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Mini Review: The Relationship between Energy Status and Adult Hippocampal Neurogenesis

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Abstract

The ability to generate new hippocampal neurons throughout adulthood and successfully integrate them into existing neural networks is critical to cognitive function, while disordered regulation of this process results in neurodegenerative or psychiatric disease. Consequently, identifying the molecular mechanisms promoting homeostatic hippocampal neurogenesis in adults is essential to understanding the etiologies of these disorders and developing therapeutic interventions. For example, recent evidence identifies a strong association between metabolic function and adult hippocampal neurogenesis. Hippocampal neural stem cell (NSC) fate dynamically fluctuates with changes in substrate availability and energy status (AMP/ATP and NAD^+/NADH ratios). Furthermore, many metabolic hormones, such as insulin, insulin-like growth factors, and leptin exhibit dual functions also modulating hippocampal neurogenesis and neuron survivability. These diverse metabolic inputs to NSC's from various tissues seemingly suggest the existence of a system in which energy status can finely modulate hippocampal neurogenesis. Supporting this hypothesis, interventions promoting energy balance, such as caloric restriction, intermittent fasting, and exercise, have shown encouraging potential enhancing hippocampal neurogenesis and cognitive function. Overall, there is a clear relationship between whole body energy status, adult hippocampal neurogenesis, and neuron survival; however, the molecular mechanisms underlying this phenomenon are multifaceted. Thus, the aim of this review is to analyze the literature investigating energy status-mediated regulation of adult neurogenesis in the hippocampus,

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highlight the neurocircuitry and intracellular signaling involved, and propose impactful future directions in the field.

Keywords

hippocampus; neurogenesis; metabolism; energy balance; metabolic disease; neurodegenerative disease

1. Introduction:

Adult neurogenesis (AN) is the complex process through which neural stem cells (NSC's) differentiate into newborn neurons and are integrated into existing neural networks [1]. The extent of AN in humans throughout the lifespan is still somewhat debated [2-4]; however, accumulating evidence indicates AN is critical to learning, memory, stress response, and mood regulation [5-7]. AN occurs primarily in two neurogenic niches, the subgranular zone (SGZ) of the dentate gyrus (DG), and the subventricular zone (SVZ) of the lateral ventricles [8]. Furthermore, NSC's are subject to multifaceted regulation determining their fate, including inputs from presynaptic signals, hormones, and neuropeptides, while disturbed function of this neurocircuitry is associated with epilepsy, depression, and neurodegenerative disease [5,9]. Considering the importance of AN to healthy brain function, many studies have focused on deciphering the physiological mechanisms underlying homeostatic AN regulation.

Many circulating factors have dual functions regulating both metabolism and AN, including liver-derived insulin-like growth factor 1 (IGF-1) [10], ghrelin from the stomach [11], leptin from adipose [12], and irisin from skeletal muscle [13]. These diverse signals to NSC's from various metabolically active tissues seemingly provide an ideal system in which energy status can dynamically and finely regulate neurogenesis. Supporting this hypothesis, epidemiological studies have revealed a strong association between metabolic disorders, cognitive impairment, and neurodegenerative diseases [14,15]. Recently, caloric restriction, intermittent fasting, and physical activity have been shown to stimulate hippocampal AN and improve neuronal survival by increasing circulating neurotrophic factors, bolstering stress resistance, improving autophagy, and modulating the transcriptome [16-18]. As a result, these approaches have demonstrated promising potential in improving cognitive function and reducing the risk/severity of psychiatric and neurodegenerative disorders [16-18].

Excessive neuronal differentiation can also be detrimental due to inadequate NSC self-renewal and NSC exhaustion. For example, the benefits of energy deficit to AN exhibit a negative parabolic relationship, where excessive caloric restriction or chronic energy surplus both impair AN and neuronal survivability (Figure 1) [16-18]. This phenomenon is referred to as hormesis; during which, a moderate amount of something, such as caloric restriction, produces favorable effects; however, excessive amounts have deleterious effects. Hormesis is a recurring theme when examining the connections between energy status and AN.

Overall, there is a clear relationship between whole body energy status, AN, and newborn neuron survival, although the molecular mechanisms underlying this phenomenon are

incompletely understood. The following review analyzes the literature investigating energy status-mediated regulation of AN in the hippocampus, highlights the neurocircuitry and intracellular signaling involved, and proposes impactful future directions in the field.

2. Adult Hippocampal Neurogenesis and Circuitry:

In adult humans, 700 new neurons are formed in each hippocampus daily, accounting for an annual turnover of approximately 1.75% [3]. These newborn neurons originate from self-renewing and multipotent NSC's in the SGZ between the granule cell (GC) layer and the hilus. Briefly, when radial NSC's transition from the quiescent to activated state, they commit to self-renewal [19], gliogenesis [20], or neurogenesis [4,20]. Rodent studies reveal that within the first week of neuronal fate specification, radial NSC's become Type II intermediate progenitors and then Type III neuroblasts, which are transition cells to postmitotic immature neurons [21]. In week 2, immature granule cells extend dendrites to the molecular layer and migrate to the GC layer [21]. During these first couple weeks, gamma aminobutyric acid (GABA) uniquely elicits depolarizing effects on NSC's and immature neurons due to high expression of the NKCC1 $Na^+/K^+/Cl^-$ cotransporter maintaining high intracellular Cl^- concentrations [22]. Consequently, tonic GABA released from local parvalbumin interneurons and synaptic GABAergic inputs have been shown to be driving factors to progenitor differentiation and neuroblast integration [22,23].

Two to three weeks after activation, newborn neurons undergo glutamatergic and synaptic integration [24,25]. While approximately 50% of the newborn neurons die during integration, the remaining send primarily glutamatergic outputs to the CA3 region and the hilus to form synapses with hilar interneurons, mossy cells, and CA3 pyramidal cells [26]. Additionally, the immature neurons begin to receive presynaptic afferents from the cortex and are capable of generating action potentials [1]. During week 3, GABA begins to elicit hyperpolarizing effects on granule cells due to reduced NKCC1 expression and increased KCC2 K^+/Cl^- cotransporter expression maintaining low intracellular Cl^- concentrations [27]. Finally, weeks 4-6 of newborn neuron are characterized by increased excitability and plasticity [28,29], during which, optogenetic inhibition of these neurons impairs spatial and contextual learning [28,29].

Ultimately, it takes approximately 8 weeks for newborn hippocampal neurons to reach maturity in rodents [30]. Functional DG neurons receive sensory input from the perforant path of the entorhinal cortex and deliver excitatory signals to the CA3 hippocampal region via non-myelinated mossy fibers [31]. This intra-hippocampal circuitry, termed the "trisynaptic circuit" then sends long-distance projections to a plethora of brain regions including the medial septum [32], entorhinal cortex [32], prefrontal cortex [33], striatum [34], septum [35], amygdala [36], and insular cortex [36]. Interference with these connections significantly impairs performance in a multitude of learning-related tasks [37,38].

3. Metabolic Characteristics Drive NSC Fate:

Quiescent NSC's rely primarily on glycolysis [39] and fatty acid oxidation [40], while active NSC's are characterized by increased mitochondrial oxidative phosphorylation and lipogenesis (Figure 2) [41]. These distinct characteristics are largely dictated by metabolic gene signatures, which are critical to their fate [42]. For example, disturbed lipogenesis in mice via NSC-specific fatty acid synthase deletion promotes NSC quiescence and impairs AN [43]. Furthermore, NSC quiescence appears to be regulated by genes related to fat metabolism, such as Spot14, which reduces malonyl CoA availability, and subsequently reduces lipogenic substrate and promotes fatty acid oxidation [43]. On the contrary, dysfunction of fatty acid oxidation genes, such as Trimethyllysine Hydroxylase Epsilon, Carnitine Palmitoyltransferase I, or PPARδ, promotes NSC differentiation, but sacrifices renewal and results in NSC pool depletion [44,45]. These studies demonstrate the importance of homeostatic lipid metabolism in NSC's to healthy AN and may provide insight into the relationship between dyslipidemia observed in metabolic disease states and neurodegenerative disorders.

Mitochondrial function in NSC's is also critical to their differentiation and survival [46]. Ablation of mitochondrial transcription factor A in NSC's impairs AN, while treatment with the mitochondrial function enhancer piracetam has opposite effects [46]. Mechanistically, disrupted mitochondrial function in the hippocampus increases reactive oxygen species (ROS), which increases activity of the transcription factor nuclear factor erythroid 2–related factor 2 (nrf2) [47]. Nrf2 then inhibits the self-renewal-favoring Notch signaling pathway, resulting in aberrant differentiation and NSC pool depletion [47]. Overall, both mitochondrial function and substrate metabolism are key driving factors in NSC fate, and manipulation of these metabolic phenomena has been a promising focus of research into homeostatic AN. The following sections overview how changes in energy status, through dietary interventions or physical activity, can alter the metabolic environment and subsequently modulate AN.

4. Overnutrition and AN:

4.1. Metabolic disorders are associated with impaired AN

Epidemiological studies have established a strong relationship between metabolic disease states, such as obesity and diabetes, and neurodegenerative pathologies [14,15]. Additionally, many studies have used high-fat-diet (HFD), leptin-deficient, or other genetic rodent models of metabolic disease and observed impaired AN and accelerated age-related cognitive deficits [48-62]. Even short term high fat or palmitic acid rich diets (2-4 weeks) impair AN, independent from changes in body weight, implicating lipotoxicity as an important factor in HFD-mediated hippocampal pathologies [58,63]. Particularly, saturated fats have been shown to have greater detrimental effects than unsaturated [61,64].

Despite the clear relationship between metabolic disease states and impaired AN, the mechanisms underlying this phenomenon are complex. While total NSC's remain unchanged, most studies observe diminished proliferative capacity in obese/diabetic rodents [48,54,57,62,63]; however, in some cases hyperproliferation is observed [50,51,53]. The

discrepancies in these findings may be due to differences in metabolic disease models used, which vary in onset and cause of metabolic dysfunction, as well as animal age during observations. More consistently, models of metabolic disease exhibit increased apoptosis [49,53,59], decreased neurotrophic factors [55,56], and decreased synaptic complexity in the DG and CA1 regions of the hippocampus [52,60].

4.2. Hormonal resistances likely contribute to metabolic disease related impairments in AN

Considering metabolic disease states often are accompanied by insulin resistance [14], insensitivity to insulin may play a causal role in metabolic disease-related AN impairments. As a result, focus has been put into the connection between insulin resistance and neurodegenerative diseases, even sometimes referring to Alzheimer's Disease as a "Type 3 Diabetes" [14]. For example, studies in cell culture and rodent models have demonstrated that insulin and insulin-like growth factors 1 and 2 (IGF1 and IGF2) are critical to hippocampal AN [10,65-68], memory [69,70], learning [69,70], and long term potentiation [70]. Insulin, IGF1, and IGF2 directly stimulate hippocampal NSC proliferation and neuronal differentiation via multiple downstream signaling pathways including PI3kinase→AKT and MAPKK signaling [10,65-70]. For example, insulin-mediated PI3kinase→AKT signaling inhibits quiescence-inducing forkhead box O (FOXO) transcriptional activity [71]. Additionally, insulin activates mammalian target of rapamycin (mTOR) to negatively regulate NSC autophagy and stimulate AN [72-75]. Interestingly, glycogen synthase kinase 3 (GSK3) is inhibited by insulin, but GSK3α and GSK3β both promote AN by negatively regulating β catenin and Notch1 transcription of hairy and enhancer of Split1 (hes-1). Despite being susceptible to negative regulation by insulin, C/EBPβ and GSK3β are activated specifically by IGF2 and IGFR2 signaling to stimulate AN [70], while genetic knockdown of GSK3 results in hyperproliferation and reduced neuronal differentiation [70]. These findings possibly demonstrate the existence of GSK3 hormesis, during which, a balance between insulin-mediated GSK3 inhibition and IGF2-mediated GSK3 activation is critical to homeostatic AN.

Insensitivity to the anorexigenic adipokine leptin also develops in metabolic disease states [76], and leptin protects hippocampal neurons from neurotrophic factor withdrawal, excitotoxic damage, and oxidative stress [77]. Via PI3kinase→AKT and janus kinase (JAK) →signal transducer and activator of transcription 3 (STAT3) signaling, leptin directly stimulates NSC proliferation and AN [12]. Through similar pathways, leptin increases expression of antioxidative and antiapoptotic genes superoxide dismutase (SOD) and bclxl, respectively, and stabilizes mitochondrial membrane potential [77]. Lastly, leptin increases NMDA receptor expression and calcium conductance in the hippocampus via MAPK, PI3K, and src kinase signaling mechanisms [78].

4.3. Other contributors to metabolic-disease related impairments in AN

Increased ROS and inflammatory cytokines also contribute to many metabolic-disease related hippocampal pathologies [59,63,79]. Overnutrition leads to increases in tumor-necrosis factor α (TNFα) and IκB/NF-κB -mediated hippocampal apoptosis [59,80], while increases in ROS result in oxidative damage, reduced proliferative capacity, and depleted

NSC pool [47,55,81]. There are also likely many other factors contributing to impaired AN in metabolic disease states. Considering the increasing prevalence of metabolic disease today, and the clear connection to disordered hippocampal AN, determining the causal relationship between the two is critical. For example, perturbations in gut microbiota and subsequent effects on inflammation and AN is an emerging topic of research [82]. Additionally, since NSC fate is driven by specific substrate metabolism characteristics, hyperglycemia and dyslipidemia observed in metabolic disease states likely have direct impacts on AN [59,83,84]. Altering substrate availability in the neurogenic niche likely has drastic effects on metabolic flux, NSC fate, and hippocampal cell health, providing an interesting direction for future research.

4.4. Summary of overnutrition and AN

Those with diabetes or obesity have a greater risk of neurodegenerative disease and cognitive decline [14,15]; however, there remain many questions regarding the causal relationship between metabolic disease and disordered AN. There are mixed reports on the effects of energy surplus and metabolic disease on NSC proliferation, but studies consistently observe even acute overnutrition to elicit increased apoptosis [49,53,59], decreased neurotrophic factors [55,56], decreased synaptic complexity [52,60], and impaired AN in the hippocampus [48,54,57,62,63]. Mechanistically, diminished function of pro-neurogenic hormones such as insulin [71-75], IGF1/2 [70], and leptin [12] likely are directly related to the metabolic disease-related hippocampal pathologies (Figure 3). Increased cell damage from ROS and inflammation are also likely involved [59,63,79]; however, etiology of AN pathologies is multifaceted and more mechanistic insights are needed. Overall, despite increased awareness and scientific advancements, diabetes and obesity remain unrelenting epidemics. As a result, continued research into interventions promoting energy homeostasis, such as through diet and physical activity, is increasingly imperative.

5. Caloric Restriction (CR) and AN:

5.1. Moderate CR improves AN and cognitive function

In humans, lifelong caloric intake positively correlates with incidence of neurodegenerative disease, and accumulating evidence suggests CR can improve cognitive function [85]. For example, one study demonstrated 30% CR for 3 months in older adults improves verbal memory [64], while another observed improvements in pattern separation after only 4 weeks CR (500kcal/day) [86]. These encouraging findings suggest a potential ability of CR to promote homeostatic AN in humans, a hypothesis that has been supported by many studies using animal models.

Briefly, 10-40% CR improves hippocampal AN [87,88], cognitive function [56,64,89,90], neuronal survivability [91,92], ROS buffering [93], autophagy [72], and anti-inflammatory capacity [87] in rodents and primates. Moreover, studies utilizing IF (alternating days of fasting and ad libitum food intake) demonstrate that even isocaloric intermittent CR elicits neurogenic effects independent from changes in total caloric intake or weight loss [86,94-98]. While the mechanisms underlying CR/IF-mediated neurogenesis are incompletely understood, in most cases increases in brain-derived neurotrophic factor

(BDNF) [91,92,97,99-101], glial-derived neurotrophic factor (GDNF) [99], neurotrophin-3 [101], and/or fibroblast growth factor 2 [97] are observed, which all directly stimulate hippocampal AN. Particularly, the beneficial effects of CR on NSC proliferation are blunted in BDNF knockdown mice, highlighting the importance of this neurotrophic factor [100].

5.2. CR improves stress-resistance in hippocampal NSC's via mTOR, sirtuins, and CREB

CR/IF and low substrate availability may pose a minor hormetic stress to NSC's, and subsequently prime the neurogenic niche to better respond to future stressors [93]. For example, stress response mediators like heat shock protein 70 and glucose regulated protein 78 are elevated in response to CR, which protect NSC's from excitotoxic and oxidative damage [93]. Low energy status is also characterized by low ATP and high AMP levels, and high intracellular AMP:ATP ratios improve autophagy by stimulating AMPK activity, subsequently inhibiting mTOR, and ultimately relieving inhibition of autophagy related genes [72,74]. Although homeostatic mTOR activity is important to AN (Section 4.2), overactive mTOR sacrifices NSC renewal, results in NSC pool depletion, increases ROS production, and impairs autophagy [74].

Intracellular reductions in NADH and subsequent increases in NAD^+ are also consequences of low energy status. Sirtuins are deacetylases that sense these elevations in NAD^+ and exhibit multiple pro-neurogenic functions [102-104], providing another mechanism through which the hippocampus can finely couple energy status to AN. Hippocampal SIRT1 expression enhances stress-resistance by deacetylating stress-related p53, NFκB, and FOXO proteins, which improves cell survival, inflammation, and microglia development [102-104]. Consequently, CR-mediated SIRT1 activation promotes dendritic development, NSC activation, and neuronal differentiation [102-104]. Mechanistically, SIRT1 activates cyclic AMP response element binding protein (CREB) signaling to induce stress resistance and hippocampal AN [105,106]. CREB is also activated by AMPK, calcium/calmodulin dependent protein kinases, protein kinase A, and protein kinase C, further coupling energy status to hippocampal AN regulation. Interestingly, the popular anti-diabetic drug metformin targets AMPK→PKC→CREB signaling and has been shown to promote both AN and NSC renewal in adult mice [107,108]. Despite this, long term metformin treatment in humans is associated with cognitive impairment and increased neurodegenerative disease risk, possibly demonstrating metformin hormesis [109,110]. These findings are further complicated by another study observing CREB-deficient mice have enhanced hippocampal AN [111].

The molecular mechanisms facilitating SIRT1 and CREB function regarding AN are dynamic in response to energy status and substrate availability, possibly explaining mixed findings in the literature [112]. While studies demonstrating the AN-inducing effects of SIRT1 are encouraging [102-104], other studies have observed SIRT1 activation to have opposite effects [113,114] or to promote glial differentiation [115]. These discrepancies are likely due to fluctuating functions of SIRT1 and CREB with changes in substrate availability. SIRT1 and CREB increase hes-1 expression to facilitate NSC self-renewal in hypoglycemic environments, but drive AN in hyperglycemic environments [112]. While these regulatory phenomena remain incompletely understood, they highlight how subtle

changes in energy status and substrate availability in the neurogenic niche drastically change NSC fate and hippocampal health.

5.4. Malnutrition has detrimental effects on AN

While modest CR/IF elicits encouraging effects on AN and cognitive function, adequate energy and nutrient availability is essential to homeostatic AN. Some studies have shown CR/IF can lead to overactive SIRT1, anxiety, reduced BDNF levels, and impaired DG neurogenesis, especially in younger rodent models [56,116,117]. In extreme cases, IF even can result in premature death due to hypoglycemia in rodent amyloid precursor protein mutant models of Alzheimer's Disease [118]. These studies highlight the existence of CR/IF hormesis, by underscoring the detrimental effects of insufficient energy intake and excessive cellular stress to hippocampal AN. They also suggest that energy balance, perhaps with energy deficit in moderation to prime stress responses, is likely the optimal strategy for homeostatic AN. For example, while excessive fat intake is harmful to AN (Section 4.1), inadequate intake of certain fats, such as omega 3 fatty acids, is equally as detrimental [119]. In fact, increased intake of omega 3 fatty acids is associated with attenuated cognitive decline in older populations, suggesting quality and nutrient content of energy intake is also important [120]. Overall, while IF/CR studies observe promising evidence promoting AN, caution should be taken to ensure adequate baseline intake of critical nutrients.

5.5. Summary of CR and AN

In summary, studies utilizing 10-40% CR, and even isocaloric IF, promote AN and cell survival in the hippocampus. While these dietary strategies may have indirect benefits due to weight loss, they also directly enhance ROS buffering capacities, autophagy, anti-inflammatory mechanisms, and neurotrophic factor activity. Additionally, they may elicit many of their beneficial effects by providing an acute stress to NSC's, and subsequently improving responses to future stressors. Predominant molecular mechanisms underlying CR/IF-mediated AN include increased BDNF activity, sirtuin expression, and CREB signaling, as well as negative regulation of mTOR (Figure 4). Notably, excessive CR/IF can have deleterious effects on AN, likely due to inadequate energy intake, and increased cellular stress.

6. Exercise and AN:

6.1. Aerobic exercise is neuroprotective and promotes AN

Aerobic exercise is another common method of creating energy deficit that has potent health benefits involving diverse physiological functions. For example, overwhelming evidence indicates aerobic exercise improves cognitive function, while decreasing risk of neurodegenerative disease [121-125]. Furthermore, aerobic exercise increases NSC proliferation, neuronal differentiation, newborn neuron survival, synaptic plasticity, and dendritic spine growth in healthy [126-129], aged [126,130,131], obese/diabetic [121], Alzheimer's Disease [132-134], Parkinson's [135], and Schizophrenia animal models [125]. While the benefits of exercise are well-documented, the mechanisms through which it promotes AN and hippocampal health are diverse. Aerobic exercise improves delivery of nutrients and energy substrates to the neurogenic niche via enhanced angiogenesis and

increased blood-brain-barrier (BBB) permeability [136-138]. Particularly, the improved delivery of oxygen in response to exercise training prevents activation of anti-neurogenic hypoxia-inducible factors (HIF's) [139]. Inadequate oxygen delivery stimulates HIF's, which increase glycolytic genes to favor NSC quiescence and stimulate Notch→hes signaling to favor NSC renewal rather than neurogenesis [139].

Similar to CR hormesis, the acute stress of exercise also elicits a plethora of neuroprotective effects improving health of NSC's and survivability of newborn neurons. Anti-inflammatory effects and improved immune function are demonstrated by reductions in interleukin 1β and TNF-α, as well as increases in IL6, IL10, interferon gamma, and macrophage inflammatory protein 1-alpha [124,140,141]. Anti-oxidative effects include increased anti-oxidative proteins like thioredoxin, superoxide dismutase, glutathione reductase, glutathione peroxidase, and glutathione transferase [121]. Additionally, one study determined β2 adrenergic signaling was essential to exercise-mediated upregulation of some of these anti oxidative proteins [121].

6.2. Aerobic exercise increases activity of neurotrophic factors in the hippocampus

Aerobic exercise also directly promotes hippocampal AN and synaptic plasticity through expression of various factors like BDNF, GDNF, synaptophysin, and postsynaptic density protein 95 [121,135,142]. Acute increases in core temperature after exercise may also directly stimulate VEGF and hippocampal AN [143]. Specifically, an important hippocampal signaling axis involving peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α)-mediated transcription of fibronectin type III domain-containing protein 5 (FNDC5) and subsequent BDNF activity has been identified in the process of exercise-induced AN [142,144]. Knockout or pharmacological inhibition of PGC1α or the BDNF receptor tropomyosin receptor kinase B (TrkB), abolishes the hippocampal benefits of exercise [142,144]. Furthermore, FNDC5 facilitates release of the myokine irisin during exercise, which, through unknown receptors, promotes synaptic plasticity, increases AN, and improves cognitive function [13,145].

As mentioned previously (Section 4.2), impaired leptin and insulin sensitivity are hallmarks of metabolic disease, and preservation of these hormones' functions is critical to hippocampal AN. Aerobic exercise training increases leptin concentrations and leptin receptor expression in the hippocampus, while leptin-deficient mice experience resistances to exercise's cognitive benefits [146]. Aerobic exercise also improves insulin/IGF1 signaling, which has been shown to directly stimulate DG AN, increase BDNF, and improve cognitive function [147,148]. However, the exercise-mediated insulin signaling mechanisms are complicated and have produced mixed findings in the DG. For example, 10 days voluntary wheel running increases phosphorylation of AKT which results in inhibitory phosphorylation of GSK3β and FOXO1 to promote NSC self-renewal and neuron survivability [149]. Conversely, another study demonstrates 30 days voluntary wheel running stimulates DG AN by decreasing inhibitory phosphorylation of GSK3β, independent from insulin signaling and possibly via dopamine→cAMP→PKA signaling [148]. Notably, these two studies utilized different experimental timelines, and insulin-dependent and insulin-independent effects of exercise on GSK3β activity are intriguing. These results support the

hypothesis of GSK3β hormesis and suggest the existence of an evolutionarily beneficial mechanism promoting homeostatic AN post-exercise. More specifically, insulin mediated inhibition of GSK3β post-exercise may be an essential negative feedback mechanism to prevent aberrant GSK3β-mediated AN and NSC depletion. Overall, these studies reveal exercise simultaneously promotes insulin-dependent hippocampal NSC survival and insulin-independent, GSK3β-mediated, AN.

6.3. Aerobic exercise modulates diverse micro-RNA's (miRNA's)

Recent evidence suggests a potent ability of aerobic exercise to modulate expression of diverse miRNA's to alter hippocampal gene expression. These miRNA-induced gene expression changes favor AN, NSC proliferation, and cell survival through regulation of various pathways including IP3, insulin, and NFκB signaling [150-152]. Improta-Caria et al. reviews this emerging research focus in detail, and highlights commonalities among physiological functions of miRNA's subject to regulation by exercise [153]. Prominent physiological functions associated with exercise-mediated miRNA changes include: fatty acid metabolism, ubiquitin-mediated proteolysis, endocytosis, cell growth and division, apoptosis, p53 signaling, insulin signaling, endoplasmic reticulum protein processing, and transforming growth factor β signaling [153]. Moreover, that review identifies many specific miRNA's that are pathologically altered in Alzheimer's Disease, but may be rescued in response to exercise, therefore, demonstrating promising therapeutic potential for exercise in Alzheimer's Disease at the post-transcriptional level [153].

6.4. Summary of exercise and AN

Convincing evidence demonstrates exercise promotes hippocampal AN and neuron survivability to enhance cognitive function. In response to exercise, increased angiogenesis and BBB permeability facilitate adequate nutrient and energy substrate availability for the neurogenic niche, while improved antioxidative, immune, and anti-inflammatory capacities enhance newborn neuron health (Figure 5). Aerobic exercise also increases function of many neurotrophic factors and other neurogenic proteins including BDNF, GDNF, irisin, insulin/IGF's, leptin, and GSK3β. Additionally, studies have identified a potent ability of exercise to modulate gene expression through regulation of various miRNA's.

Overall, the neurogenic effects of exercise are well-documented; however, further research is necessary to comprehensively map out the complex, multifaceted physiological mechanisms involved. Many additional molecular mediators have been identified (Figure 5) including: 1) vascular endothelial growth factor [154], 2) Uncoupling protein 2 [155], 3) Bone morphogenic protein 4 (BMP4)→SMAD1/5/8 transcriptional activity [156,157], 4) Adiponectin→AMPK signaling [158], and 5) Lactate [159]. Moreover, while most studies have focused solely on aerobic exercise, recent evidence indicates resistance exercise may elicit similar hippocampal benefits [160,161]. In summary, there are clear benefits of exercise to hippocampal AN, and further identification of its many complicated mechanisms of action could be valuable to designing exercise mimetics in the future.

7. Future Directions: Hippocampal – Hypothalamic Connections:

Considering the accumulating evidence suggesting hippocampal AN dynamically fluctuates with energy status, the hypothalamus may be an intriguing brain region for future research. The hypothalamus is a critical control center regulating energy balance and substrate metabolism [162], and many hormones/neuropeptides involved in hippocampal AN exhibit dual functions regulating modulating hypothalamic neuron activity to regulate metabolism. For example, while BDNF, insulin, leptin, and cholecystokinin, stimulate hippocampal AN, they also regulate hypothalamic neurons to decrease food intake, increase energy expenditure, and reduce circulating glucose levels [163-165]. Surprisingly, the orexigenic hormone ghrelin also stimulates hippocampal AN via PI3kinase→AKT, ERK, and STAT3 signaling [166]. These studies imply the existence of a regulatory mechanism between energy status and hippocampal AN, in which both hunger and satiety hormones promote AN.

The synaptic connections between hypothalamic and hippocampal neurons remain relatively underexplored, although prominent neuron populations are co-expressed in these regions. For example, neuropeptide Y/agouti-related peptide (NPY/AgRP) -expressing neurons in the arcuate nucleus (ARC) of the hypothalamus stimulate food intake and reduce energy expenditure, while NPY receptors (Y1 receptors) are also expressed in the hippocampus and promote DG AN [167,168]. A recent report even observed optogenic stimulation of ARC NPY/AgRP neurons to improve memory in mice [169]. Furthermore in the hypothalamus, pro-opiomelanocortin-expressing (POMC) neurons synapse with melanocortin 4 receptor (MC4R)-expressing neurons to induce satiety, while intra-hippocampal POMC→MC4R circuitry regulates synaptic plasticity and cognitive function in mouse models of Alzheimer's Disease [170].

Overall, commonalities in regulatory hormones/neuropeptides in the hippocampus and the hypothalamus suggest the existence of a complex circuitry between these regions. Synaptic connections between the hypothalamus and the hippocampus could allow for nutrient/energy sensing by hypothalamic neurons bordering the CSF in the third ventricle and subsequent communication with the hippocampus to finely regulate neurogenesis. Further complicating this system is the recently discovered prevalence of neurogenesis in the hypothalamus, which is critical to homeostatic metabolic regulation and therefore indirectly important to hippocampal AN [171]. Regulation of hypothalamic neurogenesis is a controversial topic, but studies suggest, similar to in the hippocampus, BDNF and exercise promote this process, while chronic overnutrition is detrimental [172-174]. Thus, the hippocampus and hypothalamus are likely intricately connected regarding function, regulation, and neurocircuitry; however, this concept remains relatively unexplored.

8. Closing Remarks:

Hippocampal AN is finely modulated by changes in substrate availability, nutrient access, and metabolic hormones, establishing a connection between metabolic and cognitive health. Consequently, metabolic disease and chronic overnutrition are highly associated with increased neurodegenerative disease risk, highlighting the value of metabolic interventions

promoting homeostatic hippocampal AN. Promising dietary interventions include moderate CR and IF, which not only improve metabolic function, but directly promote homeostatic hippocampal AN. Exercise has also demonstrated a potent capacity to promote health AN, suggesting a combination between dietary and exercise interventions could yield optimal results. Overall, these interventions yield encouraging neurogenic effects; however, the mechanisms underlying their effects remain incompletely understood. Continued research into the complex neurocircuitry connecting energy status and hippocampal AN is critical to establishing exercise and diet mimetics as therapeutic tools for metabolic and neurodegenerative diseases.

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ABBREVIATIONS:

AN	adult neurogenesis
NSC	neural stem cell
GC	granule cell
SGZ	subgranular zone
SVZ	subventricular zone
BBB	blood-brain barrier
IGF	insulin-like growth factor
GABA	gamma aminobutyric acid
DG	dentate gyrus
nrf2	nuclear factor erythroid 2–related factor 2
HFD	high fat diet
MAPKK	mitogen-activated protein kinase kinase
GSK3	glycogen synthase kinase 3
C/EBP	CCAAT-enhancer-binding proteins
FOXO	forkhead box O
SOD	superoxide dismutase
CR	caloric restriction
IF	intermittent fasting
BDNF	brain-derived neurotrophic factor

GDNF	glial-derived neurotrophic factor
TNFα	tumor necrosis factor α
ROS	reactive oxygen species
CREB	cyclic AMP response element binding protein
HIF1α	hypoxia-inducible factor α
PGC1α	proliferator-activated receptor gamma coactivator 1-alpha
FNDC5	fibronectin type III domain-containing protein 5
TrkB	tropomyosin receptor kinase B
NPY/AgRP	neuropeptide Y/agouti-related peptide
POMC	proopiomelanocortin
ARC	arcuate nucleus
ERK	extracellular-regulate kinase
JAK	janus kinase
STAT3	signal transducer and activator of transcription 3
hes-1	hairy and enhancer of Split1
mTOR	mammalian target of rapamycin
miRNA	micro RNA
MC4R	melanocortin 4 receptor
CSF	cerebrospinal fluid

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HIGHLIGHTS:

- Specific metabolic characteristics drive neural stem cell fate
- Circulating metabolic factors couple energy status with hippocampal neurogenesis
- Overnutrition perturbs hippocampal neurogenesis and exacerbates apoptosis
- Caloric restriction and exercise promote homeostatic neurogenesis

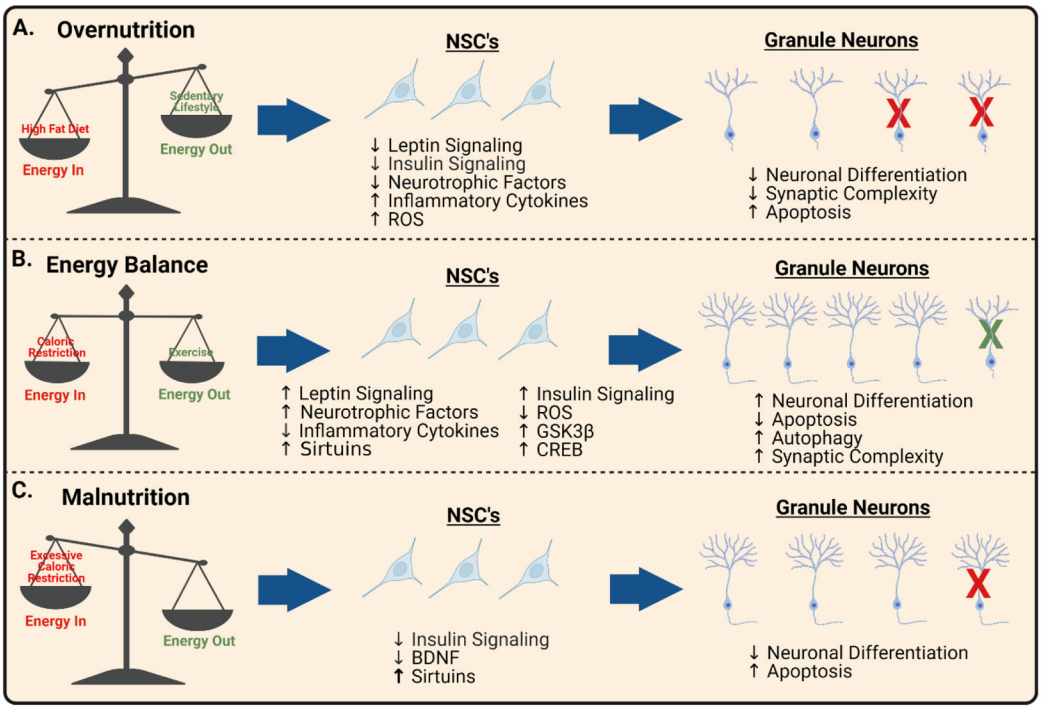

Figure 1. Energy Balance and Hippocampal Neurogenesis.

(A) Overnutrition due to excess caloric intake, lipotoxicity, and/or sedentary lifestyle results in decreased neuronal differentiation, reduced synaptic complexity, and increased apoptosis (red X's) in hippocampal NSC's. These impairments in AN are, in part, due to leptin and insulin resistance, decreased neurotrophic factors, increased inflammatory cytokines, and increased oxidative damage in the neurogenic niche. (B) Energy balance is promoted by moderate caloric restriction and physical exercise, resulting in augmented neuronal differentiation, increased autophagy (green X's), improved synaptic complexity, and reduced apoptosis in newborn hippocampal neurons. These neurogenic benefits are mediated, in part, due to increased leptin and insulin signaling, neurotrophic factors, stress resistance, sirtuins, GSK3β signaling, and CREB signaling. (C) Malnutrition due to excessive caloric restriction or poor nutrient intake results in inadequate substrate availability, reduced neuronal differentiation, and increased apoptosis (red X's) in the hippocampus. These impairments in AN are, in part, due to reduced insulin signaling, decreased BDNF, overactive sirtuins, and excessive cellular stress. Created with BioRender.com.

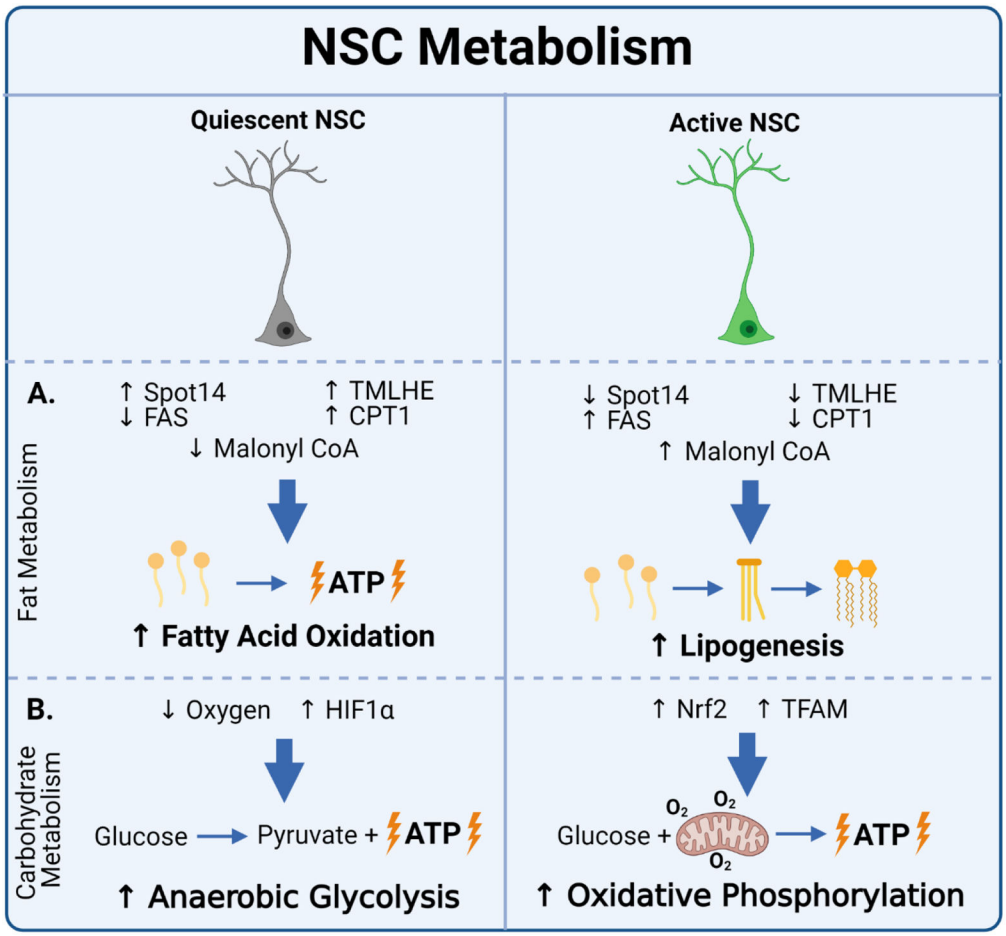

Figure 2. NSC Metabolism.

(A) Fat metabolism: Quiescent NSC's exhibit increased fatty acid oxidation (characterized by increased Spot14 expression, TMLHE expression, and CPT1 activity, and decreased FAS expression and malonyl CoA levels). Active NSC's exhibit increased lipogenesis (characterized by decreased Spot14 expression, TMLHE expression, and CPT1 activity, and increased FAS expression and malonyl CoA levels). Spot14 = thyroid hormone response protein 14; TMLHE = trimethyllysine hydroxylase epsilon; CPT1 = Carnitine palmitoyltransferase I; FAS = fatty acid synthase;. (B) Carbohydrate metabolism: Quiescent NSC's regulated by HIF1α rely primarily on anaerobic glycolysis. Active NSC's exhibit primarily oxidative phosphorylation, characterized by elevated TFAM and NRF2 expression. HIF1α = hypoxia-inducible factor 1α; Nrf2 = nuclear response factor 2; TFAM = mitochondrial transcription factor A. Created with BioRender.com.

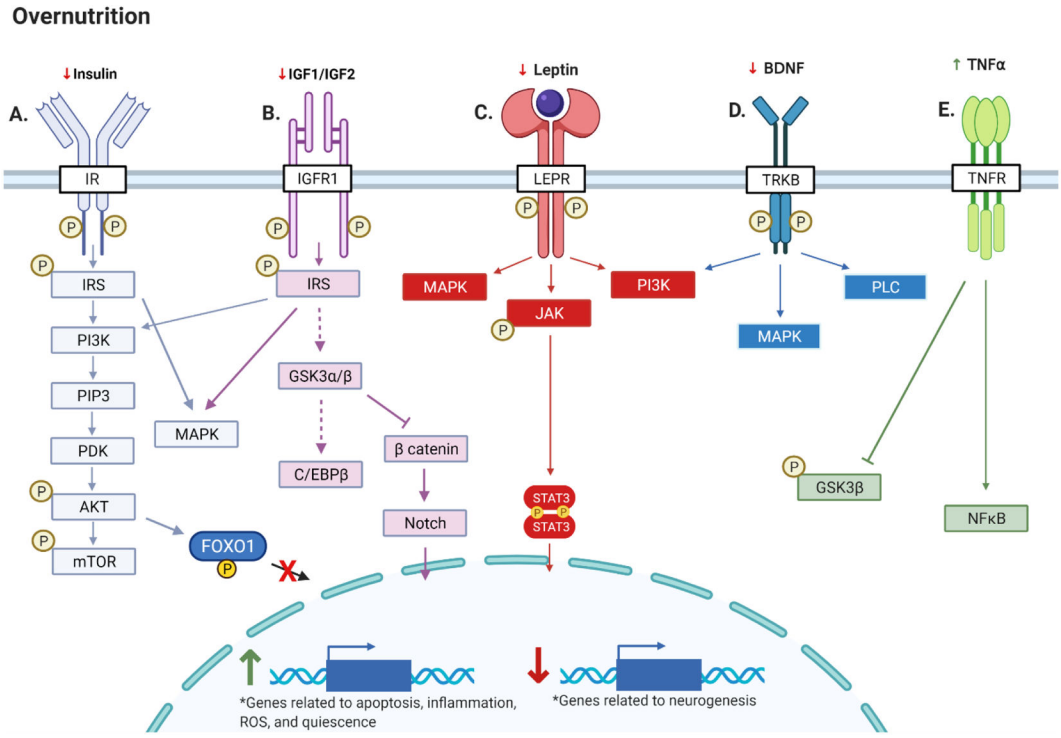

Figure 3. Overnutrition and AN.

Chronic energy surplus: (A) Results in resistance to insulin, which decreases mTOR activity and increases FOXO1 activity to reduce AN and promote quiescence, respectively; (B) Results in resistance to IGF1 and IGF2, which decreases GSK3β signaling and increases Notch signaling, to decrease AN and promote NSC renewal, respectively; (C) Results in resistance to leptin and decreased downstream neurogenic, anti oxidative, and antiapoptotic JAK→STAT3 signaling; (D) Decreases concentrations and activity of BDNF; (E) Increases TNFα, inflammatory pathways, and inhibition of GSK3β. Created with BioRender.com.

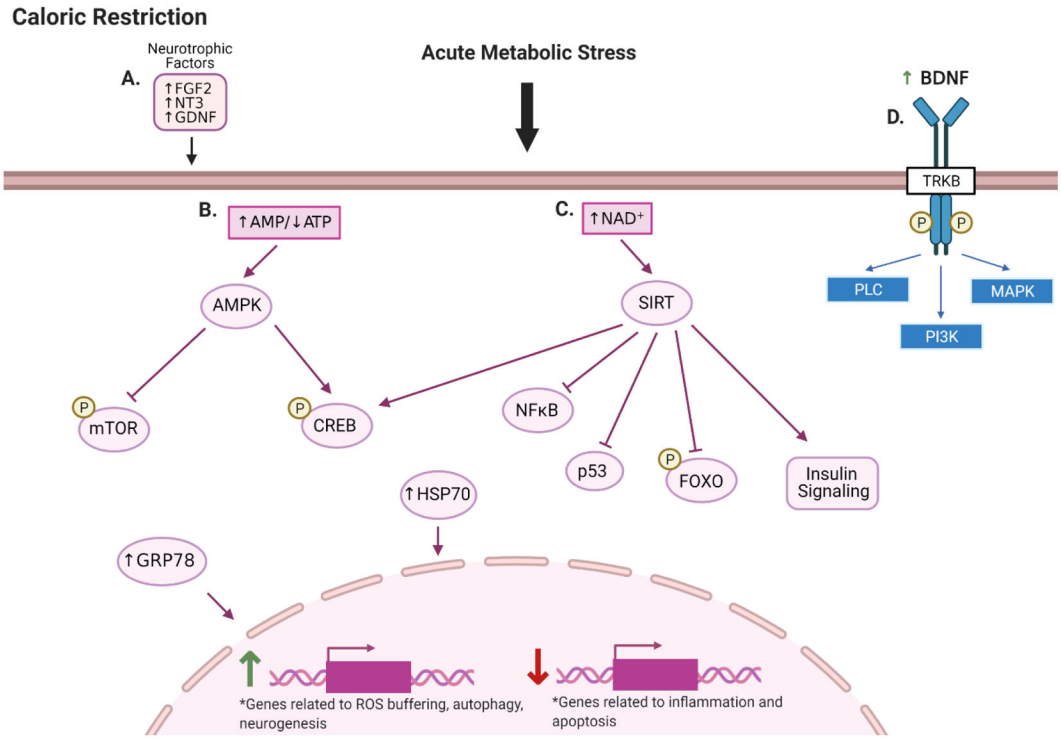

Figure 4. CR and AN.

Moderate caloric restriction: (A) Increases expression of neurotrophic factors; (B) Provides acute metabolic stress increasing the AMP/ATP ratio and activating AMPK. AMPK inhibits mTOR to promote autophagy and preserve the NSC pool and activates CREB which elicits neurogenic and neuroprotective effects. (C) Increases NAD^+ levels and activates sirtuins. Sirtuins deacetylate and inhibit inflammatory, apoptotic, and quiescent signaling, and improve insulin signaling. (D) BDNF and its receptor TrkB are particularly important to CR-mediated AN. Created with BioRender.com.

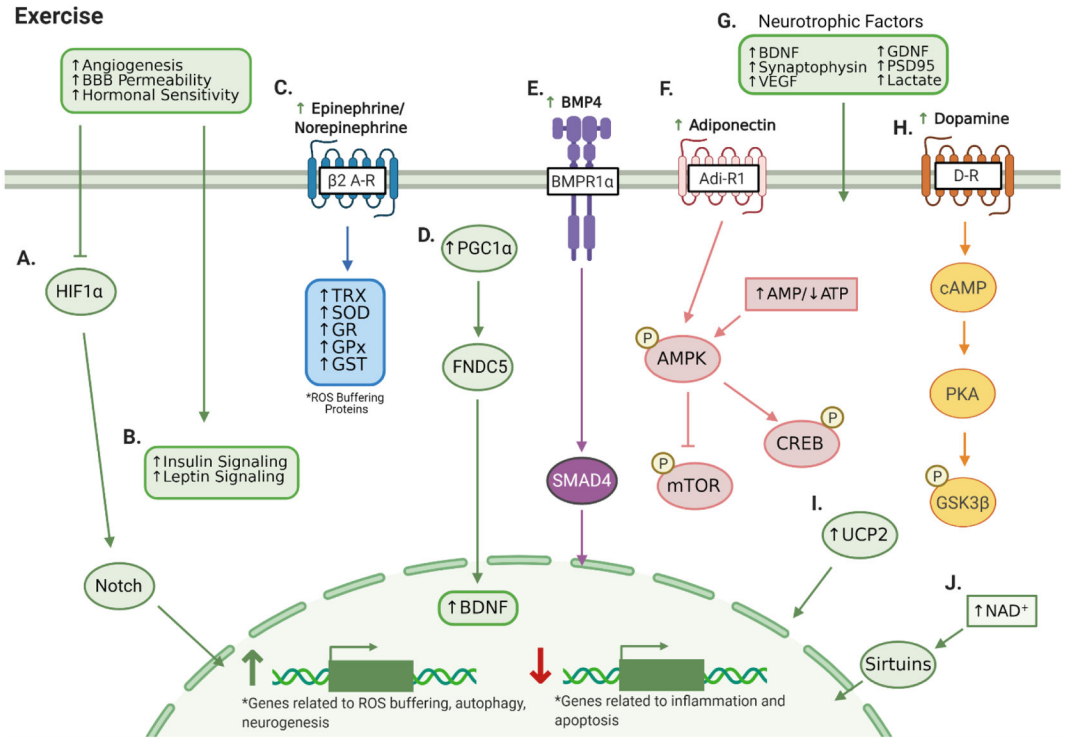

Figure 5. Exercise and AN.

Aerobic exercise improves angiogenesis, BBB permeability, and hormonal sensitivity, (A) Enhancing oxygen availability which inhibits HIF1α and downstream Notch signaling to reduce glycolytic gene expression and promote AN. (B) Improved angiogenesis and hormonal sensitivity also increases insulin and leptin signaling. (C) Exercise-mediated β2 adrenergic receptor signaling increases expression of ROS buffering proteins thioredoxin (TRX), superoxide dismutase (SOD), glutathione reductase (GR), glutathione peroxidase (GPx), and glutathione-S-transferase (GST). (D) Exercise-induced PGC1α stimulates FNDC5, which is critical to increasing BDNF. (E) Exercise increases circulating bone morphogenic protein 4, which binds to hippocampal bone morphogenic protein receptor 1α to stimulate neurogenic transcriptional activity of SMAD4. (F) Exercise increases adiponectin levels and AMP/ATP ratios to activate AMPK. AMPK inhibits mTOR to promote NSC renewal and autophagy and activates CREB to promote stress resistance and AN. (G) Exercise increases expression and activity of a plethora of neurotrophic factors. (H) Exercise stimulates dopamine→cAMP→PKA signaling to increase GSK3β activity. (I) The neuroprotective effects of exercise are greatly blunted in UCP2 knockout mice. (J) Exercise increases NAD^+ levels, which stimulates the neurogenic and neuroprotective effects of sirtuins. Created with BioRender.com.