxic in high doses, it will be important to develop formulations and dosing schedules that trigger adaptive neuronal responses while preventing or reducing the risk of overdose. Another approach is to administer compounds that bolster neuronal mitochondrial bioenergetics and stress resistance rather directly; examples include nicotinamide riboside and a ketone ester [171, 205]. Such interventions are particularly attractive because they appear to be very safe. While efficacy of all of these compounds has been demonstrated in preclinical studies, randomized controlled trials in human subjects with a neurological disorder remain to be performed.

A major advantage of bioenergetic challenge-based interventions that bolster the health and stress resistance of neurons is that they apply to all types of neurons in the nervous system, and so may be beneficial in a wide array of neurological disorders. However, pharmaceutical companies are largely focused on the development of disease-specific drugs. It will therefore be important to develop and implement policies and programs that encourage and enable the incorporation of bioenergetic challenge-based prevention and treatment into medical practice.

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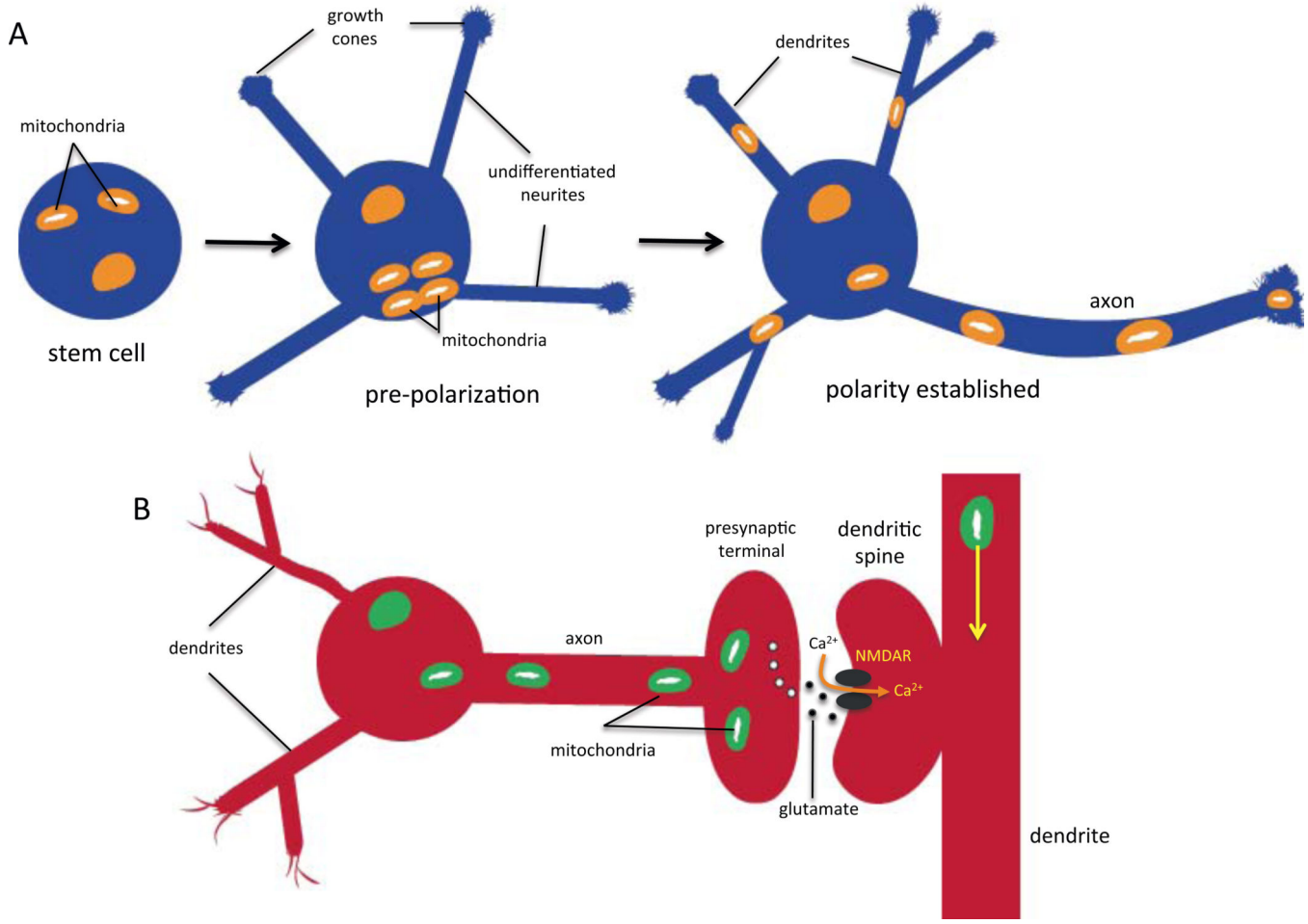

Figure 1. Roles for mitochondria in neuronal differentiation and synaptic plasticity

A. As a neuron differentiates from a stem cell and begins to elaborate undifferentiated neurites (pre-polarization stage), mitochondria congregate at the base of one of the neurites; that neurite then grows rapidly and differentiates into the axon and the remaining neurites differentiate into dendrites, thus establishing cell polarity. **B**. Mitochondria also play important roles in synaptic plasticity as they provide the ATP necessary for the rapid restoration of transmembrane ion gradients in the presynaptic neurons after it fires an action potential, and in the postsynaptic neuron after glutamate-induced depolarization of the postsynaptic dendrite. By virtue of its abilities to sequester and release Ca^{2+}, mitochondria may influence the cytoskeletal dynamics involved in neurotransmitter release and in structural adaptations of dendritic spines, such as occur during learning and memory. Interestingly, the activation of a synapse can result in the selective movement of mitochondria in the dendrite to a position at the base of the spine of the activated synapse, perhaps to provide the additional energy and Ca^{2+}-buffering necessary to support the more active synapse.

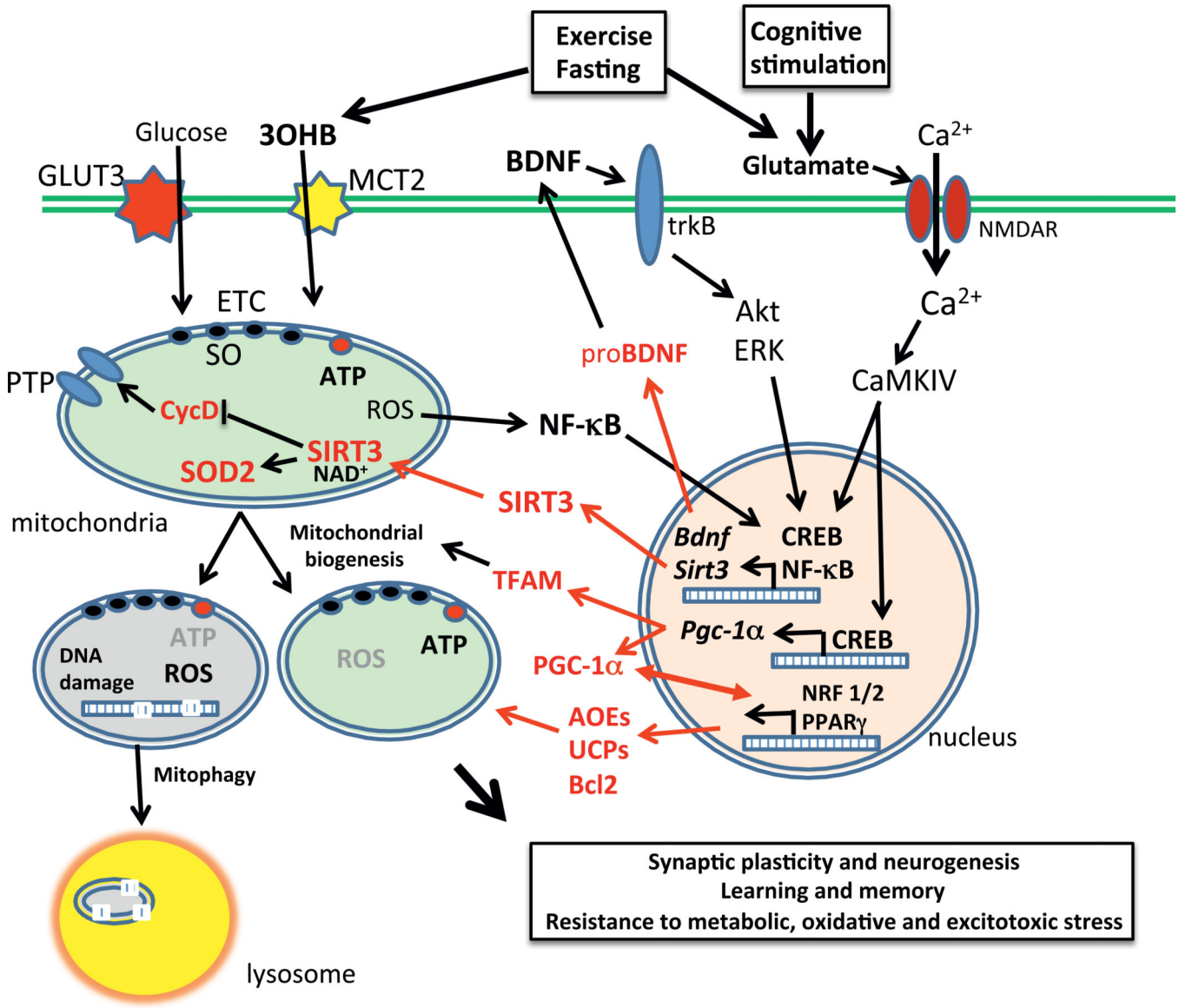

Figure 2. Mechanisms by which physiological bioenergetic challenges improve mitochondrial health and thereby promote neuroplasticity and resistance to brain injury and disease

Activity in neuronal circuits increase in response to exercise, fasting/dietary energy restriction and cognitive challenges. Such excitatory synaptic activity is mediated by the neurotransmitter glutamate, which binds to ionotropic receptors in the plasma membrane resulting in Ca^{2+} influx/ and the activation of kinases such as Ca^{2+} /calmodulin-dependent kinase IV (CaMKIV). CaMKIV in turn activates the transcription factor cyclic AMP response element-binding protein (CREB) which induces the expression of multiple genes that encode proteins that influence mitochondrial function and stress resistance including brain-derived neurotrophic factor (BDNF), sirtuin 3 (SIRT3), peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) and mitochondrial transcription factor A (TFAM). BDNF, which is generated by enzymatic cleavage of the precursor protein proBDNF, is released from neurons and activates specific high affinity cell surface receptors

(trkB) on adjacent neurons or the same neuron. TrkB, in turn engages intracellular signaling pathways that include the kinases Akt and extracellular signal-regulated kinase (ERK) and downstream transcription factors including CREB. SIRT3 is a mitochondrial NAD^+-dependent protein deacetylase that plays important roles in mitochondrial function and stress resistance in neurons. Two protein substrates of SIRT3 in mitochondria are SOD2 and cyclophilin D; deacetylation by SIRT3 increases the enzyme activity of SOD2 to reduce mitochondrial superoxide levels, while deacetylation of cyclophilin D prevents opening of mitochondrial membrane permeability transition pores, thereby preventing apoptosis. PGC-1α and TFAM regulate multiple nuclear (PGC-1α) and mitochondrial (TFAM) genes that are required for mitochondrial biogenesis. PGC-1α also promotes the transcription of genes that are responsive to the nuclear transcription factors nuclear regulatory factors 1 and 2 (NRF1/2), and peroxisome proliferator-activated receptor γ (PPARγ). The latter two transcription factors induce the expression of genes encoding proteins that protect the mitochondria against stress including antioxidant enzymes, uncoupling proteins and anti-apoptotic Bcl-2 family members. Via similar pathways involving synaptic activity and BDNF, exercise, fasting and cognitive stimulation can enhance the clearance of damaged dysfunctional mitochondria via a process called mitophagy in which the damaged mitochondria are degraded in the lysosomes. In the metabolically unchallenged state (i.e., sedentary and fed) neurons utilize mainly glucose as an energy source which is transported into the neurons by the cell surface glucose transporter (GLUT3). By depleting liver glycogen stores and mobilizing fatty acids from adipose cells, fasting and vigorous exercise and also cause the production of the ketone body 3-hydroxybutyrate (3OHB), which is transported into neurons via the activity of monocarboxylic acid transporter 2 (MCT2). 3OHB can induce the production of BDNF in neurons by a mechanism involving mitochondrial ROS production, and activation of the transcription factor NF-κB. Altogether, neuronal circuits respond to intermittent bioenergetic challenges in ways that enhance synaptic plasticity and neurogenesis, improve cognitive function, and increase neuronal resistance to metabolic, oxidative and excitotoxic stresses.

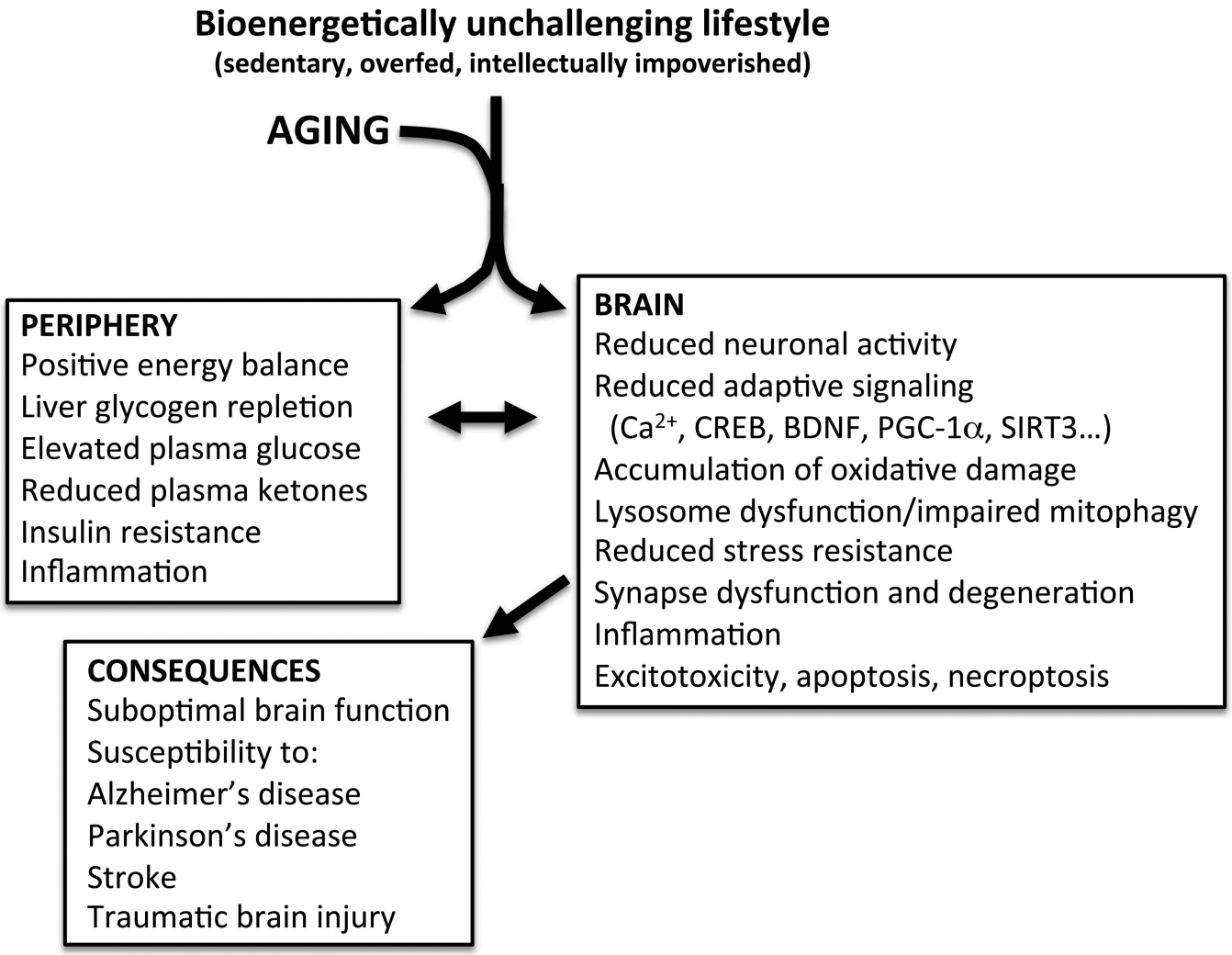

Figure 3. Roles for bioenergetic complacency in age-related decline in brain function and the pathogenesis of neurodegenerative disorders

Unfavorable changes in the body and brain that occur during normal aging (oxidative molecular damage, impaired mitochondrial function, accumulation of molecular waste, chronic inflammation) are amplified by a lifestyle that includes little or no exercise, excessive energy intake and few cognitive challenges. In the periphery such adverse changes include a chronic positive energy balance with elevated plasma glucose levels, low amounts of ketones, insulin resistance and inflammation in many organ systems. In the brain, there is reduced neuronal activity and so reduced levels of activation of signaling pathways involved in neuroplasticity and stress resistance. As a consequence, neurons experience excessive oxidative stress and the accumulation damaged proteins and mitochondria, secondary to impaired function or overload of lysosome and proteasome pathways. As synapses and neurons begin to degenerate, brain tissue inflammation accelerates. Neurons may die by excitotoxicity, apoptosis and/or necroptosis.