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Exercise and the brain: something to chew on

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Evidence is accumulating that exercise has profound benefits for brain function. Physical activity improves learning and memory in humans and animals. Moreover, an active lifestyle might prevent or delay loss of cognitive function with aging or neurodegenerative disease. Recent research indicates that the effects of exercise on the brain can be enhanced by concurrent consumption of natural products such as omega fatty acids or plant polyphenols. The potential synergy between diet and exercise could involve common cellular pathways important for neurogenesis, cell survival, synaptic plasticity and vascular function. Optimal maintenance of brain health might depend on exercise and intake of natural products.

Introduction

'To get back my youth I would do anything in the world, except take exercise, get up early, or be respectable' (Oscar Wilde, The Picture of Dorian Gray, 1891).

Unfortunately for those of us who subscribe to this outlook, physical activity is the most effective way to maintain a healthy body and mind. This might seem obvious; however, the evidence that exercise is beneficial for general health (i.e. prevention of hypertension, heart disease, type II diabetes, osteoporosis and depression) began to be taken seriously in western society only towards the end of the previous century. Indeed, in 1975 it was observed that 'physical fitness and physical education have no respected place in the American public health movement. Their practitioners have been labeled by at least one elder statesman of public health as "the big-muscle boys", and this contemptuous attitude has persisted to this day' [1]. However, a decade later, in view of the increasing evidence for the health benefits of exercise 'the Public Health Service specified "Physical Fitness and Exercise" as 1 of the 15 areas of greatest importance for improving the health of the public' [2].

Study after study has now shown that the risk of contracting cardiovascular, metabolic and metastatic diseases is mitigated by exercise and a diet containing fruits and vegetables [3,4]. However, it is not as well appreciated that exercise and a healthy diet also provide substantial benefits for brain function. Physical activity improves cognition and might delay age-related memory decline [5,6]. In addition, exercise protects against brain damage caused by stroke [7], promotes recovery after injury [8] and is an antidepressant [9].

Similar to exercise, nutrition affects brain function. Consumption of food high in saturated fats and cholesterol increases the risk of cognitive decline, whereas dietary restriction benefits learning and protects the brain from oxidative stress [10]. There is also increasing evidence that dietary supplements enhance learning and memory. Of interest are the omega fatty acids, certain spices, teas and fruits [11]. Interestingly, these supplements enhance the benefits of exercise for brain function [11–13]. Possible common mechanisms of action for exercise and diet on cognition are discussed.

Exercise and cognition
Young and aged humans

Few studies pertaining to exercise and cognition have been carried out in children and young adults [6]. However, a positive correlation between physical activity and learning and intelligence scores was reported in a meta-analysis of school-age children [14]. In addition, in college students reaction time [15] and vocabulary learning were faster immediately after intense running [16]. Similar results were obtained in young adults after 12 weeks of aerobic training (average age 33) [17]. This research indicates that, rather than observing a ceiling effect of exercise in young people, being active makes a functional difference. In addition, aerobic exercise in childhood might increase the resilience of the brain later in life, resulting in a so-called cognitive reserve. Indeed, a positive correlation between physical activity at ages 15–25 and information processing speed in older men (62–85) was reported [18].

In aging humans the cortex and hippocampus atrophy [19] and memory function declines [20]. These deleterious consequences of aging might be attenuated by exercise [6]. Physically fit aged individuals, identified by self-report of activity level, performed better on measures such as reasoning, working memory, vocabulary and reaction time than their sedentary counterparts [21]. In intervention studies healthy sedentary adults between the ages of 60 and 85 years participate in an exercise regime several times per week over the course of several months to several years. Cognition and fitness is assessed before and after the intervention. Although studies vary in duration, intensity and type of exercise, overall physical activity improves cognitive function [6,22]. This positive outcome is reflected in neurophysiological measures such as electroencephalogram, event related potential (ERP) and functional magnetic resonance imaging (MRI) studies [6]. For example, ERP latency is decreased and amplitude is increased in

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aerobically fit individuals indicating improved neuronal conduction and cortical activation [23]. Moreover, MRI studies showed that prefrontal and temporal gray matter volume was increased in active elderly subjects as compared with sedentary controls [24].

Objective measurements of aerobic fitness and exercise intensity, such as VO_2 max, would optimize research validity. In a recent intervention study in subjects with mild cognitive impairment all participants wore a pedometer during the 6 month study and recorded the number of steps per day [25]. Independent measures of activity are particularly important given the extrinsic and intrinsic sources of variance within the human population. Indeed, with the advent of the identification of Alzheimer's Disease (AD)-related genes, research has begun to focus on specific population groups. For example, Apoliprotein (ApoE)-ε4 allele carriers are considered to be at increased risk for AD [26]. In recent years the benefits of exercise in ApoE-ε4-positive subjects have been analyzed. Epidemiological studies showed that this particular subpopulation could benefit relatively more from maintaining an active lifestyle than non-carriers [27]. In older ApoE-ε4-positive women aerobic fitness was positively correlated with better performance on auditory, visual and spatial learning tasks [28]. In another study a positive correlation between exercise, temporal cortex activation during a learning task and cognition was reported that was stronger in carriers than non-carriers of this gene [29]. However, in a 6 month intervention study there was an attenuated effect of exercise in ApoE-ε4 carriers that showed symptoms of memory decline [25]. Further studies are needed to determine whether early intervention with an active lifestyle (combined with certain dietary supplements) might be particularly beneficial for this at-risk population.

Young and aged rodents

In recent years many exercise and cognition studies have been carried out in adult rodents. This research strongly supports the benefit of exercise for brain function and has provided insight into the underlying cellular mechanisms. Both voluntary and forced exercise paradigms enhanced spatial memory in Morris water maze, Y-maze, T-maze and radial arm maze tests [30]. Running also improved performance in hippocampus-dependent tasks that require limited movement, such as contextual fear conditioning, passive avoidance learning and novel object recognition [31,32]. Moreover, non-hippocampal dependent, anxiety-related behavior, such as performance in the elevated plus maze [33], benefits from voluntary and forced exercise. Interestingly, it remains to be determined whether voluntary and forced exercise is equivalent. Differences have been reported in the extent of behavioral and cellular effects even when activity parameters in both paradigms are closely matched [34].

Similar to elderly humans, the ability to learn new tasks decreases with age in rodents. On the cellular level, the number of synaptic contacts, synaptic strength and plasticity are reduced in the hippocampus [35] and cortex [36]. Recent research has shown that physical activity benefits spatial memory in aging rodents, even upon late-life onset. Housing aged C57Bl/6 male mice with a running wheel for one month improved their acquisition and retention of the water maze task [37]. Furthermore, treadmill training (15 min per day for 7 weeks) improved learning in the Morris water maze in aged rats [38]. Similar results were obtained in studies using transgenic mouse models for AD. Specifically, long-term exercise started 5 months before disease onset improved water-maze learning. In addition, running reduced the load of β-amyloid plaques in both hippocampus and cortex [39]. Moreover, short-term running (3 weeks), initiated after disease onset [40], improved both working and reference memory in aged AD mutant mice. Thus, exercise is beneficial for cognition in normal rodents and in transgenic mouse models of dementia, even if started late in life or after the onset of disease symptoms.

Diet and cognition

In recent years there is increasing evidence that changes in diet can benefit cognition. The most rigorous alterations are intermittent fasting and caloric restriction. Research in animals has shown these regimens enhance learning, neurogenesis and neurotrophin levels. In humans limited calorie intake correlates with a reduced risk for AD [10]. However, dietary restriction regimens are difficult to maintain. In fact, the search for caloric restriction mimetics is a focus of intense research [41]. A variety of dietary supplements have been reported to be beneficial for learning in animals and humans. Positive effects on brain function have been reported for fish oil, teas, fruits, folate, spices and vitamins [11]. Particularly interesting are plant-derived products such as grapes, blueberries, strawberries, tea and cocoa, which benefit memory in rodents [42].

The importance of natural plant products for cognition has been underestimated, in part because the active ingredient(s) in the plant extracts remained unknown, limiting data interpretation. In the majority of studies the compounds under investigation are a mixture of ingredients in which the most potent factor is likely to be diluted. Indeed, animal studies were often performed in aged rodents or transgenic mouse models for neurodegenerative disease [43] because compounds had minimal effects in normal young subjects [44]. However, it seems that plant polyphenols, which are the principal sources of flavanols, a subclass of phytochemicals known as flavonoids, might mediate the observed cognitive effects [42]. In cell culture, flavanols have neuroprotective, antioxidant and antiapoptotic properties [45]. *In vivo*, individual flavanols can enhance synaptic plasticity and learning [12,46]. The flavanol (−)epicatechin is of particular interest because this compound crosses the blood–brain barrier after ingestion in food or drink [12,42]. Consumption of this flavanol improved retention of spatial memory in the water maze, whereas the approved AD drug memantine did not [12].

Interestingly, (−)epicatechin was especially effective in enhancing memory function and synaptic plasticity when combined with voluntary exercise [12]. Similar results were reported for the combination of fish oil and wheel running in rats. Omega-3 fatty acid consumption boosted the effect of exercise on spatial learning, synaptic plasticity and hippocampal brain-derived neurotrophic factor (BDNF) protein levels [13]. This research indicates that

effects of dietary supplementation and physical activity on brain function are synergistic.

Mechanisms that mediate the effects of exercise and nutrition on the brain

Research pertaining to mechanisms underlying the effects of exercise on brain function has focused on changes in neurotransmitters, neurotrophins and vasculature [5]. Specific to the hippocampus, a brain area important for learning and memory, is the robust increase in new neurons with exercise [30]. The beneficial effects of running on cognition could be mediated, at least in part, by enhanced hippocampal neurogenesis [30,47]. Elucidation of effects of nutrition on the brain, by contrast, has concentrated on the antioxidant and neuroprotective aspects of various dietary supplements. More recent work, however, indicates that diet might exert direct effects on neuronal signaling [42]. The effects of diet and exercise could be additive and/or synergistic through activation of common intracellular pathways (Figure 1).

Neurogenesis

The adult mammalian brain produces new neurons in the olfactory bulb and dentate gyrus of the hippocampus throughout life. Many extrinsic and intrinsic (epi)genetic factors can regulate the production of new neurons [48]. Increasing evidence indicates that this process has a role in learning and memory. Ablation of the new cells results in spatial memory deficits [49]. In addition, using markers for immediate early gene expression it has been shown that the new cells are preferentially activated during learning tasks [50]. Furthermore, an increase in neurogenesis is associated with improved cognition. The strongest neurogenic stimulus is exercise. Wheel running in rodents results in a 3–4-fold or even greater increase in the production and survival of new neurons in the dentate gyrus of the hippocampus [30]. The onset of the effect of running on cell genesis is rapid. Cell genesis peaks at three days. After 32 days of running the pro-proliferative effect has returned to baseline. Interestingly, the number of immature neurons continues to increase at this time-point [51].

The robust effect of exercise on neurogenesis is maintained throughout life in rodents. In mice that exercised continuously from young to middle age, the normal age-related decline in cell genesis was significantly less than in their sedentary counterparts [51]. Moreover, in mice that started wheel running in middle age [52] or old age [37], new neuron number was elevated. Furthermore, recent studies showed that physical activity can reverse pregnancy- [53] and radiation-treatment-related [54] decline in hippocampal neurogenesis. It should be noted however, that in certain transgenic mouse models for neurological disease the beneficial effect of physical activity on neurogenesis is equivocal [30]. Transgenic mice that express human presenilin-1 variants linked to early-onset familial AD [55] and a mouse model for Huntington's disease [56] do not show exercise induced neurogenesis. Therefore, the neurogenic and cognitive effects of physical activity should be evaluated carefully across the spectrum of neurological diseases.

Several studies have addressed the issue of whether dietary changes can enhance neurogenesis. Caloric restriction increases the production of new neurons [57]. Dietary folic acid deficiency decreases dentate gyrus cell proliferation [58]. Interestingly, systemic injection of the phytochemical curcumin enhances the new hippocampal cell survival by ~15% [59]. Other plant extracts, such as ginseng and the flavonoid containing gingko biloba might also improve neurogenesis [60–62]. It remains unclear which component(s) of these natural products affects neurogenesis. For example, the individual flavanol (−)epicatechin had no effect on new cell survival in the dentate gyrus [12]. Overall, neurogenic effects of dietary supplements are modest in comparison with exercise.

Synaptic plasticity

The structural changes associated with exercise are reflected in improvements in synaptic plasticity in rodents that run. Long-term potentiation (LTP) was enhanced in hippocampal tissue slices in the dentate gyrus of running versus sedentary mice [63] and *in vivo* in rats that had been housed with a running wheel [64] or given forced treadmill exercise [32]. This change in synaptic plasticity seems to be specific for the dentate gyrus, indicating that neurogenesis might be important [30]. Indeed, although the new cells are a small percentage of the granule cell layer, individual new neurons have a transient increase in LTP amplitude and a decreased induction threshold [65,66]. A proposed mechanism is increased expression of *N*-methyl-D-aspartic acid (NMDA) NR2B receptors in new neurons [66]. Thus, an exercise-induced 3–4-fold increase in highly plastic cells in the dentate gyrus might explain, in part, the profound effect of physical activity on memory function.

Effects of dietary changes on synaptic plasticity have also been investigated. Caloric restriction does not seem to change basal levels of LTP but does protect against aging- [67] and injury-related [68] decline in synaptic plasticity. In addition, several dietary supplements have been shown to influence LTP, albeit all under conditions of aging, drug treatment or injury. The flavanol gingko biloba enhanced synaptic plasticity in aged rats [69]. Ginseng reversed a reduction in LTP associated with chronic morphine treatment [70]. In addition, the green tea polyphenol (−)-epigallocatechin-3-gallate facilitated LTP in a mouse model for Down's syndrome [71]. The aforementioned studies all include mixtures of polyphenols, leaving the active ingredient unknown. The only study in which a single plant product induced LTP, the hippocampal tissue slices were pre-exposed to a weak tetanic stimulation [46]. Thus, the dietary effects on synaptic plasticity are modest. These mild beneficial effects could be additive or synergistic with those of exercise.

Spine density

The positive effects of physical activity extend to fine cell morphology. In particular, exercise affects the properties of dendritic spines, which are actin-rich protusions on the dendrites that contain excitatory synapses. Changes in spine size and quantity are associated with LTP induction and are considered to support changes in synaptic strength. In a recent study it was shown that running
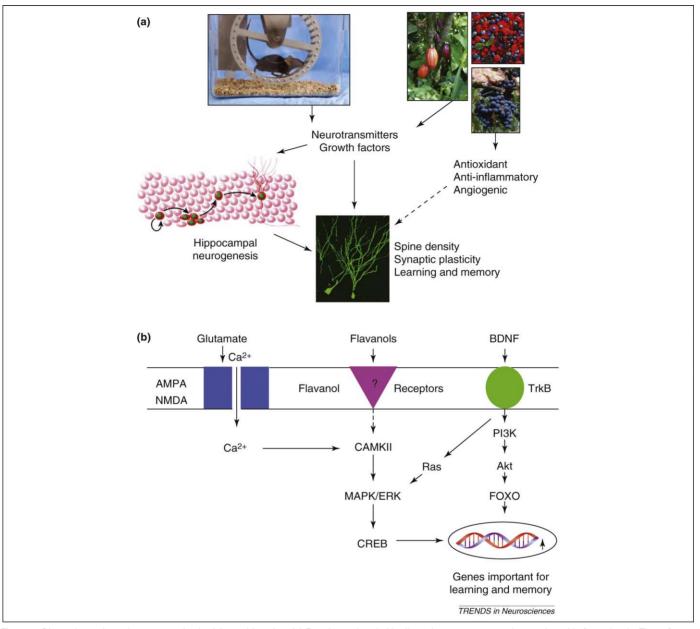
Figure 1. Diet and exercise enhance synaptic plasticity and learning. **(a)** Exercise and probably diet enhance neurotransmitter and trophic factor levels. These factors directly enhance the function of mature neurons and stimulate the production of new neurons in the hippocampus. **(b)** Nutrition and exercise affect neuronal signaling pathways important for synaptic plasticity and cognitive function. BDNF and glutamate act at receptors that regulate calcium/calmodulin-dependent protein kinase II (CaMKII) and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) systems. Flavanols might activate similar signaling pathways, raising the possibility that natural compounds have a selective neuronal receptor (? indicates a hypothetical receptor). BDNF also influences the phosphatidylinositol 3-kinase (PI3K)/ Akt and the FOXO subfamily of forkhead transcription factors, elevating expression of genes important for learning and memory. Running mouse image photo courtesy of Marc Lieberman.

enhanced spine density in the dentate gyrus, area CA1 and entorhinal cortex layer III [72], extending previous work [73]. Physical activity also accelerates the maturation of dendritic spines in newborn neurons [74].

The effects of plant products on neuronal morphology have mainly been studied in culture, in which research showed that plant polyphenols enhance neurite outgrowth [45]. Interestingly, *in vivo* the effect of dietary supplementation with the flavanols on neuronal morphology was very effective combined with running. Using DiI labeling it was shown that spine density was significantly increased in hippocampal granule cells. Upon microarray analysis of hippocampal tissue of mice that consumed this compound,

expression of genes associated with neurite extension and synaptic plasticity was enhanced [12].

Angiogenesis and vascular growth factors

Exercise influences brain vasculature. In particular, physical activity increases the proliferation of brain endothelial cells and angiogenesis throughout the brain [5]. The growth factors insulin-like growth factor (IGF) and vascular endothelial growth factor (VEGF) have an important role in the angiogenic and neurogenic effects of exercise on the brain. Running enhances hippocampal IGF gene expression [75] and increases serum levels of both IGF [75] and VEGF [76]. These factors also play an important

part in hippocampal neurogenesis. Hippocampal gene transfer of VEGF [77] and peripheral infusion of IGF-1 enhanced neurogenesis [78]. Blockade of peripheral VEGF and IGF-1 inhibited the increase in neurogenesis observed with running [76,79].

Although vasculature and neurogenesis are closely associated [80], it is unclear whether cell genesis requires angiogenesis. Using MRI imaging in mice and humans a correlation between exercise, dentate gyrus blood flow and neurogenesis was reported. It was suggested that changes in brain blood flow might be an indirect measure for neurogenesis in humans [17]. However, the MRI findings were not accompanied by histological evidence for running-induced changes in vasculature in mice [17]. In contrast to the MRI study, in aged mice voluntary exercise did not affect angiogenesis but did enhance neurogenesis [37]. Moreover, in young mice limited running robustly increased the survival of newly generated cells with no change in angiogenesis [12]. These findings provide evidence for an uncoupling of neurogenesis and vascularization.

The effect of plant polyphenols on angiogenesis might be superior to exercise [12]. Human research shows that flavanols improve cardiovascular function and lower blood pressure [81]. In addition, imaging studies in humans drinking a flavanol-rich cocoa beverage showed enhanced cortical blood flow [82]. In mice flavanols enhanced hippocampal vascularization, especially in combination with exercise [12]. It is of interest that both flavanols [83] and exercise [84] increase endothelial nitric oxide synthesis. Altogether, these findings indicate that a diet rich in plant products might stave off vascular dementia, especially when combined with exercise [85] (Figure 2).

Neurotransmitters and growth factors
There is large a body of research showing that physical activity can change the function of neurotransmitter systems in the brain. Initial research into the central effects of exercise indicated that the 'joggers high' resulted from enhanced opioid function [86]. More recently, exercise has been found to upregulate genes related to synaptic plasticity. In particular, the glutamatergic system is enhanced [87]. Running increased both NR2A and NR2B subtypes of the NMDA receptor in the hippocampus [64,87]. In addition, in mice lacking the NMDA receptor ε1 subunit (NR2A) the increase in neurogenesis and BDNF protein levels did not change with exercise [88]. Interestingly, the predominant effect of physical activity seems to be on NMDA-receptor-mediated glutamatergic transmission. It remains to be determined whether more subtle changes such as enhanced recruitment of AMPA receptors to the synapse occur with exercise.

Physical activity also activates the monoamine system [89] and promotes recovery from depression [9]. Indeed, the antidepressant effect of exercise in humans has been shown to be just as potent as that of serotonergic medications [90]. Exercise increases tryptophan hydroxylase, which is the rate-limiting enzyme of serotonin biosynthesis in brainstem raphe neurons [89]. The dentate gyrus contains 5-hydroxytryptamine 5-HT$_{1A}$ receptors and receives serotonergic input from the raphe nucleus. Similar to exercise, serotonergic antidepressants such as fluoxetine [91] can enhance cell genesis, whereas administration of the serotonin 5-HT$_{1A}$ receptor antagonists decreases cell proliferation in the dentate gyrus [92]. It has been suggested that enhanced neurogenesis might be a common underlying treatment mechanism between exercise and antidepressants. However, it should be noted that exercise has acute and robust neurogenic effects, whereas fluoxetine requires chronic administration and has variable effects on cell genesis [93–95].

The effects of running on neurotrophin gene expression and protein levels have also been investigated extensively
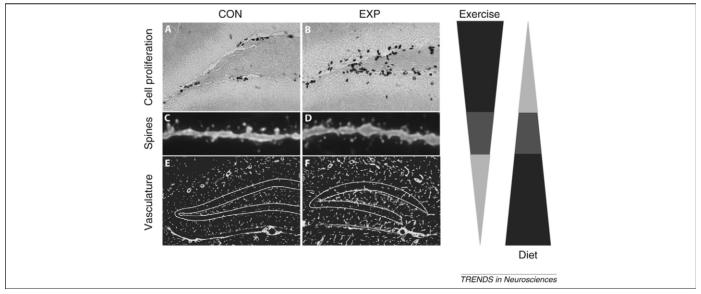

Figure 2. Exercise and diet have complementary and synergistic effects on brain function. The most profound effect of exercise is on hippocampal neurogenesis, whereas the strongest influence of a flavanol-rich diet might be on vascularization of the brain. **(A,B)** Bromodeoxyuridine (BrdU) labeling of new cells in the dentate gyrus of the hippocampus of C57Bl/6 mice. In comparison with sedentary controls (A), running wheel exercise (B) enhances the number of new cells. **(C,D)** Dendritic spines labeled with DiI in mature hippocampal granule cells. Relative to controls (C), running and/or a flavanol-containing diet (D) increase neuronal spine density. **(E,F)** Tomato lectin staining visualized hippocampal blood vessels; the granule cell layer of the dentate gyrus is outlined in white in the panels. A flavanol-rich diet enhanced dentate gyrus vascularization, especially when combined with running (F), as compared with control mice (E). Abbreviations: CON, control group; EXP, experimental group. Panels A and B were reproduced from Ref. [103]. Panels C, D, E and F: Copyright 2007 by the Society for Neuroscience.

[5,96]. The neurotrophin BDNF is considered to be the most important factor upregulated by physical activity because it has an important role in synaptic plasticity, cell genesis, growth and survival [5]. Interestingly, there is a positive interaction between BDNF expression and serotonin. Serotonin receptor activation enhanced BDNF expression in hippocampal cells [97], and BDNF treatment increased tryptophan hydroxylase expression in raphe nucleus neurons [98]. With exercise, levels of BDNF mRNA in the hippocampus increased rapidly and remained elevated for weeks. BDNF protein levels also increased with running [5]. Selective knockout of the tyrosine receptor kinase B (trkB) in hippocampal neural progenitor cells prevented the exercise-induced increase in neurogenesis [95]. Furthermore, intracerebral infusion of BDNF increased cell genesis in the dentate gyrus [99], but not in the subventricular zone [100], consistent with data showing that the neurogenic effect of exercise is limited to the hippocampus [101].

The traditional view of natural products is that they are antioxidant and anti-inflammatory agents but do not directly affect central neuronal signaling. More recent work indicates otherwise [42]. For example, the flavanol fisetin was found to improve LTP through a CREB/ERK (cAMP-response-element-binding protein/extracellular signal-regulated kinase) mechanism in acute tissue slices [46]. *In vivo*, supplementation with a blueberry diet enhanced spatial working memory in rats and increased hippocampal BDNF and CREB levels. Component analysis of the blueberry extract showed that, although the rats consumed more anthocyanins than flavanols, brain and plasma levels of flavanols were the highest. This indicates that flavanols might be directly involved in the observed effects [102]. Furthermore, the combination of fish oil and exercise elevated levels of hippocampal BDNF and its downstream effectors synapsin I and CREB, which are important for learning [13]. Ingestion of cocoa-derived flavanol (−)epicatechin increased expression of hippocampal genes important for synaptic plasticity, such as *Notch* and *Cadherin*. A different set of genes was altered with flavanol consumption and wheel running, such as *SNAP-25* and *Kif17*. However, in both sedentary and exercise conditions expression of genes associated with learning was enhanced [12]. The interaction between exercise and natural products, together with evidence for common cellular signaling pathways, indicates that these compounds might have specific neural receptors, analogous to plant products such as opiates and cannabanoids. If such receptors exist it might open new avenues for treatment of neurodegenerative diseases (Figure 1b).

Concluding remarks

Exercise is a quantifiable activity that improves cognition in young and aged animals and humans. The beneficial effects of exercise are likely to be mediated in part by hippocampal neurogenesis. Further investigation into the functional significance of neurogenesis, by designing behavioral tasks that are specific for the dentate gyrus, will help to determine the relative contribution of the new cells. The effects of exercise are enhanced by dietary supplements. However, the concept that nutrition has a direct influence on brain function is not well accepted. This is due, in part, to the large number of natural products that claim benefits for cognition, the lack of identification of specific active molecules and the limited number of intervention studies in humans. Future studies could focus on identifying the individual factor(s) in natural substances that are cognitive enhancers and select the most potent ones for further investigation. Of particular interest would be to investigate whether a selective receptor exists for such compounds. Finally, the common cellular mechanisms between diet and exercise remain to be defined. Even so, implementation can be immediate: 'All is foreseen, but freedom of choice is granted' (Rabbi Akiba, Perkei Avot, The Ethics of the Fathers, Chapter 3, Mishna 15).

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