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REVIEWED BY

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(CINVESTAV), Mexico

*CORRESPONDENCE

Robert R. Kraemer
✉ robert.kraemer52@gmail.com

†These authors have contributed
equally to this work and share
first authorship

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The effects of peripheral hormone responses to exercise on adult hippocampal neurogenesis

Robert R. Kraemer^{1*†} and Bradley R. Kraemer^{2†}

¹Department of Kinesiology and Health Studies, Southeastern Louisiana University, Hammond, LA, United States, ²Department of Biological Sciences, University of Alabama in Huntsville, Huntsville, AL, United States

Over the last decade, a considerable amount of new data have revealed the beneficial effects of exercise on hippocampal neurogenesis and the maintenance or improvement of cognitive function. Investigations with animal models, as well as human studies, have yielded novel understanding of the mechanisms through which endocrine signaling can stimulate neurogenesis, as well as the effects of exercise on acute and/or chronic levels of these circulating hormones. Considering the effects of aging on the decline of specific endocrine factors that affect brain health, insights in this area of research are particularly important. In this review, we discuss how different forms of exercise influence the peripheral production of specific endocrine factors, with particular emphasis on brain-derived neurotrophic factor, growth hormone, insulin-like growth factor-1, ghrelin, estrogen, testosterone, irisin, vascular endothelial growth factor, erythropoietin, and cortisol. We also describe mechanisms through which these endocrine responses to exercise induce cellular changes that increase hippocampal neurogenesis and improve cognitive function.

KEYWORDS

testosterone, insulin-like growth factor (IGF- I), exercise, neurogenesis, Brain-derived Neurotrophic Factor (BDNF), growth hormone, vascular endothelial growth factor (VEGF), estrogen

Introduction

In the adult mammalian brain, the production of new neurons is restricted to two distinct regions, the subventricular zone, which supplies new neurons for the olfactory bulb, and the subgranular zone of the dentate gyrus, which produces new granule cells in the hippocampus (1). Neurogenesis in the hippocampus is particularly important for learning and memory (2). Rates of hippocampal neurogenesis can be influenced by a variety of factors, among which exercise has been established as a potent stimulus (3, 4). Regulation of neurogenesis in response to exercise may significantly affect cognitive

performance. For example, sedentary activity is associated with greater risk of cognitive decline, whereas a greater level of cardiorespiratory fitness is associated with a larger prefrontal cortex in older adults (5). Moreover, exercise reduces the decline in performance of independent living activities of those with early Alzheimer's disease (4) and can change the structure and function of the hippocampus, a brain region that is critical for learning and memory (5, 6). Over the last decade, an abundance of other studies using animal models and human subjects have revealed positive effects of exercise in stimulating neurogenesis and reducing cognitive decline with aging. [e.g (3, 7–10)]. Thus, understanding the molecular interactions underlying these beneficial effects of exercise has become increasingly pertinent.

The effects of exercise on neurogenesis partially relate to changes in the brain in several neurotransmitter systems, including those for serotonin, dopamine, acetylcholine, and norepinephrine (for review, see (11)). However, our lab and others have also revealed a variety of peripheral endocrine responses to specific forms of exercise that are important for metabolism, tissue growth and repair, cardiovascular function, and other functions. [e.g (12–15)]. While many of these circulating hormones that respond to exercise stress, including estrogens and androgens (12, 13), somatotrophs (GH, IGF-1) (3, 13, 16, 17), VEGF (7) irisin (18, 19), and cortisol (20) are peripherally produced, emerging evidence indicates that these hormones and/or their effectors can cross the blood-brain barrier to profoundly influence neurogenesis and cognitive function. A number of these peripheral hormones can modulate neurogenesis during or after exercise by regulating activity of the neurotrophin, brain-derived neurotrophic factor, [e.g (21)], as well as through other pathways. Moreover, there is increasing interest in targeting these endocrine systems to reduce cognitive impairment associated with neurodegenerative diseases [e.g (22, 23)]. In the present review, we discuss changes in circulating hormone levels in response to different modes of exercise and the possible mechanisms through which these endocrine factors regulate neurogenesis.

Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) is a neurotrophin that regulates diverse neural functions, including neurite growth, synaptic plasticity, neuronal differentiation, and cell survival (24). BDNF performs these functions through interactions with two different receptors. Activation of the tropomyosin-related kinase B (TrkB) receptor by BDNF stimulates signaling via the extracellular signal-regulated kinase (ERK), phospholipase C γ , and phosphoinositide 3-kinase (PI3K) pathways (25). BDNF can also activate the p75 Neurotrophin Receptor (p75^{NTR}), a transmembrane protein that can promote c-Jun N-Terminal Kinase signaling, induce Nuclear Factor κ B (NF κ B) activity, and regulate Rho family members, among other functions (26). BDNF is produced at high levels in several brain regions, including the amygdala, cerebellum, cerebral cortex, and hippocampus (27) (28), and it is also synthesized by various non-neuronal cells, including vascular endothelial cells (29, 30), lymphocytes (31),

and skeletal muscle cells (32, 33). There are two different pools of BDNF circulating in the blood, including platelet-bound BDNF and unbound plasma concentrations that can bind to TrkB or p75^{NTR} receptors (34, 35). Like other neurotrophins, BDNF is initially synthesized as a precursor, termed proBDNF, that can be proteolytically processed in the Golgi apparatus or in the extracellular milieu to yield mature BDNF. However, in certain physiological contexts, secreted proBDNF persists in its uncleaved form, which lacks affinity for Trk receptors and functions as a high-affinity ligand for the p75^{NTR}-sortilin complex (26, 36).

Multiple lines of evidence have established BDNF as a key regulator of hippocampal neurogenesis. Several *in vitro* studies involving cultured neural precursor cells from the dentate gyrus or organotypic mice hippocampal slice cultures have revealed that BDNF induces cell proliferation, neuronal differentiation and neuronal survival (37–40). These findings have been corroborated by a variety of *in vivo* studies. For example, an analysis of heterozygous BDNF knockout mice revealed deficits in neurogenesis and reduced hippocampal volume (41), while another investigation demonstrated that intrahippocampal administration of BDNF increased the number of mature granule cells in the dentate gyrus (42). Beyond stimulating the genesis of new hippocampal granule cells, it is also well-established that BDNF promotes synaptogenesis, dendritic spine formation, and synaptic strengthening within the hippocampus (43). Thus, BDNF critically regulates the formation and modulation of hippocampal circuitry. Unfortunately, levels of BDNF decline in the periphery with age (44, 45), and aging-related loss of BDNF may occur in the hippocampus as well (46–48). Moreover, reductions in BDNF have been associated with decreased hippocampal volume and increased risk of dementia (44, 49, 50). Thus, studies elucidating strategies to enhance BDNF-induced neurogenesis and synaptic remodeling in the hippocampus may be of important therapeutic benefit. For example, 28-day infusions of BDNF into the entorhinal cortex, a region of the hippocampal formation that serves as an interface between the hippocampus and neocortex, were reported to enhance spatial memory in aged rats (51). Moreover, interventions that modulate BDNF signaling have been demonstrated to alter synapse loss or neuronal death in several rodent models of neurodegenerative disease (37), including models of Huntington's disease (52), Parkinson's disease (53), and Alzheimer's disease (51).

Exercise is a powerful stimulus for increasing circulating BDNF. Transient increases in circulating BDNF occur in response to a variety of exercise modalities, including moderate-intensity aerobic exercise (54, 55), resistance training (54, 56), and high-intensity interval training (57, 58). Mechanisms through which exercise increases BDNF production may involve activation of Sirtuin-1 deacetylase by the metabolite lactate (59), stimulation of fibronectin type III domain-containing protein 5 (FNDC5) (60), production of beta-hydroxybutyrate (61), or induction of pro-BDNF cleavage by tissue-type plasminogen activator (tPA) (62), among other mechanisms. Additionally, BDNF production is regulated by multiple endocrine systems, as discussed in later sections of this article. Due to conflicting reports, the type of training modality that is most effective in enhancing circulating BDNF levels remains unclear. However, given that lactate concentrations stimulate

hippocampal expression of BDNF, exercise regimens that are above an individual's lactate threshold would be expected to induce greater circulating BDNF concentrations. Fittingly, multiple studies have indicated that the magnitude of increase in BDNF is intensity-dependent (63–65). Beyond the well-established effects of exercise in transiently increasing circulating BDNF, exercise training may also modestly enhance resting BDNF levels, though reports in this regard have been variable (34, 66). Tissue sources responsible for exercise-induced increases in circulating BDNF remain incompletely understood. While a small number of reports suggest that BDNF does not cross the blood-brain barrier (BBB) (67, 68), direct and indirect evidence from a greater number of studies indicate that BDNF bidirectionally traverses the BBB, as well as that circulating BDNF levels reflect brain levels (34, 69–73). Thus, exercise-induced increases in circulating BDNF may not only stem from peripheral sources such as release from vascular endothelial cells and platelets, but also from the brain (34, 72). Importantly, BDNF production is critical for exercise-induced cognitive benefits, since knockdown or antagonism of hippocampal BDNF prevents exercise-associated improvements in spatial reasoning and memory in rodents (66, 74, 75). Circulating BDNF likely serves a key role in these exercise-associated cognitive benefits, since peripheral administration of BDNF was sufficient to enhance hippocampal neurogenesis and hippocampal-dependent learning (73).

While a wealth of evidence has established BDNF as a positive regulator of hippocampal neurogenesis, the specific mechanisms through which BDNF increases the abundance of mature granule cells remain incompletely understood. One possibility is that BDNF stimulates proliferation of neural precursor cells (NPCs). Indeed, BDNF has been demonstrated to enhance NPC proliferation in neurosphere cultures (38, 76), and conditional disruption of BDNF signaling in hippocampal NPCs *in vivo* was reported to decrease proliferation (77). This ability of BDNF to stimulate NPC proliferation may involve activation of the transcription factor CREB via the TrkB-ERK pathway, since disruptions in hippocampal neurogenesis have been reported in animal models with genetically altered TrkB, ERK, or CREB signaling (77–79). CREB activation can stimulate cell proliferation through regulation of multiple targets, including CyclinD1, Replication Factor C3 (RFC3), proliferating cell nuclear antigen (PCNA), and JunD (80–85). However, the role for this pathway in promoting NPC proliferation has been contradicted by studies yielding evidence that BDNF, TrkB, and CREB do not positively impact NPC proliferation (86–90). Another possibility is that BDNF increases the number of granule cells by promoting NPC or granule cell survival. This hypothesis has been supported by multiple studies revealing decreased survival of hippocampal progenitor cells in mice with genetic depletion of BDNF (86, 87). This role for BDNF may be mediated through the TrkB-Akt pathway, since in injury models this pathway promotes survival of mature hippocampal neurons (91, 92). CREB, which can be activated by ERK or Akt, has also been demonstrated as necessary for the survival of newborn hippocampal neurons (89). However, the hypothesis that BDNF stimulates neurogenesis by facilitating the survival of hippocampal neurons has been contradicted by a report that deletion of *BDNF* in

the central nervous system does not alter the survival of new hippocampal cells. Rather, the study indicated that BDNF promotes neurogenesis by facilitating the terminal differentiation of NPCs into mature granule cells (88). Altogether, the conflicting findings pertaining to the effects of BDNF on hippocampal NPCs may partially relate to developmental adaptations that may occur in animal models with genetic deletions. Thus, performing fate-mapping and thorough time-course assessments in models with temporally induced-genetic deletions may help to clarify the specific effects of BDNF-TrkB signaling on NPC proliferation, survival, and neuronal differentiation.

Of note, BDNF may not only regulate hippocampal neurogenesis through interaction with TrkB, but also through p75^{NTR}. Multiple studies have revealed deficits in hippocampal neurogenesis in adult mice lacking p75^{NTR}, suggesting that p75^{NTR} positively regulates neurogenesis (93–95). This promotion of neurogenesis by p75^{NTR} likely occurs through its crosstalk with TrkB, as p75^{NTR} has been demonstrated to augment TrkB signaling in hippocampal neurons (96). Interestingly, negative regulation of neurogenesis has also been reported in response to proBDNF, which binds to p75^{NTR} and sortilin but not TrkB (97, 98). Moreover, multiple types of exercise training have been demonstrated to enhance mature BDNF production in the hippocampus while concurrently stimulating in the brain the activity of tPA, a proteinase that cleaves proBDNF to yield mature BDNF (62, 99–102). Altogether, these findings suggest that exercise training can stimulate hippocampal neurogenesis by enhancing BDNF-TrkB-p75^{NTR} cascades while limiting activation of proBDNF-p75^{NTR}-sortilin signaling.

Growth hormone (somatotropin), insulin-like growth factor-1, and ghrelin

Growth hormone releasing hormone (GHRH) is a hypothalamic peptide hormone that is released during different forms of exercise. GHRH acts upon growth hormone releasing hormone receptor (GHRHR), a G protein-coupled receptor, activating the G_s-PKA-cAMP signaling pathway and stimulating growth hormone (GH) release from the anterior pituitary (103, 104). Growth hormone (GH) is a somatotropin that is composed of a polypeptide chain with approximately 190 amino acid residues. It contains two disulphide bridges with four alpha helices and has two binding sites for two receptor molecules (105). GH is released in a pulsatile manner from the anterior pituitary and circulates to the liver, where it acts directly upon GH receptors (GHR) in hepatocytes. Activation of GHR induces Janus kinase (2)/signal transducers and activators of transcription 5 (JAK2/STAT5) signaling and stimulates production of insulin-like-growth factor 1 (IGF-1) from liver hepatocytes, as well as paracrine production of IGF-1 from other tissues (103). IGF-1 is a 70 amino-acid single chain peptide that has a molecular weight of 7.6 kDa and contains three disulphide bridges creating a tertiary structure important for optimal binding to the IGF-1R (106). Most IGF-1 polypeptides are

transported by carrier proteins that determine the amount of IGF-1 available to different tissues (107). The actions of IGF-1 occur via IGF-1R, a membrane-bound receptor tyrosine kinase (RTK). IGF-1R activation can result in mitogen-activated protein kinase signaling, as well as activation of the PI3K-Akt signaling pathway, thereby promoting cell growth and maturation (108).

A variety of forms of exercise stimulate the GHRH/GH/IGF-1 axis, causing increased circulating concentrations of GH and IGF-1 (13, 16, 109, 110). Data from the Kraemer lab has revealed increases in circulating GH concentrations in response to three sets of four different resistance exercises, with GH averaging over an eight-fold increase during recovery (12). Additional research groups have reported strong GH increases in response to other resistance exercise protocols (111). GH response to anaerobic cycling has also been reported (112). We have also reported elevated circulating concentrations of both GH and IGF-1 in response to treadmill running at four progressively increased exercise intensities, with GH increase averaging approximately 5 times resting values while area under the curve values for IGF-1 revealed significantly higher levels over time (13). Others have reported GH increases in response to prolonged treadmill running at 60% VO₂ max (113). In the aforementioned study of older men averaging 60.8y (54), increases in IGF-1 were observed in response to 30 min of both moderate intensity running and moderate intensity circuit weight training exercise. Collectively, these studies reveal that both aerobic exercise at moderate and high intensity as well as resistance exercise will stimulate acute increases in GH and IGF-1. In addition to acute responses to exercise, a systemic review of multiple aerobic and resistance training studies revealed that both forms of exercise training increase resting levels of GH and IGF-1 (114).

Secretion of GH from the pituitary gland is not only controlled by GHRH but also regulated by ghrelin, a 28 amino acid hunger hormone primarily produced in the stomach. There is some evidence that exercise training increases resting ghrelin levels (115–118), thus implicating ghrelin as a hormone that can potentially modulate GH-induced neurogenesis. However, for several of these studies, result interpretations are confounded by training-induced reductions in body weight (116–118), and conflicting studies have reported training-induced reductions in circulating ghrelin concentrations (119, 120). Additionally, circulating ghrelin concentrations do not increase in response to acute running or cycling (121, 122). Overall, due to limited and conflicting findings, further research is needed to clarify the relationship between various forms of exercise, ghrelin, and GH-IGF-1 signaling.

GH and IGF-1 are important regulators of neurogenesis and neuronal connectivity in the adult hippocampus. Both hormones can cross the blood-brain barrier (123, 124) and have specific receptors expressed in the central nervous system, including the hippocampus (125–127). Peripheral administration of GH has been demonstrated to enhance cellular proliferation in the dentate gyrus of healthy adult rats (128), as well as to increase the number of newborn neurons in the hippocampus in a rodent model of hypopituitarism (129). *In vitro* experiments from the aforementioned study suggest that GH increases hippocampal neurogenesis by stimulating NPC proliferation. However, GH has

also been demonstrated to have a variety of neurotrophic actions in the central nervous system, including neuroprotection, axonal growth, and synaptogenesis (130, 131). Like GH, peripheral administration of IGF-1 has been demonstrated to enhance hippocampal neurogenesis (132). Evidence of the neurogenic potential of IGF-1 has also been corroborated by studies revealing that central infusion of IGF-1 increases the number of immature neurons in the dentate gyrus of rodent models of aging and traumatic brain injury (133, 134). Moreover, IGF-1 has been demonstrated to enhance synaptic complexity in the hippocampus, thereby suggesting that the hormone not only regulates hippocampal circuitry through modification of neuron abundance but also via regulation of neural connectivity (135). While the mechanisms through which GH and IGF-1 promote hippocampal neurogenesis remain incompletely understood, both hormones stimulate production of BDNF (136, 137). Additionally, IGF-1 has been shown to promote the proliferation of hippocampal NPCs and induction of pro-neural gene expression through a novel cascade involving activation of Sox2 by the Ras-related GTPase, RIT1 (138). IGF-1 signaling has also been linked to a variety of other signaling events, including suppression of proinflammatory cytokine signaling by IL-1 β and TNF- α (137), activation of CREB (139), and modulation of glutamatergic neurotransmission (137). Interestingly, beyond stimulation of hippocampal neurogenesis by GH and IGF-1, hippocampal neurogenesis can also be directly stimulated by the GH secretagogue ghrelin. Ghrelin will bind to the GH secretagogue receptor GHS-R1a that has been identified in the rat brain, and *in vitro* experiments have revealed that ghrelin acts through the ERK1/2, PI3K/Akt, and STAT3 signaling pathways to stimulate neurogenesis cultured hippocampal NPCs (140). However, due to the aforementioned conflicting reports on ghrelin responses to various forms of exercise, the role of ghrelin in exercise-induced neurogenesis remains unclear.

In a process termed somatopause, there is a considerable and progressive reduction in circulating GH and IGF-1 with aging (141). Additionally, multiple human studies have indicated that higher levels of circulating GH and IGF-1 correlate with improved cognitive performance (142, 143). Thus, the GHRH-GH-IGF-1 axis may represent a promising target for therapeutic interventions to improve cognitive deficits. Indeed, administration of GH has been demonstrated to improve cognitive deficits associated with cortical impact in rats (136), as well as reduce tissue loss and enhance memory function in a mouse model of stroke (144). Moreover, while the cognitive benefits of exercise have been well-established (145), emerging evidence suggests a key role for GH-induced neurogenesis in exercise-induced cognitive improvement. For example, a recent investigation by Blackmore et al. revealed that GH signaling and neurogenesis are necessary for exercise-induced improvement in hippocampal-dependent spatial learning in aged mice (146).

In summary, utilizing different forms of acute exercise at the proper exercise intensity could be helpful in promoting neurogenesis in patients with neurodegeneration via increases in GH and IGF-1. In addition, exercise training may be helpful in maintaining hippocampal function by increasing resting circulating ghrelin levels. (147).

Estradiol

17 β estradiol (Estrogen/E₂) is a steroid hormone that exerts diverse actions after being produced in the ovaries, liver, heart, muscle, bone and brain (148). The production of E₂ occurs via activation of the hypothalamic-pituitary-gonadal axis (149). Gonadotropin-releasing hormone (GnRH), a 10-amino acid peptide, is secreted by hypothalamic neurons into the median eminence and is then transported through the hypophyseal portal system to act upon GnRH receptors in pituitary gonadotrope cells (150). This signals production and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (151). Circulating LH and testosterone act on receptors in the gonads, stimulating release of the sex steroids, androgens and estrogens (151). Circulating E₂ can cross the blood-brain barrier and bind to ER α , ER β , and the G protein-coupled estrogen receptor 1 (GPER1) that are expressed in in both genders and found in multiple areas of the brain, including the hippocampus (152). A majority of the actions of E₂ are thought to be induced through ER α and ER β receptors (153). Binding of E₂ to ER α and ER β stimulates formation of a receptor-ligand complex that dimerizes and translocates to the nucleus, where it binds to estrogen response elements on DNA (154) and regulates gene transcription (155). There are also estrogen receptors in the cell membrane, and their binding induces quick, non-genomic effects such as changing cell permeability and stimulating 2nd messenger cascades (156).

Changes in circulating E₂ have been reported to respond to a variety of forms of exercise. Bunt et al. revealed that 60 min of treadmill running at 60% VO₂max in trained and untrained male and female runners elicited significant increases in E₂ in all subjects (157). Similarly, Gray et al. reported a 45% increase in E₂ in young men after an average of 15.6 one-minute treadmill runs (158). Our lab has reported increases in E₂ in young women in response to three sets of four resistance exercises with greater increases during the luteal than the follicular phase of the menstrual cycle (17). Interestingly, in the aforementioned studies, elevated levels of E₂ after exercise correlated with increases in GH (158). Moreover, hormone replacement therapy (HRT) in post-menopausal women has been demonstrated to induce greater GH responses to 30 min of treadmill exercise compared to those not taking HRT (159). Thus, higher E₂ concentrations with exercise can increase GH levels and may thereby potentially exert positive effects on adult neurogenesis.

Accumulating evidence also suggests that E₂ can function as a direct, positive regulator of adult neurogenesis. The E₂ receptors ER α and ER β are expressed in the hippocampal NPCs (160) and multiple studies have indicated that E₂ signaling enhances NPC proliferation. For example, E₂ treatment was demonstrated to induce proliferation in NPC cultures of both embryonic rat and human cell-line origin (161–163). In a separate study, chronic estradiol treatment of spontaneous hypertensive rats resulted in reduced blood pressure, increased neurogenesis in the hippocampus, and increased BDNF RNA and protein expression in the dentate gyrus (164). Considering that the BDNF gene contains an estrogen-sensitive response element (ERE), the upregulation of BDNF expression may represent one mechanism

through which E₂ stimulates NPC proliferation (165). However, the effects of E₂ on NPC proliferation have also been attributed to ER β -mediated activation of ERK and subsequent centrosome amplification (163).

Fitting with the potential role of E₂ in regulating hippocampal neurogenesis, the hormone has also been demonstrated to confer cognitive benefits in specific physiological contexts. For example, E₂ hormone therapy has been shown to be more protective of cognition in women with greater risk for Alzheimer's Disease who continue to use it up to two years following menopause onset (166). Given that E₂ has been shown to protect neural tissue (167, 168) more research is needed to establish the optimal exercise protocols for enhancing the effectiveness of medication in patients taking hormone replacement therapy to prevent cognitive decline following menopause.

Testosterone

The hypothalamic-pituitary-gonadal axis is responsible for regulating testosterone production. Secretion of gonadotropin-releasing hormone (GnRH) by the hypothalamus induces release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary (169). LH stimulates production and release of testosterone from the testes and adrenal glands in men (170) and from ovaries, adrenal glands and peripheral tissues in women (171). In a variety of tissue types, testosterone can be metabolized via the enzyme 5 α -reductase to dihydrotestosterone (DHT) (172). Testosterone and DHT function as androgens that bind to nuclear receptor subfamily 3, group C, member 4 (NR3C4) (173). Upon activation in the cytoplasm, the androgen receptor translocates to the nucleus, where it functions as a transcription factor (174). Testosterone circulating in men will be converted into both active metabolites, E₂ and DHT, that will mediate some testosterone action in the target tissues (175).

Multiple studies have revealed acute changes in testosterone levels in response to different forms of exercise in males and females. Strenuous intermittent exercise consisting of treadmill running at 60%, 75%, 90% and 100% of VO₂max was shown to increase circulating testosterone levels in young males (176). Moreover, testosterone levels were reported to significantly increase in young women athletes in response to a discontinuous treadmill test to exhaustion, with 4- and 7-week training resulting in higher testosterone responses than 1-week training (177). Both concentric as well as eccentric muscle actions during resistance exercise have been reported to increase total and free testosterone levels in males (16). Heavy resistance exercise has been shown to significantly increase circulating levels of total and free testosterone in younger and older men, with greater responses found in younger than older men (178). These studies reveal the positive effects of acute and chronic exercise on increased circulating testosterone levels.

As a steroid hormone, circulating testosterone can permeate the blood-brain barrier (179) to interact with androgen receptors, which are located in multiple regions of the brain (180), including

the human hippocampus (181). Additionally, testosterone in the hippocampus can be converted by 5 α -reductase to DHT, which has a strong binding affinity for androgen receptors in the brain (169). There is some evidence that androgen signaling increases adult neurogenesis in the dentate gyrus of the hippocampus. For example, two weeks of light exercise has been shown to increase synthesis of 5 α -reductase, DHT, and androgen receptors in the hippocampus of adult rats, and pharmacological antagonism of androgen receptors blocked exercise-induced neurogenesis (182). Additionally, systemic administration of testosterone or DHT, but not estradiol, was found to enhance hippocampal neurogenesis in male rats (183). However, in a separate study, DHT administration had inconsistent effects on hippocampal proliferation and the number of newborn hippocampal neurons in rats of different age and sex, thereby indicating that the pro-neurogenic effects of androgens on neurogenesis are sex- and age-dependent (184). Interestingly, the manner in which the gonadal steroids, testosterone and estrogen, act on neurogenesis differs in that estrogens appear to induce cell proliferation, whereas androgens increase neuron number via increasing cell survival (185). The pro-survival effects of androgen signaling on hippocampal neurons has been suggested to involve upregulation of BDNF and PKC-dependent phosphorylation of CREB, among other pathways (169). Further investigations are needed to understand the degree to which androgen-stimulated neurogenesis influences cognitive performance in individuals of different age and sex, as well as how such effects are modulated by different forms of exercise. However, a variety of studies have reported positive effects of androgen signaling on spatial working memory (186, 187), and some of the memory-enhancing effects have been verified using memory tasks affected by neurogenesis (169). Considering that andropause, a decline in circulating androgens, occurs in males with aging (188), utilizing exercise to increase circulating levels could represent an important method for maintaining cognitive function.

Dehydroepiandrosterone

Dehydroepiandrosterone is an endogenous steroid hormone produced in the adrenal glands and nervous system from pregnenolone in the delta-5 pathway via activity of the enzyme cytochrome P450c17 in humans (189). Circulating DHEA can be converted to androstenedione or androstenediol, which subsequently can be converted to testosterone (190). Circulating DHEA declines with age and regulates hippocampal neurogenesis as well as regulates suppression effects of cortisol on formation and survival of new neurons (191). DHEA and its sulfated form, DHEAS, bind to GABA receptors and alter neurosecretion affected by N-Methyl-D-Aspartate (NMDA) receptors (192, 193). In addition, DHEA crosses blood-brain barrier (194). A study of post-menopausal women both on and off of estrogen and progestin replacement therapy reported increases in DHEA and its sulfated form, DHEAS, in response to 30 min of high intensity treadmill running (80% of VO_{2max}) (195). Moreover, the DHEA responses to exercise were greater in those taking hormone replacement therapy, suggesting that women with higher circulating estrogen

concentrations would have greater DHEA responses to exercise. A study involving teenage female runners over the course of 7 weeks of a competitive season examined the effects of a graded treadmill test to exhaustion on DHEA and DHEAS across the 7 weeks. The investigators reported significant increases in DHEA and DHEAS in response to each of the graded treadmill tests after weeks 1, 4, and 7; However, the increases in DHEA and DHEAS were similar in response to each exercise bout even through participants aerobic fitness level (VO_{2max}) increased across the season (177). In an investigation of well-trained and untrained young adults, DHEA concentrations increased in the untrained in response to 15-min bouts of cycle ergometry at 40% and 70% VO_{2peak}, and increased cycling at 100% of VO_{2peak} until exhaustion; however, DHEA only increased in the well-trained young adults after exercising at 100% VO_{2peak} (196). Results altogether suggest that well trained individuals would need to exercise at higher intensities to stimulate increases in circulating DHEA. A recent systematic review of exercise training studies found that regular training of both males and females over the age of 40 increased circulating basal levels of DHEA as well as testosterone and GH (114). In the harvested rat brain cortex, DHEA treatment increased neurotrophin expression as well as neurite extension (197). An older study revealed that subcutaneous treatment of male rats with DHEA pellets caused increases in newly formed cells in the dentate gyrus of the hippocampus (191). It also reduced the suppressive effect of corticosterone. A review of studies investigating the effectiveness of DHEA for treatment of older adults for dementia reported that there was not enough positive evidence for use of DHEA to treat dementia (193).

Irisin

In 2010, Bostrom et al. discovered a peroxisome proliferator-activated receptor-gamma co-activator 1 α (PGC-1 α)-dependent myokine named irisin and demonstrated that PGC-1 α stimulates expression of the membrane protein FNDC5, which is cleaved and released from muscle as the hormone irisin (198). The irisin receptors in the brain were recently identified as integrin α V β 5 heterodimers (199).

A skeletal muscle response to exercise is the expression of the transcriptional co-activator, PGC-1 α (200). Fittingly, numerous studies have revealed increases in irisin in response to different forms of exercise, including moderate to high intensity exercise (201). The first author has reported increases in circulating irisin in men and women in response to 90 min of moderate (60% VO_{2max}) treadmill exercise (18). Qui et al. (202) also reported increases in irisin in response to aerobic exercise (cycling and running). Interestingly, irisin is significantly lower in patients with Alzheimer's disease (203). However, there is recent evidence that resistance exercise training increases circulating irisin levels in older men. Zhao et al. (204) compared circulating irisin concentrations in older men who had performed resistance training 2x/wk for 12 weeks versus a control group. They reported that the trained group had significantly higher irisin resting levels than the group that did not perform resistance training. Interestingly, the effect of exercise

training on irisin levels is influenced by environmental temperature. McCormick et al. (205) recently conducted a study comparing irisin responses to exercise in older and younger men under hotter and more temperate conditions. They reported elevated irisin responses to aerobic exercise in hotter conditions in younger and older men with greater responses in younger men. Jurimae et al. (206) recently reported that three weeks of sprint interval training in older men (63+/-8 y) significantly increased resting circulating irisin concentrations while reducing inflammatory cytokines.

Both FNDC5 and irisin have been found in mouse and human brains (21, 207), and exercise has been shown to increase hippocampal FNDC5 levels and upregulate the expression of BDNF. Additionally, knockdown of FNDC5 has been reported to reduce central BDNF expression (208), while adenoviral mediated irisin expression increases BDNF in hippocampal cultures (207, 209). Cyclic AMP element response binding protein (CREB) is a cellular transcription factor known for inducing neuronal plasticity and long-term memory formation in the brain (210). Lourenco et al. found that in human cortical slices, recombinant irisin stimulated the cAMP/PKA/CREB pathway (21). When considered with the aforementioned evidence for the role of BDNF and CREB signaling in the regulation of hippocampal neurogenesis, these findings suggest that beneficial effects of different forms of exercise in younger and older individuals may occur through positive effects on neurogenesis mediated by increased circulating irisin concentrations.

Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is an important angiogenic factor for endothelial cells. Platelets are known to be major contributors of circulating VEGF (211). VEGF binds to two tyrosine kinase receptors (VEGFRs), VEGFR-1 and VEGFR-2 (212).

Multiple forms of exercise have been reported to stimulate increases in VEGF. For example, acute sprint training has been shown to increase circulating levels of VEGF (213). A study of older men (72 +/- 6.5y) who performed 5 sets of unilateral leg extensions at 20% 1-repetition maximum of both limbs using either vascular occlusion or no vascular occlusion, reported increased circulating concentrations of VEGF as well as GH in response to the resistance exercise with vascular occlusion (214). A recent investigation on effects of only 15 min of aerobic exercise on circulating VEGF, GH and IGF-1 reported no change in older men and women, suggesting longer bouts of aerobic exercise may be required for alterations in these hormones (215). They also reported that cerebral blood flow increased in the hippocampus of the participants including those with genetic risk factor for Alzheimer's. A recent study compared the effects of cycling at 60% of VO₂max in older and younger participants on VEGF and reported significant increases immediately following exercise in older, but not younger participants (216). Three hours post-exercise VEGF values were

at baseline levels. Another recent study compared the effects of training that included walking and resistance band exercise 3x/week for 12 weeks in young/old (65-74y) and old/old (75-84y) individuals (217). They found increases in resting VEGF levels in the young/old but not the old/old group after 12 weeks of training, suggesting that this form of training in individuals >74y may not increase resting VEGF values.

A large number of studies have shown that VEGF receptors VEGFR-1 and VEGFR-2 are expressed in neurons (218). VEGF can exert a variety of important functions in the brain, including increasing the permeability of the blood-brain barrier (219) and regulating blood flow in the hippocampus to stimulate neurogenesis (220). A recent review of studies determining the effects of acute aerobic and resistance exercise on VEGF as well as BDNF reported that both forms of exercise increase VEGF and BDNF to potentially affect neurogenesis (221). VEGF-R1 is prevalent in postnatal neurons of the cortex, striatum, and hippocampus but declines with age; however, VEGF-R2 signaling has been shown to lead to proliferation, migration and differentiation of neurons, with expression persisting during adulthood. (218). Sun et al. (222), using a 3-day old rat model, reported increased angiogenesis via altering VEGF with concomitant neural stem cell proliferation and differentiation in the premature brain. Another study found that implantation of biodegradable nanospheres of VEGF in the cerebral cortex of a transgenic mouse model of Alzheimer's Disease caused cellular proliferation in the hippocampus and dentate gyrus (223). Thus, evidence indicates that VEGF responses to exercise could play a positive role in neurogenesis.

Erythropoietin

Erythropoietin (EPO) is produced by the peritubular cells of the cortex/medullary border of the kidney (224). EPO gene expression is stimulated by hypoxia that will induce elevated red blood cell number, hemoglobin levels and O₂ capacity in the blood (225). Binding of EPO to the EPO-R results in receptor trans-autophosphorylation, resulting in activation of JAK2-STAT5, PI3-kinase, PKC, and MAPK pathways (226, 227).

EPO levels have been shown to increase in women completing three sets of 12 repetitions of bench press, dumbbell curl, dumbbell squat, and standing dumbbell upright row at either 60%, 70%, or 80% of one-repetition maximum. EPO levels increased to the greatest degree in the groups completing the exercise at 80% one-repetition maximum (228), revealing that heavier workloads resulted in greater EPO response. Female runners completing a marathon were found to not have increased erythropoietin levels until three days following the run (229). After running a marathon, EPO levels have been shown to increase in male runners; however, the increases were reported to be dependent upon serum iron levels (230). Another study reported a 26% increase in EPO levels in eight males following completion of a half-marathon (231). A recent study compared EPO responses of participants (age 31+/- 6y) to

running at high intensity for 30 min vs. running at moderate intensity for 90 min. The moderate intensity runners showed increases in EPO during exercise that returned to baseline at the end of the exercise bout, but there was no significant change in EPO in the high intensity runners (232). Another investigation examined the effects of eight weeks of 1-hr cycle ergometry training sessions, three to four times per week for eight weeks, on regulators of erythropoiesis (233). They reported mild, transient increases in EPO with training over the 8 weeks. A recent study compared circulating EPO levels in men cycling at 60% of power output at VO_2 max in an environmental chamber under either hot-hypoxic, hypoxic, or normoxic conditions (234). They reported increases in EPO after the hot-hypoxic and hypoxic conditions, but not under normoxic conditions. Altogether, results of these studies suggest there are increases in EPO in response to fairly intense resistance exercise and long aerobic exercise bouts. There is some evidence that longer, less intense aerobic exercise results in EPO increases; whereas shorter, more intense aerobic exercise does not. Aerobic training appears to cause transient increases in resting EPO. Finally, moderate exercise under hot or high altitude conditions appear to increase circulating EPO concentrations.

Despite its large molecular weight and susceptibility to glycosylation, circulating EPO is able to cross the blood-brain barrier (235, 236). EPO-R brain expression has been observed during development and adulthood in humans, non-human primates, and other mammals; and the binding of I^{125} -labeled EPO localized EPO binding sites in the hippocampus, cortex and midbrain in mouse. While brain expression of EPO-R is low during adulthood, expression of the receptor increases in response to hypoxia or other types of stress (237). During the past two decades, an abundance of studies has established that circulating EPO can exert robust neuroprotective effects in the brain. For example, systemic administration of EPO has been found to reduce neural tissue damage in mouse models of ischemia, traumatic brain injury, autoimmune encephalitis, seizures, Alzheimer's disease, and amyotrophic lateral sclerosis (227, 236, 238–240). The beneficial properties of EPO in the brain likely relate to the ability of EPO-R signaling to stimulate anti-apoptotic proteins such as B-cell lymphoma 2 (Bcl2) and B-cell lymphoma-extra large (BclxL) (241), to inhibit pro-apoptotic proteins cytochrome-c and p53 (242, 243), and to promote the release of anti-inflammatory cytokines (239, 227). However, such beneficial effects may also relate to modulation of neurogenesis. For example, in a rat model of Alzheimer's disease, systemic injection of EPO enhanced neuronal proliferation in the dentate gyrus (244). Additionally, a recent study by Wakhloo and colleagues indicates that cognitive challenge induces local hypoxia in hippocampal pyramidal neurons, thereby stimulating upregulation of EPO and EPO-R. Subsequently, EPO signaling promotes the formation of new hippocampal pyramidal neurons and enhances dendritic spine densities (245). Given this evidence for the role of EPO signaling in facilitating hippocampal circuitry formation in response to cognitively-demanding tasks, and considering the aforementioned

effects of exercise in increasing circulating EPO, EPO may serve as a central mediator of exercise-induced cognitive benefits.

Cortisol

Cortisol is a glucocorticoid (GC) hormone that is released from the adrenal glands in response to activation of the hypothalamic-pituitary-adrenal (HPA) axis (246). Higher levels of stress will stimulate the neurons in the paraventricular nucleus of the hypothalamus to secrete corticotropin-releasing hormone (CRH) into the hypophyseal portal system, thereby stimulating the anterior pituitary to release adrenocorticotropic hormone (ACTH) (246). ACTH will circulate to the adrenal glands and stimulate the release of cortisol into circulation. Cortisol, a glucocorticoid hormone, will bind to corticosteroid binding globulin and be carried in the blood (247). Corticosteroid-binding globulin (CBG) is the main GC-binding protein in the plasma, with about 80–90% of the GCs bound to it. It will circulate in the blood stream and bind to mineral corticoid receptors and glucocorticoid receptors (248). Cortisol and other glucocorticoids are soluble lipids that easily cross the blood-brain barrier and are able to bind to glucocorticoid receptors in the amygdala, prefrontal cortex, and the hippocampus (249).

Exercise at higher intensities as well as extended exercise duration at moderate intensities will activate the HPA axis (250, 251). For example, a study involving adolescent female runners examined hormone responses to a maximal graded exercise test at week 1, 4, and 7 of a high school track season. There were significant increases in circulating cortisol levels in response to each of the graded exercise tests to max. However, there were no changes in resting cortisol levels over the 7-week time period (177). A separate study compared the effects of 30 minutes of treadmill exercise at 80% of VO_2 max in postmenopausal women on and off of hormone replacement therapy (HRT) (250). Results revealed that the strenuous exercise increased cortisol levels in both groups, but women on HRT had significantly higher cortisol responses than those not on HRT (195).

In addition to exercise at higher intensities, mental stress with lower exercise intensities has been shown to increase circulating cortisol levels (250). However, lower intensity exercise without mental stress has been shown to not increase circulating cortisol levels (250, 252). Similarly, treadmill running by male and female 10K runners for 30 min at 80% heart rate maximum was shown to not increase circulating cortisol levels (20). A study on effects of 3 sets of 4 resistance exercises (bench press, lat-pull, leg extension, and leg curl) at a 10-repetition maximum load (a moderate intensity), revealed no change in circulating cortisol concentrations in young men (253). Another study was designed to compare the effect of acute psychological stress and moderate as well as vigorous exercise on intense HPA responses and working memory performance. Salivary cortisol concentrations were increased similarly by vigorous exercise and by psychological stress, but not by moderate exercise (254).

The effects of exercise training on circulating cortisol were analyzed in a recent systematic review (114). The results suggested there was not a consensus on whether exercise training changed resting circulating cortisol levels. Another recent study examined the effects of training on resting cortisol levels. The investigators examined the effects of six types of training for six weeks on resting cortisol levels. The training groups were endurance running, endurance/interval running, resistance training, explosive training, speed-endurance 50-meter running, and speed-endurance training. Results from the study revealed that the endurance training groups and strength training programs reduced resting cortisol levels (255).

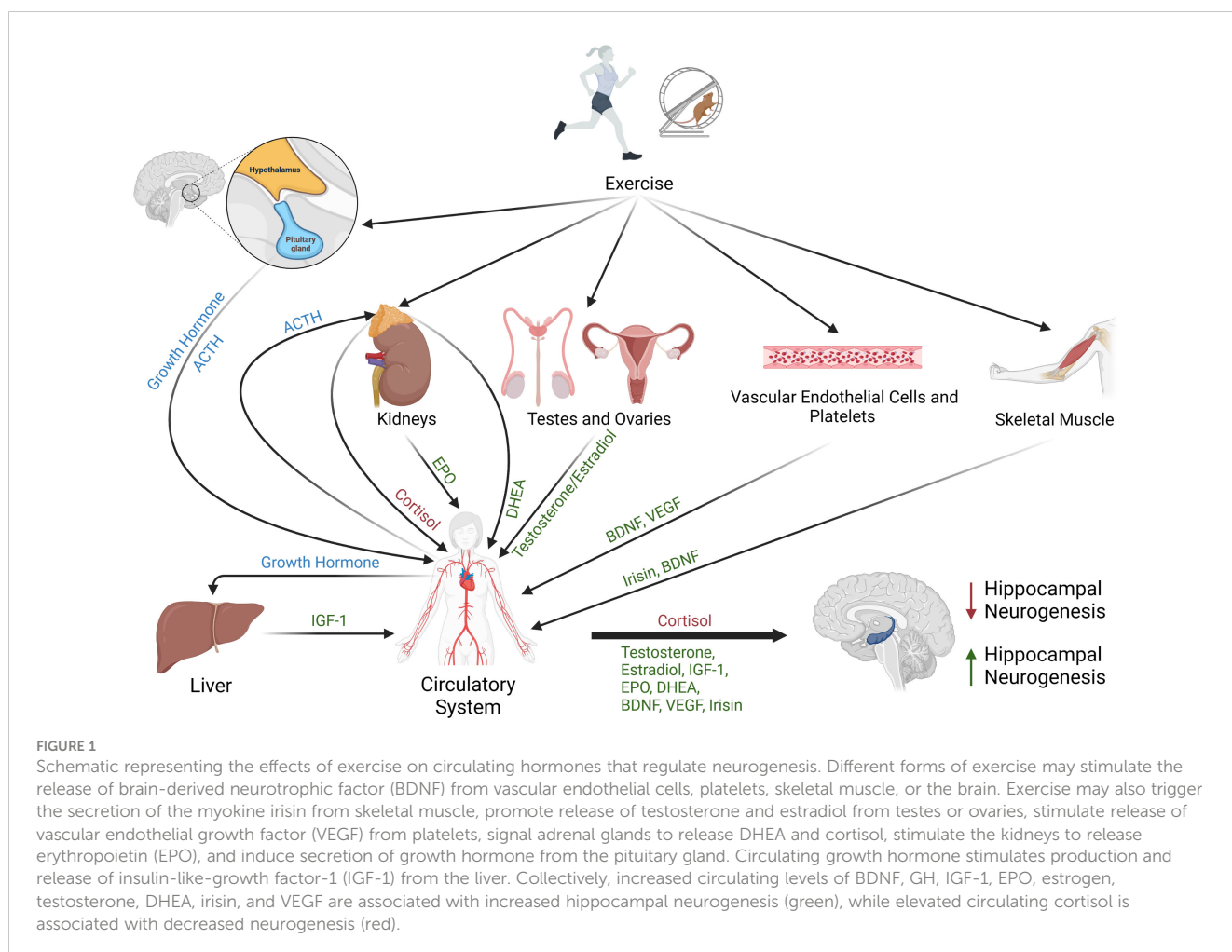
In the brain, cortisol can bind to receptors and subsequently inhibit expression of a variety of specific genes (256). It has been shown that activation of the glucocorticoid receptor (GR) results in an increase in the expression of serum- and glucocorticoid-inducible kinase 1 (SGK1) in human stem cells and neurons of rodents (257, 258) and that SGK1 mediates a cortisol-induced reduction in neurogenesis (259). Furthermore, a separate study revealed that GC signaling promotes apoptosis in NPCs and immature hippocampal neurons (260). Although there is evidence of a negative effect of cortisol on neurogenesis, it should also be kept in mind that only approximately 10% of circulating cortisol is able

to cross the blood-brain barrier (261). Nonetheless, a recent study examined the effects of rigorous resistance exercise in military trained power-lifting subjects on salivary cortisol, memory, and learning ability. After completing a strenuous resistance exercise protocol, the subjects' salivary cortisol levels had significantly increased and importantly, their learning ability and memory were reduced (249).

Collectively, these findings suggest that low and moderate training intensities will not acutely affect circulating cortisol levels, but high intensity exercise can increase circulating cortisol and potentially result in an inhibitory effect on neurogenesis. However, there is evidence that endurance training and strength training of moderate intensities could reduce resting cortisol levels, thereby conferring a positive effect on neurogenesis.

Discussion

In summary, different forms of exercise increase circulating levels of a broad range of hormones. Numerous investigations have revealed important roles for these endocrine factors in the stimulation of neurogenesis (see Figure 1), and substantial evidence indicates that exercise-induced changes in these factors



can positively affect the maintenance and improvement of cognitive function. There can be differences in circulating levels of the aforementioned hormones with variation in exercise mode, duration, and intensity, as well as effects of age, training status, and gender. Future studies are needed to evaluate combinatorial signaling between these endocrine factors, as well as identify the most effective training methods to increase these circulating hormones to promote neurogenesis in patients with traumatic brain injury or neurodegenerative disease. These data will be important for recommending exercise regimens that will effectively increase neurogenesis. Additionally, more data may facilitate the development of effective procedures for infusion of hormones to treat patients with neurodegeneration.

Author contributions

RK and BK contributed to the conception of the review. RK and BK retrieved the main articles to be included in the review. RK and BK wrote the first draft of the manuscript. BK developed the figure. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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