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Adult Hippocampal Neurogenesis: A Possible Way How Physical Exercise Counteracts Stress

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It was considered that neurogenesis only occurred during the embryonic and developmental stage. This view has greatly changed since the discovery of adult neurogenesis in two brain regions: the hippocampus and the olfactory bulb. Recently, it is suggested that altered hippocampal neurogenesis is related to pathophysiology of mood disorders and mechanism of antidepressant treatments. Accumulating knowledge about the effects of physical exercise on brain function suggests a special role of adult hippocampal neurogenesis in cognitive and mental health, even though the functional significance of adult neurogenesis is still debated. The beneficial effects of running correlating with increased adult neurogenesis may provide a hint that newborn neurons may be involved, at least in part, in the counteractive mechanism of physical exercise on stress-related disorders, like depression. The present review provides an overview of recent findings to emphasize the possible involvement of hippocampal neurogenesis in mediating the beneficial effects of physical exercise on counteracting stress.

Key words: Hippocampal neurogenesis; Physical exercise; Stress; Dendritic plasticity

INTRODUCTION

The initial description of adult neurogenesis in the early 1960s (4) was viewed with skepticism since this discovery was against the traditional view that neurogenic activity was limited to the developmental stage (102). It is now widely accepted that the adult mammalian brain contains a population of active progenitor cells that give rise to new neurons and glial cells (27). This discovery has inspired the hope for regenerative capability of the brain and the therapeutic application of those endogenous stem cells in the central nervous system after damages, like stroke (25,134). An explosion of research over the past decade has focused on understanding the functional significance, regulation, and molecular mechanism of adult neurogenesis. In recent years, it has been proposed that deficit in adult neurogenesis may result in depressive disorders (36). The hypotheses on pathophysiology of mood disorders and on antidepressant mechanisms have greatly changed

from classical monoamine hypothesis: depression is a chemical imbalance of the brain with a deficiency in monoaminergic neurotransmission (60) to an adult neurogenesis hypothesis. The adult neurogenesis hypothesis of depression was suggested by three lines of evidences (41): 1) volumetric loss of the hippocampus (a brain region with continuous adult neurogenesis) in the depressed patients; the diminished volume associated with depression is likely to be caused by reduced adult neurogenesis; 2) adult neurogenesis can be increased by treatments for depression (i.e., antidepressants, electroconvulsive shock, and physical exercise); 3) latency of therapeutic effect of antidepressant treatment is similar to the time required for maturation of newborn neurons (~4–5 week).

Clinical data indicate that depressed patients show impaired declarative learning and memory and diminished cognitive functions (47). With the magnetic resonance imaging technique, reduced hippocampal volume is found in depressed patients (17) and the magnitude of

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volume loss is linked to the frequency of depressive episode and the duration of depression development (112). Other factors like neuronal loss and decreased dendritic complexity may contribute to the volume loss of the hippocampus; however, adult neurogenesis is likely to play an important role as it is critical for the therapeutic effect of antidepressant treatments (105). These data strengthen the convergent hypothesis that change in neuroplasticity in the hippocampus may be critical for the development of depression and therapeutic effects of antidepressant treatments. Similar to antidepressant treatments, the promoting effect of physical exercise on neurogenesis seems to link to its therapeutic effect on mood and cognition.

NEUROGENESIS IN THE ADULT BRAIN

Neurogenic Niches in Adult Mammalian Brain

Neural stem cells are undifferentiated cells that are the main component for generating the nervous system (86). They are characterized by two key features: unlimited self-renewal ability and potency to generate at least two types of cells (128). Self-renewal is the principle characteristic of stemness in which at least one of the identical copies of the mother cell should be generated after cell division. There are two types of cell division: symmetric and asymmetric. Symmetric division yields two identical copies of stem cell whereas asymmetric division generates one identical copy of the mother cell and one other cell with more determined cell lineage for differentiation. The daughter cells with reduced ability of self-renewal are termed as “progenitor” cells.

One of the main differences between progenitor cells and stem cells is the unlimited self-renewal. In addition, progenitor cells are more proliferative than the dormant stem cells so that they are referred as “transiently amplifying” progenitor cells. After symmetric division, progenitor cells can generate two identical daughter cells, which are different from the mother cell. During brain development, a precursor cell can produce two differentiating cells. Precursor cells in the neural tube are the origin of brain development. The neural tube forms the walls of the ventricular system, including ventricular zone and the subventricular zone (SVZ). Regionalization of the precursor cells during development is maintained in the adult brain.

Radial glia play an essential role during brain development in which they act as precursor cells (99) and provide structure for guiding the migration of new neurons to the appropriate position in the cortex (99). After brain development, radial glia are retained in adulthood in the neurogenic regions like the SVZ and the subgranular zone (SGZ) (7). Those in the nonneurogenic regions will transform into astrocytes (88). Radial glia-like cells retain stem cell characteristics in the adult SGZ

and SVZ; hence, they are suggested to be the source of adult neurogenesis (7). Several results have been updated to support the speculation that glial-fibrillary acidic protein (GFAP)-positive cells are the stem cell origin for the two neurogenic regions: SGZ and SVZ. Doetsch and colleagues demonstrated that neurospheres of multipotent neural progenitor cells can be formed from the astrocytes isolated from the SVZ (33). Furthermore, after withdrawing the blockade of cell proliferation in the SVZ and the SGZ of the hippocampus in the adult brain using cytostatic drug cytosine- β -D-arabino-furonoside (Ara-c), the first type of cell to reappear is the GFAP-positive cells (34). Using the viral infection technique to transmit a reporter gene specifically into only astrocytes in the SVZ, it was reported that those genetically engineered GFAP-positive cells are found in neurons in the olfactory bulb (33). Although progenitor cells express GFAP, the terms “astrocyte” may not be appropriate for neural stem cells in the neurogenic zones. “Astrocyte-like” or “radial glia-like” terms are more suitable for describing the precursor cells.

Neurogenesis was initially claimed to occur only during embryonic and early postnatal development. In 1960s, Joseph Altman and colleagues are the first to report the production of new neurons in the dentate gyrus of the hippocampus (6) and the migration path of the new neurons in the SVZ to the olfactory bulb (5). However, these findings were not generally accepted in the neuroscience field at that time until confirmatory studies were published in 1980s and 1990s. These include Goldman and Nottebohm’s findings in which new neurons can be generated in the song system of adult birds in 1980s (51) and discovery by Cameron et al. and Gould et al. on adult neurogenesis in rodent hippocampus using advanced techniques [5-bromo-3'-deoxyuridine (BrdU) labeling for proliferating cells] in 1990s (23,54). These results brought a lot of excitement to the field and resulted in intensive research in recent years. It has been shown that adult neurogenesis occurs not only in rodent, but also in the tree shrew (55), marmoset (56), and even in human (postmortem tissue) visualized using BrdU (40) and Ki-67 labeling (104).

Adult Hippocampal Neurogenesis

The hippocampus is a bilateral structure located in the medial temporal lobes of the cerebral cortex. It is part of the limbic system and is critically important for memory and emotional regulation. Similar to other cortical circuits, the hippocampal network can be dynamically changed in which its connectivity can be modified by altering the synaptic strength and number in an activity-dependent manner. In response to the neuronal activity, synaptic plasticity can be changed via altering synaptic connection (i.e., addition, strengthening, weakening,

or elimination of synapse). Synaptic plasticity in the hippocampus plays an important role in memory formation and hippocampal-dependent learning tasks (96). Besides synaptic remodeling of the existing neurons, incorporation of new neurons in the dentate gyrus provides additional capacity to the adult hippocampus in modifying the existing neuronal circuitry (110).

The primary components of the hippocampal network are GABAergic interneurons and glutamatergic principal cells. Based on the anatomical properties of the glutamatergic principal neurons, subregions of the hippocampus are defined as dentate gyrus (DG), CA3, and CA1 regions. There are two circuitry systems in the hippocampus: the trisynaptic and monosynaptic systems. The dentate gyrus and CA fields essentially construct the trisynaptic core circuit of the hippocampus. In the trisynaptic system, glutamatergic synaptic input from the entorhinal cortex first approaches the dendrite of the granule cells in the dentate gyrus (synapse 1). The axons of those granular cells form the mossy fiber tract and project to the pyramidal neurons in the CA3 region (synapse 2). CA3 neurons project to the neurons of CA1 through the Shaffer collateral pathway (synapse 3). The axons of the CA1 pyramidal neurons project to the subiculum, then out of the hippocampus to the entorhinal cortex. For the monosynaptic system, direct projection from the entorhinal cortex to CA3 or CA1 pyramidal neurons can be found for information processing in the hippocampus. Newborn neurons are only generated in the SGZ of the dentate gyrus in the hippocampus, thus mossy fiber connection between the dentate gyrus and the CA3 region can be modified by adult neurogenesis.

It is generally accepted that there are two neurogenic zones in the adult brain: the hippocampus and the SVZ of the olfactory system. Although it has been reported that neurogenesis occurs in other brain areas such as the neocortex (118), striatum (12), amygdala (14), and substantia nigra (137), the level of neurogenesis is at a relatively lower level in these regions. Hippocampal neurogenesis is much more locally confined in comparison to neurogenesis in the SVZ. In the SVZ, precursor cells reside in one to two cell-thick regions lateral from the ventricular wall. Those developing new neurons migrate a relatively long distance along the rostral migratory stream to the olfactory bulb and finally develop into the inhibitory interneurons (81). For hippocampus neurogenesis, precursor cells reside in a narrow band of tissue, the SGZ, which is defined as approximately 20–25 μm (approximately two cell nuclei wide) from granular cell layer. Precursor cells that proliferate in the SGZ only migrate a short distance to the granular cell layer and differentiate into functional neurons in the dentate gyrus. Quantitative analysis revealed that around 30,000–80,000 SVZ-derived newborn cells generated in the ol-

factory bulb every day, which is dramatically greater in comparison to the hippocampus with around 9,000 new neuronal cells, equivalent to 0.1% of the granule cell population, are generated per day in adult rat dentate gyrus (21).

Neural precursor cells of the hippocampus located in the SGZ can be divided into three types: 1) type 1 cells: radial glial-like stem cells, 2) type 2 cells: transiently amplifying progenitor cells that give rise to 3) type 3 cells: the migrating neuroblast that expresses doublecortin. The type 3 cells, following completion of the cell cycle, undergo postmitotic neuronal differentiation into granular cells. The majority of dividing cells are type 2 cells in the dentate gyrus. Injection of BrdU (a thymidine analog inserted into DNA of the dividing cells during the S phase of cell cycle) is commonly applied for investigating the neural stem cell proliferation. Single BrdU injection protocol revealed that around 2–10% of neural stem cells are labeled and this indicated that the mitotic activity of these cells is relatively low (45). Transiently amplifying cells (type 2 cells) show high mitotic activity in a short period of around 3–5 days. With evidence from Ki-67 staining (a molecular expressed in proliferative cells in G₁, S, and G₂ phase of the cell cycle), it is known that approximately 80% of labeled cells are neural progenitor cells, and only 25% of neural stem cells are labeled (121).

Upon exit from the cell cycle, postmitotic cells establish axonal connection with the CA3 region rapidly within 4–10 days (59). As newborn cells undergo differentiation, the dendritic morphology becomes progressively complex and the neurites extend deeper into the granular cell layer. The new granular cells show similar electrophysiological responses to the surrounding older cells after division (124). It is shown that neuronal maturation takes approximately 3–4 weeks to enable new neurons to be functionally integrated into the existing circuit (42). No more mature granule cell morphology is observed at day 7 while apical dendritic tree and basal dendritic projection to the hilus is observed at day 14. Although 2-week-old neurons are still immature compared to fully differentiated neurons, they do receive synaptic inputs from GABAergic interneurons at day 8. Immature neurons display enhanced synaptic plasticity in the adult hippocampus in which those cells demonstrate a lower threshold for the long-term potentiation (LTP) induction in response to theta-burst stimulation (110). GABA is excitatory in the immature neurons, but is inhibitory around the time that the excitatory glutamatergic synapses are established. This may explain why immature neurons have a distinct physiology of showing more depolarized resting potentials and increased LTP (2), which is not seen in the mature neurons.

Elimination of new proliferating cells is rapid. Most of the newborn neurons are eliminated by cell apoptosis (around 50–80% of new neurons die within the first month after division if they are not incorporated into the existing circuit) (65). However, this process can be counteracted in an activity-dependent and survival-promoting manner. External stimuli like exposure to physical activity, enriched environment, and hippocampal-dependent learning have been shown to positively regulate the process (53,66,125).

FUNCTIONAL RECRUITMENT OF NEWBORN NEURONS IN THE ADULT BRAIN

Although there is convergent evidence supporting the view that newborn cells in the dentate gyrus of the adult hippocampus can be functionally integrated into the existing neuronal circuitry (84), the role of these new neurons in hippocampal functions remains poorly defined. Both physical activity and enriched environment improve learning and memory (28,125), and are associated with increased adult neurogenesis. Specific training on hippocampal-dependent learning, like Morris water maze training and eye blink conditioning, promotes the survival of newborn neurons in rodents (53). Intensive research has been focused on this topic in recent years to prove that adult neurogenesis in the dentate gyrus is involved in the hippocampal-dependent spatial learning and memory (57).

Functional integration of newly generated neurons into the existing neuronal circuitry has been demonstrated in several studies in which doublecortin-expressing cells (newborn neurons) in the dentate gyrus receive synaptic input from other neurons (8). Those newborn neurons at approximately 7 weeks old demonstrate similar electrophysiological features to the existing mature neurons (124). It is suggested that immature neurons might be able to functionally integrate into the circuits approximately 1–3 weeks after mitosis, and display enhanced synaptic plasticity in the adult hippocampus in which those cells demonstrate a lower threshold for the LTP induction in response to theta-burst stimulation (110).

For studying functions of adult neurogenesis in the hippocampus, ablation of neurogenesis is the most straightforward and common method to explore its involvement in hippocampal functions. If adult neurogenesis is involved in the hippocampal-dependent behaviors like learning and memory, ablation of new cells should impair learning and memory formation. There are three methods for blocking hippocampal cell proliferation: 1) antimetabolic drug administration, 2) irradiation, and 3) genetic manipulation. Administration of methylazoxymethanol (MAM) is a DNA methylating

agent that prevents dividing cells from exiting the cell cycle. MAM treatment for 14 days demonstrated that blockade of hippocampal neurogenesis impairs the hippocampal-dependent task, trace eye-blink conditioning, but did not affect the hippocampal-independent task. Interestingly, another study by Shors and colleagues showed that the same MAM treatment does not cause deficit in contextual fear conditioning and spatial learning in the Morris water maze (114). It might be due to either blockade of hippocampal neurogenesis is incomplete or adult neurogenesis is not required for this kind of hippocampal-dependent memory (110) or there is some compensatory mechanism from the existing neurons. Nevertheless, nonspecific effect of MAM on affecting the protein synthesis and signaling pathway for learning and memory cannot be excluded (77).

Differential effect of ablating hippocampal neurogenesis was found using the second method: irradiation. Impaired contextual fear conditioning is found in mice and rats with irradiation focused either at the hippocampus or at the head (109,129). However, irradiation has also been shown to not affect spatial memory in the water maze test (109). Interestingly, rats with cranially irradiation showed impaired long-term memory retentions after 2–4 weeks of the treatment. This result may suggest that adult neurogenesis is involved in long-term storage of spatial memory (116). Discrepancy among the above studies may be due to different ablation methodologies and the difficulties of behavioral tests, since timing and difficulty of the behavioral tests may affect the involvement of hippocampal neurogenesis (11). Furthermore, it is known that irradiation might damage the stem cell niche in addition to suppressing hippocampal cell proliferation (89). It is difficult to conclude that memory impairment after irradiation is due to either inhibition of cell proliferation or damage on stem cell niche (11).

Both irradiation and antiproliferative drug treatment block hippocampal cell proliferation nonspecifically and can cause detrimental effects on brain physiology and function (19). With advanced research techniques, a more specific and noninvasive genetic approach has been applied to block the proliferation of neural progenitors. However, divergent results are still found. In transgenic mice expressing herpes virus thymidine kinase in GFAP-positive progenitor cells in all neurogenic brain regions, proliferating thymidine kinase cells are killed after oral delivery of the antiviral prodrug gancyclovir (49). Animals show normal spatial memory but impaired contextual fear conditioning. Dupret and colleagues blocked the nestin-positive neural precursors in mice by using the reverse tetracycline-controlled transactivator regulatory system to overexpress proapoptotic protein Bax in the nestin-positive neural precursors (38). This

group demonstrated that ablation of adult neurogenesis in mice resulted in deficits in spatial learning and memory in the water maze test, but not fear-conditioned learning. This observation is echoed with the finding from Zhang and colleagues (136) using the ablation method of inducible removal of the orphan nuclear receptor TLX. These findings may suggest that adult hippocampal neurogenesis is involved in some specific type of hippocampal-dependent behaviors, which might involve the trisynaptic system of the hippocampus.

Even with contradictory results from the above experiments, strong correlation has been found between neurogenesis, learning, and LTP. In mice with access to a running wheel, increased neurogenesis in those mice show association with improved spatial learning and enhanced LTP (123). It is known that immature neurons have lower LTP induction threshold in the adult hippocampus and increased new dentate granular cells results in enhancement in LTP (110). The observation on the correlations might be due to increased neuronal plasticity, which contributed by increased axonal contacts of newborn neurons. In a correlative study, Kempermann and Gage (64) reported that there is a significant correlation between spatial learning and baseline level of hippocampal neurogenesis. They suggested that baseline level of hippocampal neurogenesis in different strains of mice predicts the performance in the acquisition phase of water maze training, but not probe trial performance. They proposed that adult neurogenesis is involved in specific aspects of hippocampal function, especially for acquisition of new information. By the same token, water maze performance in aged mice predicts the level of adult neurogenesis in the hippocampus (35). External stimuli like environmental enrichment and voluntary exercise, which increase hippocampal neurogenesis, improve the performance in hippocampal-dependent tasks (18). The functional role of neurogenesis is also revealed by examining the learning effect on neurogenesis. Hippocampal-dependent learning, but not hippocampal-independent learning, is shown to enhance survival of newborn neurons (53). Both cell proliferation and cell survival are reported to be enhanced after learning (32).

Furthermore, alteration in neurogenesis is proposed to be the underlying cause of psychiatric disorders including depressive disorders and schizophrenia (39). The key role of neurogenesis in therapeutic effects of antidepressants on anxiety-related behaviors has been demonstrated recently by Santarelli and colleagues (106). They proposed that reduced latency of a novelty-suppressed feeding is associated with decreased anxiety behavior, which is mediated by increased neurogenesis. Discovery of a promoting effect of antidepressants (83) and antipsychotics (79) on neurogenesis suggests an al-

ternate mechanism of those drugs on psychiatric disorders. Those findings may also suggest the functional role of adult neurogenesis in behavioral and cognition aspects.

ENVIRONMENTAL REGULATION OF HIPPOCAMPAL NEUROGENESIS

Adult neurogenesis consists of three major steps: proliferation, neuronal determination, and maturation. Every step of neurogenesis is tightly regulated so as to allow the adult brain to tailor its production of newborn neurons in response to the demands from environmental challenges.

Stress/Glucocorticoid Effect on Adult Neurogenesis and its Mechanisms

Potent inhibition on hippocampal neurogenesis by stress has been demonstrated in different mammalian species including the mouse, rat, tree shrew, and marmoset (87) using several experimental stress models: resident-intruder model in territorial tree shrew (55), predator odor (120), restraint (101), social isolation (78), and electrical foot shocks (83). Although effects of stress on suppressing hippocampal cell proliferation are well documented, detailed mechanisms still remain unclear. Substantial evidence indicates that stress hormone glucocorticoids, which are secreted from adrenal gland, play an essential role on suppressive effect on hippocampal neurogenesis. The process of cell proliferation (132), differentiation (131, and survival (130) of newborn cells are reported to be affected by stress hormones.

Stress exposure activates the limbic hypothalamic–pituitary–adrenal (HPA) system (a classic neuroendocrine circuit that integrates emotional, cognitive, and autonomic inputs in response to stress), which in turn triggers the secretion of corticotrophin-releasing hormone (CRH) from the hypothalamic paraventricular nucleus (PVN). This activates the anterior pituitary gland to release adrenocorticotrophic hormone (ACTH), and then causes secretion of glucocorticoids (corticosterone in rodents, cortisol in humans) from the adrenal cortex into the blood circulation. Under physiological condition, glucocorticoids exert a wide range of effects on raising the glucose levels for stress response, like increasing the carbohydrate and lipid metabolism and inducing catabolic actions on the muscle and bone tissues. Acute exposure to stress is harmless and triggers behavioral adaptation. Chronic stress, however, induces dysfunction of the HPA feedback regulation that results in overexposure of the brain and body to the glucocorticoids, and in turn increases the vulnerability to pathological insults (30). Activation of the HPA axis is regulated by a feedback regulation, which involves activation of

mineralocorticoid receptor (MR) and glucocorticoid receptor (GR). MR has a 10-fold higher affinity to corticosterone compared to GR. MR is highly expressed in several brain regions, like the hippocampus, lateral septum, and amygdala, whereas GRs are ubiquitously distributed and with a higher expression level in the brain regions (e.g., hippocampus, paraventricular nucleus, and pituitary), which are the feedback sites of stress response following the glucocorticoid release. Owing to difference in the binding affinity for corticosterone and circadian rhythm, MR is substantially occupied by low levels of glucocorticoids like at resting stage during the circadian trough, while GR is fully activated only with high levels of the stress hormone like after stress exposure or in the circadian peak prior to the onset of activity period. A change in MR/GR occupation ratio may affect the electrophysiological properties of the hippocampus, and hence influence plasticity of the hippocampal network, particularly affecting the relevant cells that express both MR and GR, such as CA1 pyramidal neurons and the granular cells in the dentate gyrus. Nevertheless, glucocorticoids are able to influence intrinsic properties of hippocampal neurons by increasing the level of endogenous Ca^{2+} level and thereby activate Ca^{2+} -gate K^{+} channels (67), in turn promoting the gene expression of channels that increases Ca^{2+} influx (95).

Salivary cortisol level increases rapidly after stress exposure in human subjects (69). Chronic stress increases cortisol level and predisposes to depression in humans (108). Accumulative evidence suggests that stress suppresses neurogenesis through the activation of HPA axis and glucocorticoid receptors. The effect of stress is mainly mediated by glucocorticoids. Elimination of endogenous corticosterone by adrenalectomy during the postnatal period increases cell proliferation and adult neurogenesis in the hippocampus (74). Conversely, animals with corticosterone treatment show decreased progenitor cell proliferation (20). Also, exposure of rat pups during the first postnatal week (maximal neurogenesis occurs at this period) to the odor of predator results in decreased proliferation of progenitor cells, which is associated with elevated plasma corticosterone level (119). Inhibitory effects of stress on hippocampal cell proliferation or neurogenesis has been repeatedly demonstrated in different species with different stress protocols, like in the rat (120), tree shrew (55), and marmoset (58). It is known that hippocampal neurogenesis declines in aged rats (22). The increased level of corticosteroids is thought to be the culprit for the decline in neurogenesis during ageing (98). Higher expression of glucocorticoid receptor levels on precursor cells in aged rats may explain the stronger sensitivity of precursor cells to the detrimental effects of corticosteroids in age-

ing (90). In addition, activation of glucocorticoid receptors exerts similar effect on hippocampal cell proliferation (68). Pharmacological blockade of glucocorticoid receptors shows normalized stress- or corticosterone-reduced adult neurogenesis (100).

It is known that increased glucocorticoid levels not only inhibit cell proliferation, but also decrease survival and differentiation of new cells (130). It is still unclear whether glucocorticoids exert their effects directly on progenitors or indirectly through activation of mature granular cells. GRs are found in neuronal progenitors and mature neurons while MRs are only present in mature neurons (49). It is possible that the effects of stress on neurogenesis can be exerted directly on neuronal progenitors and mature neurons. However, the effect of glucocorticoids on hippocampal neurogenesis seems to be NMDA receptor dependent. Stress increases glutamate release in the hippocampus (1). Excess glutamate activates GRs of mature neurons and then results in activation of NMDA receptors, and this seems to mediate the inhibitory effect of glucocorticoids on granular cell proliferation (55). Activation of NMDA receptors is shown to suppress cell proliferation whereas blockade by an antagonist shows the reverse effect and prevents the suppression on cell proliferation (94).

In addition to increased glutamate and Ca^{2+} excitotoxicity, reduction in the neurotrophic support might also contribute to the stress effects on hippocampal neurogenesis. It is well known that both acute and chronic stress decrease the expression level of brain-derived neurotrophic factor (BDNF) in the hippocampus (37). Similarly, reduced BDNF expression might be due to increased glucocorticoid levels after stress exposure. It is shown that adrenalectomy increases BDNF level (26). Continuous administration of corticosterone showed a deleterious effect on BDNF expression levels (62).

Exercise Effect on Adult Neurogenesis and its Mechanism

Exercise is known to enhance learning and memory and counteract age-related mental decline. In human subjects, it was reported that physically fit individuals have better cognitive and memory performance in comparison to their sedentary peers (135).

The best outcomes of the effects of exercise are found in subjects with moderate exercise level. Improved cognitive performance by increased physical activity has also been demonstrated in animal studies on rats and mice (9,46). The studies on exercise effect on depression reveal that youngsters and elderly participating in exercise programs show fewer depressive symptoms and less susceptibility to developing depression (92). Mather and his colleagues classified the effect of

exercise as adjunct to antidepressant treatment (85). The antidepressant effect of exercise can even extend for 21 months (115) and 6 months (10) after the cessation of exercise training. Similar to antidepressant treatments, rodents with access to wheel running showed significantly increased neurotrophic factors and increased cell proliferation and neurogenesis in the hippocampus (97,123). Exercised animals also showed improvement in both acquisition and retention in hippocampal-dependent tasks like the Morris water maze (125) and radial arm maze (111).

The effect of exercise on mood and cognition has been hypothesized to be mediated partly by increased neurogenesis in the hippocampus. Voluntary physical exercise is known to be a strong inducer for hippocampal neurogenesis (123), but not the SVZ and olfactory bulb (18). The regulation of adult neurogenesis includes a less specific phase of cell proliferation, which can be induced by many external factors, and a more specific phase of cell survival, which is promoted specifically by hippocampal-dependent stimulus. In fact, net increase in neurogenesis is determined by survival rate of newly generated cells rather than cell proliferation (63). Physical exercise robustly increases precursor cell proliferation (primarily the type 2 progenitor cells), thereby increasing the number of progenitor cells for further maturation and functional integration (73). It is shown that wheel running increases cell proliferation and survival of new neurons in the hippocampus by three- to fourfold (123). Unlike the enriched environment that increases adult neurogenesis via enhancement on cell survival (64), physical exercise influences both expansion phase of progenitors cell and survival phase of newly generated neurons. The voluntary wheel running and forced running on a treadmill are the most suitable methods for studying the effects of exercise on adult neurogenesis in rodents (68,73,122,123). In acute condition, a similar effect on hippocampal neurogenesis is observed in treadmill training (68,122). It was found that exercise-derived promoting effect on hippocampal neurogenesis can be transmitted to offspring from pregnant mice with voluntary running (15). Studies on the kinetics of exercise effect on neurogenesis revealed that 3 days of running brought cell proliferation to its peak level in group-housed mice (73). The increase in cell proliferation could be observed at 10 days, but then reduced to baseline after a month of running.

Ageing is known to be the strongest suppressor for adult hippocampal neurogenesis; however, the exercise effect on neurogenesis is also observed in aged rodents. Ageing animals with continuous exercise demonstrate significantly fewer declines in new cell production compared to their sedentary counterparts (72). Exercise-

promoted cell proliferation and cell survival are observed in both young and old animals. In fact, mice that started physical training at either middle age or old age showed elevated levels of newborn neurons (125).

Hippocampal neurogenesis is found to be profoundly enhanced by exercise in rodent brains. However, it is still unclear whether enhancement of hippocampal neurogenesis by physical exercise contributes to the improvement in learning and memory, facilitates hippocampal plasticity, and increases resistance to stress or depression insults. Various effects of exercise on neurogenesis, learning and memory, and depression seem to be mediated by complicated mechanisms. Neurotrophic factors have found to be essentially involved in regulating the neuronal progenitor cells (61). Several classes of growth factors [BDNF, insulin-like growth factor-I (IGF-1), and vascular endothelial-derived growth factor (VEGF)] have been suggested as principal mediators for the exercise effect on the overall brain health. It is proposed that IGF-1 and BDNF work in concert to regulate the exercise effect on learning and depression while IGF-1 also works with VEGF to induce hippocampal neurogenesis and angiogenesis (29).

Convergent evidence from animal and human studies indicates that BDNF plays an important role in modulating depression and hippocampal plasticity (75). Hippocampal BDNF level robustly increased in response to exercise and this increase remained high throughout the whole hippocampus with sustained exercise for weeks (13,28). It is shown that inhibiting the BDNF signaling in the hippocampus by intrahippocampal injection of anti-TrkB (antibody that blocks the receptor of BDNF) attenuates the exercise effect on hippocampal learning and memory (126). Recent study using genetically engineered mice with lower BDNF level showed that BDNF is required for long-term survival of newborn cells (76). In addition, exercise-increased hippocampal BDNF level is linked to therapeutic effect of exercise on depression. Heterogeneous BDNF knock-out mice showed impaired antidepressant response (91). Also, antidepressant-like effects can be produced by infusion of BDNF or overexpression of TrkB receptors in the hippocampus (71,113). It is likely that BDNF-mediated TrkB signaling is required for the antidepressant-like effects for both exercise and antidepressant treatment.

Like BDNF, IGF-1 level is also increased in exercised animals in both the hippocampus and the blood. The increase in peripheral system occurs within 1 h of running (52). Peripheral increase of IGF-1 plays an important role in mediating the exercise effect on promoting hippocampal neurogenesis and hippocampal-dependent learning and memory. Depletion of circulating IGF-1 blocks the exercise-induced hippocampal cell

proliferation (24). Also, effects of exercise are absent in IGF-1 null-mutant mice (122). Injection of anti-IGF-1 to the hippocampal region diminishes improvement in spatial recall (31). IGF-1 is shown to increase BDNF signaling in response to activity stimulation, and blockade of IGF-1 signaling in exercised animals also prevents the increase in hippocampal BDNF levels. Interplay between BDNF and IGF-1 supports that BDNF works as a downstream target of IGF-1 in response to exercise, and then mediates effects of exercise on improving hippocampal neurogenesis and plasticity. Another neurotrophic factor, VEGF, is also suggested to be the sole mediator between exercise and neurogenesis in addition to the above two systemic factors. Both IGF-1 and VEGF can be increased by exercise and are able to cross the blood–brain barrier. Blocking VEGF prevents exercise-increased hippocampal neurogenesis, which is similar to the effect of IGF-1 ablation (43).

REGULATION OF HIPPOCAMPAL STRUCTURAL PLASTICITY BY STRESS AND PHYSICAL EXERCISE

Chronic stress impairs learning and memory, and increases susceptibility to affective disorders, and these observations are always associated with decreased hippocampal neurogenesis. Stress also demonstrates wide influence on cellular processes in the hippocampus, such as inducing dendritic remodeling and depleting the neurotrophic levels; therefore, it is likely that stress exerts its detrimental effect on the hippocampus in concert with multiple mechanisms in addition to inhibiting neurogenesis. Interestingly, increased neurogenesis by exercise is always associated with enhancement in hippocampal plasticity. In rodents, physical exercise is found not only to increase hippocampal cell proliferation, but also to affect dendritic morphology of newborn neurons and existing mature neurons. It is clear that not only cellular plasticity, but also structural plasticity, in the hippocampus is affected differentially by stress and exercise, which in turn can possibly affect the whole hippocampal plasticity.

Stress Effect on Structural Plasticity in the Hippocampus

Exposures to chronic stress cause diverse changes to the hippocampus and these changes can be the potential culprits for the hippocampal dysfunction associated with stress. Clinical studies indicated that hippocampal shrinkage is found in patients with depression or posttraumatic brain injury. Increased cortisol level in the elderly correlated with decreased hippocampal volume and memory deficit (80). This indicates that elevated glucocorticoid level may contribute to the volume loss. Changes in neuropil, glial number, dendritic complexity, neuronal apo-

ptosis, or decreased hippocampal neurogenesis can contribute to volumetric reduction of the hippocampus. However, it is found that stress itself does not cause loss of hippocampal pyramidal cells in the granular cell layers (93). Exposure to stress or hypercortisolism suppresses hippocampal excitability and long-term potentiation, which is always associated with impaired hippocampus-dependent memory. Reduction in neuropil of the hippocampal neurons may partly contribute to decreased hippocampal volume (48). However, other factors must contribute to the major loss of hippocampal volume after exposure to stress. Later it was shown that chronic stress causes dendritic atrophy in the hippocampus (107).

Stress-induced functional changes may involve axonal change, dendritic remodeling, and synapse loss, and hence affect the neuronal connection in the brain. It is known that stress or exogenous corticosterone application primarily induces dendritic atrophy in the apical dendrites of the CA3 regions and with lesser effect on the CA1 region and the dentate gyrus. Chronic stress mildly affects the morphology of pyramidal neurons in the CA1 region (133). However, recent study revealed that the effects of stress on the CA1 morphology are more apparent following the activation of HPA axis (3). Severe dendritic retraction in the CA3 area has been reported with various stress paradigms, like prolonged corticosterone treatment, chronic restraint stress, and the psychosocial stress model in various animal species. The atrophy is found in decreased number and length of branch points of the apical dendrites in the CA3 region. The strongest retraction of dendritic branch is found in the middle third of the apical tree, which shows changes in NMDA glutaminergic receptor's sensitivity in response to stress (70), but not the basal tree. The stress-induced morphological changes can be prevented by administration of corticosteroid synthesis inhibitor (82) and NMDA receptor antagonist (127).

Exercise Effect on Structural Plasticity in the Hippocampus

Physical exercise is known to change the basic properties of synaptic plasticity in the brain, particularly the hippocampus. LTP, a physiological form of memory and learning formation, is shown to be enhanced by physical activity (16). Comparing the hippocampal slice of runner mice to control mice, the LTP amplitude is enhanced in the dentate gyrus while there is no change in the CA1 region of the runner mice (123). Both voluntary running and forced treadmill running led to the same enhancement on LTP in the dentate region of the hippocampus (44). The structural changes after exercise may be reflected in improvement in synaptic plasticity. The exercise effect on changing synaptic plasticity in the dentate gyrus may indicate the contribution from newborn neu-

rons. In newborn neurons identified with a retroviral labeling method, it is reported that exercise accelerates the maturation of newborn neurons with special enhancement in the mushroom spine (124).

Alteration in spine size and quantity is tightly linked to LTP induction and change in synaptic strength. In fact, influence on hippocampal structural remodeling after running is so widespread that many hippocampal regions are affected (the dentate gyrus, CA1, entorhinal cortex) (117). Animals with exercise show not only increased spine density, but also increased cell proportion with one to two primary dendrites and overall dendritic length (103). In addition, physical exercise also increases the spine density in CA1 and entorhinal cortex layer III (117). Glasper and colleagues reported that enhancement on dendritic spine density after 2-week running is observed in the granular cells in the dentate gyrus and CA1 region, but not CA3 region (50). In addition, this group demonstrated that blockade of IGF-1 (using peripheral infusion of anti-IGF-1 antibody) prevents the exercise effect on increasing the spine density on the basal dendrites in the CA1 region, which may suggest the involvement of IGF-1 in mediating the exercise effect on not only the cell proliferation as previously discussed, but also dendritic plasticity.

CONCLUDING REMARKS

Exercise has been shown to improve mood and cognition in human and animals. Opposite regulation on hippocampal neurogenesis and dendritic plasticity by stress and physical exercise provides advanced knowledge on the functions of adult neurogenesis and the possible mechanism of beneficial effect of exercise on stress. The positive influence of exercise is likely to be partly mediated by hippocampal neurogenesis. However, in adult hippocampus, changes in dendritic morphology of existing neurons are likely to have profound consequences on neuronal function in the hippocampus; therefore, adult neurogenesis in the dentate region of the hippocampus in fact brings additional plasticity to hippocampal function. Maintenance of the current pool of progenitor cells in the dentate region and enrichment of dendritic complexity of existing pyramidal neurons in the hippocampus may both be essential for keeping an intact neural circuit of the hippocampus. Further investigation into the relative importance of these two factors will provide deeper understanding to the relative contribution of new cells in hippocampal functions.

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