REVIEW

Impact of diet on adult hippocampal neurogenesis

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Abstract Research over the last 5 years has firmly established that learning and memory abilities, as well as mood, can be influenced by diet, although the mechanisms by which diet modulates mental health are not well understood. One of the brain structures associated with learning and memory, as well as mood, is the hippocampus. Interestingly, the hippocampus is one of the two structures in the adult brain where the formation of newborn neurons, or neurogenesis, persists. The level of neurogenesis in the adult hippocampus has been linked directly to cognition and mood. Therefore, modulation of adult hippocampal neurogenesis (AHN) by diet emerges as a possible mechanism by which nutrition impacts on mental health. In this study, we give an overview of the mechanisms and functional implications of AHN and summarize recent findings regarding the modulation of AHN by diet.

Keywords Adult hippocampal neurogenesis ·
Neural stem cells · Diet · Nutrition ·
Learning and memory · Mood

Introduction

As much as diet has an impact on cardiovascular health, cancer risks and longevity, it has also an impact on mental health. Research over the last 5 years has now clearly established that our learning and memory abilities, as well

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as our mood, can be influenced by diet, not only during development, but also during adulthood (reviewed in [35]). For example, low intake of omega-3 fatty acids is associated with several forms of cognitive decline in the elderly [31], whereas a diet rich in it is associated with the prevention of cognitive decline [116]. Interestingly, rodents with omega-3 fatty acids deficiency showed impaired performance in spatial memory tasks, which could be rectified after dietary replenishment [26]. Moreover, omega-3 fatty acid concentrations are lower in patients with depression [68], and its supplementation has even emerged as a potential treatment for depression [30, 42]. Likewise, the intake of flavonoids is positively correlated with cognitive function [119] and mood [78]. Although these studies emphasize an important role of diet on mental health, further work is necessary to determine the mechanisms underlying these behavioural effects.

One of the brain structures associated with learning and memory, as well as mood, is the hippocampus. Interestingly, the hippocampus is one of the two structures in the adult brain where the formation of newborn neurons, or neurogenesis, persists. Adult hippocampal neurogenesis (AHN) has been linked directly to cognition and mood (reviewed in [126]); therefore, modulation of AHN by diet could emerge as a possible mechanism by which nutrition impacts on mental health. In this study, we give an overview of the mechanisms and functional implications of AHN and summarize recent findings regarding its modulation by diet.

Neural progenitor/stem cells, adult hippocampal neurogenesis and the neurogenic niche

Neural progenitor cells are self-renewing, multipotent cells that generate neurons, astrocytes and oligodendrocytes in

the nervous system [32]. Although neural progenitor cells with the potential to give rise to neurons in vitro appear to be ubiquitously present within the adult mammalian CNS, newborn neurons have been consistently found only in two privileged areas of the adult brain: the subgranular zone (SGZ) in the dentate gyrus of the hippocampus [48] and the subventricular zone (SVZ) of the lateral ventricles [2] (Fig. 1). Adult neurogenesis has been found in all mammals studied to date, including humans [24]. The process of adult neurogenesis encompasses the proliferation of resident neural progenitor cells and their subsequent differentiation, migration and functional integration into the pre-existing circuitry. During AHN (Fig. 1), neural progenitor cells proliferate in the SGZ and give rise to immature neurons. Many die within 2 weeks, but the surviving neurons then migrate into the molecular layer [51]. The surviving neurons then send axons to the CA3 region and the hilus to form functional synapses with hilar interneurons and CA3 neurons within 3 weeks [113]. Next, these new neurons start also to receive synaptic inputs from the cortex and are capable of firing action potentials [118]. Therefore, these newly generated neurons become physiologically mature and functionally integrated in the circuit.

It is still not perfectly understood why neurogenesis is restricted to the hippocampus and the SVZ, given that neural progenitor cells have been isolated from many CNS regions. It is hypothesized that the microenvironments of the SGZ and SVZ, known as the neurogenic niche, may have specific factors that are permissive for the differentiation and integration of new neurons [81]. In the SGZ, adult hippocampal progenitors are found within a dense layer of granule cells. Within this microenvironment, there are also astrocytes, oligodendrocytes, other types of neurons and blood vessels. Anatomical analysis has identified the vasculature as one potential important constituent of the neurogenic niche [90]. Hippocampal astrocytes also play an important role in AHN as they have been shown to promote the neuronal differentiation of adult hippocampal progenitor cells and the integration of newborn neurons [102]. Blockade of the Wnt signalling pathway inhibits the neurogenic activity of astrocytes in vitro and AHN in vivo, suggesting that hippocampal astrocytes may act through this pathway [66]. Another study also suggests that astrocytes in areas outside the SGZ and SVZ of adult mice express high levels of ephrin-A2 and -A3, which present an inhibitory niche, negatively regulating neural progenitor cell growth [45].

Molecular and epigenetic control of adult hippocampal neurogenesis

The control of AHN is very complex and remains to be fully elucidated. Over the last 10 years, many signals have been implicated in the regulation of AHN and they intervene at the stages of proliferation, differentiation, migration and integration. In the following, we highlight some of the important molecular players in the regulation of AHN known to date.

### Regulation of proliferation and differentiation of adult hippocampal progenitor cells

Extrinsic factors

Morphogens, growth factors, cytokines, neurotransmitters and hormones are extrinsic factors that have been found to play a role in regulating AHN (reviewed in [126]). We highlight here some of the important and potentially relevant factors relating to nutrition. Over ten growth factors and neurotrophins have been found to influence AHN. Fibroblast growth factor (FGF-2) and epidermal growth factor (EGF) are the primary mitogens used in vitro to propagate neural progenitor cells, and FGF-2 is hypothesized to play a permissive role in vivo in hippocampal progenitor cell proliferation [82]. Indeed, it has been found that deletion of fibroblast growth factor receptor-1 in the CNS decreases hippocampal progenitor cell proliferation [127]. Another key growth factor is brain-derived neurotrophic factor (BDNF), which has been shown to increase AHN when infused into the hippocampus [99]. BDNF binds several receptors, including p75 and TrkB, and decrease in either TrkB activity or BDNF protein levels causes reductions in neurogenesis [65, 97]. However, controversy still exists on how BDNF affects neurogenesis (e.g. proliferation vs. survival/differentiation). Hormones have also been shown to modulate AHN; for example, corticosterone decreases proliferation and neurogenesis [11] and male pheromones increase neurogenesis in female mice [71]. The target cells of many extrinsic factors are unknown; therefore, in addition to direct potential effect on the progenitor cells, these growth factors could promote changes in other cell types within the neurogenic niche and have an indirect influence on adult hippocampal progenitors.

Intracellular factors

We highlight here some recently identified intracellular mechanisms implicated in AHN, including some transcription factors and epigenetic modulators. Several transcription factors have been shown to play critical roles in AHN. Amongst these, TLX, an orphan nuclear receptor, is required for proliferation [17, 125] and the basic helix–loop–helix transcription factors, Neurogenin2 (Ngn2) and NeuroD, direct proliferation and specify neuronal fate, respectively [96]. In addition, genes involved in cell cycle

Fig. 1 Schematic representation of the sagittal view of a rodent brain highlighting the two neurogenic zones of the adult mammalian brain: the subventricular zone (*SVZ*) of the lateral ventricles and the subgranular zone of the dentate gyrus (*DG*) in the hippocampus. Neurons generated in the SVZ migrate through the rostral migratory stream (*RMS*) and are incorporated into the olfactory bulb. The hippocampal region contained in the *black square* is enlarged showing (*1*) neural progenitor cells in the SGZ of the DG proliferating, (*2*) migrating into the granule cell layer and (*3*) maturing into new granule neurons. These integrate into the hippocampal circuitry by receiving inputs from the entorhinal cortex and extend projections into the CA3
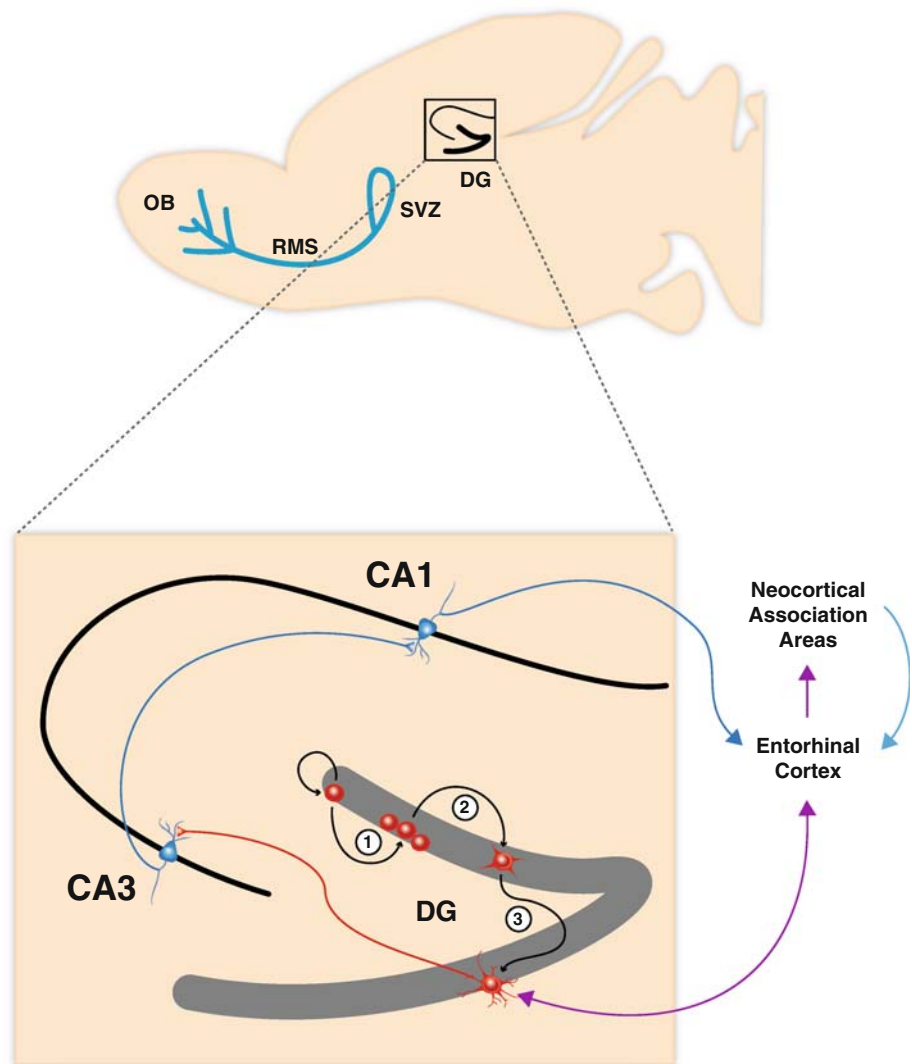
regulation, DNA repair and chromosomal stability are required for the proper function of the adult hippocampal progenitor (reviewed in [126]). Moreover, AHN is also subject to epigenetic regulation, and both DNA methylation and histone acetylation are important. For example, the histone deacetylase inhibitor, valproic acid, induces neuronal differentiation of adult hippocampal progenitors most likely through the induction of neurogenic transcription factors including NeuroD [39]. Furthermore, mice with Gadd45b deletion exhibit specific deficits in neural activity-induced proliferation. Mechanistically, Gadd45b is required for activity-induced DNA demethylation of BDNF and FGF promoters [70].

Migration

Newborn neurons in the adult hippocampus only migrate a short distance into the granule cell layer and little is know about the regulation of this step. It has been suggested that

cyclin-dependent kinase 5 (cdk5) is involved in migration, as single cell-specific knockdown of cdk5 in newborn hippocampal cells leads to aberrant growth of dendritic processes, which is associated with an altered migration pattern of newborn cells [43]. Disrupted-in-Schizophrenia (DISC1) has also been implicated as its down-regulation leads to aberrant migration further into the granule cell layer [20]. A more recent study shows that DISC1 is also involved in proliferation of adult hippocampal progenitor cells through the GSK3β/β-catenin signalling pathway [73].

Survival and integration

As described earlier, newborn neurons integrate into the hippocampal circuitry; however, the mechanisms involved in their integration are currently not well understood. Nevertheless, studies have shown that the survival of newborn neurons depends on sensory inputs. For example,

their survival is influenced by the animal's experience, such as exposure to an enriched environment. Signalling through the glutamate N-methyl-D-aspartate (NMDA) receptor plays a cell autonomous role in the neuron surviving during the third week after birth and coincides with the formation of dendritic spines and glutamatergic inputs [109].

Functionality of adult hippocampal neurogenesis

The data discussed above clearly demonstrate that adult-born hippocampal neurons are functional and integrate into the hippocampal circuitry. However, the incorporation of AHN into current concepts of hippocampal network function and behaviour is complex.

Learning and memory

The implication of AHN in learning and memory is supported by some correlative and ablation studies, as well as by computational modelling. AHN varies amongst different genetic backgrounds in mice and a correlation between the level of hippocampal neurogenesis and the performance in hippocampal-dependent learning tasks is observed between mice of different strains [49, 112]. Environment also has a major impact on AHN (this will be discussed in detail later), and changes in neurogenesis induced by the environment correlates with performance in hippocampal-dependent learning tasks. These studies establish only a correlation; therefore, it is possible that other factors such as structural plasticity, neurotrophin or hormone levels also contribute to genetically and environmentally induced changes in hippocampus-dependent learning and memory.

Newborn neurons represent only a small cell population within the adult hippocampus. It is therefore difficult to imagine how such a small number of cells can influence the function of the hippocampus. Interestingly, 3- to 5-week-old new neurons exhibit a reduced threshold for induction of long-term potentiation [33]. Accordingly, it has been hypothesized that the new neurons that are young when events occur have a specialized role in encoding, storage and in temporally relating one event to another [1], explaining a possible requirement of newborn neurons in the process of learning and memory.

To investigate whether hippocampal neurogenesis is required for hippocampus-dependent learning tasks, a variety of approaches have been taken to reduce or even ablate completely dividing cells in the hippocampus. Blockade of neurogenesis has been achieved with pharmacological, radiological and genetic strategies (reviewed in [22]). None of these methods specifically ablate adult progenitors and lead sometimes to controversial results.

These divergences might be due to differences in animal species, strains and the behavioural procedures. Moreover, all current studies have employed behavioural tasks based on lesion models where the whole hippocampus is affected. Impaired learning and memory caused by a decreased AHN would be easier to detect if the test were targeted at challenging the newborn neurons as they constitute only a small volume in the hippocampal structure. Therefore, to ultimately prove the function of AHN, approaches with selective ablation of newborn neurons in the dentate gyrus associated with specific behavioural tests need to be developed in the future.

Mood regulation

Recently, it has been proposed that AHN might play a role in mood regulation and in the aetiology of major depression [7, 120]. This idea arises from two lines of evidence. The first is that AHN is reduced by stressful experiences, a causal factor in the pathogenesis of major depression. Moreover, AHN is reduced in animal models of depression [19]. The second line of evidence indicates that many treatments for depression have been shown to enhance neurogenesis in laboratory animals; these factors include electroconvulsive therapy (ECT) [100] and common antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRIs) [72]. The long time scale for recovery when humans are treated pharmacologically for depression (several weeks) parallels the long time scale of stimulated neurogenesis that is induced by ECT and SSRIs in non-depressed animals [72, 100]. Moreover, the effects of SSRIs on neurogenesis are selective for the hippocampus, leaving the ongoing stem cell proliferation in the SVZ unchanged [23]. Finally, in several animal models of depression, disruption of neurogenesis blocks the behavioural efficacy of SSRIs [98].

One of the mechanisms thought to mediate reduction of AHN by stress is the elevation of corticosterone by an activated hypothalamic–pituitary–adrenal axis. Indeed, corticosterone decreases cell proliferation, whereas adrenalectomy increases AHN. Moreover, glucocorticoid levels are increased in a variety of stress paradigms and adrenalectomy prevents the stress-induced suppression of AHN (reviewed in [79]).

One of the molecular candidates for mediating both neurogenic and behavioural effects of antidepressant is BDNF. Indeed, the levels of BDNF expression and AHN are co-regulated by both stress and antidepressants [21]. Moreover, infusion of BDNF into the dentate gyrus mimics the effect of antidepressants, but antidepressants fail to increase AHN with compromised BDNF-TrkB signalling, suggesting that this pathway is required for neurogenesis induced by antidepressants [65].

Adult hippocampal neurogenesis in CNS pathologies

AHN responds to neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. Conflicting observations have been reported on the level of AHN in Alzheimer's disease mouse models, but the majority reports a decrease (reviewed in [58]). Mouse models of Parkinson's disease over-expressing the wild-type human α-synuclein show a decrease in the survival rate of newborn hippocampal neurons (reviewed in [111]). AHN is also influenced by many other pathological conditions. For example, it is increased in epilepsy [44] and stroke [115], whereas it is decreased in HIV infection [87], and the integration of newborn neurons is disrupted by CNS inflammation [41]. It is apparent that AHN is influenced by neurological diseases; however, further studies are needed to understand the roles and consequences of AHN changes in pathological events.

Environmental modulation of adult hippocampal neurogenesis

AHN can be modulated by various physiological conditions and the environment (Fig. 2). Ageing has a negative effect on AHN, and aged rodents display impaired learning and memory abilities (reviewed in [55]). Stress is also a major negative regulator of AHN, inducing depressive behaviour (reviewed in [79]). Sleep has recently appeared as another important regulator of AHN. Whilst disruption of sleep for a period shorter than 1 day has little effect on the basal rate of cell proliferation, prolonged restriction or disruption of sleep leads to a major decrease in hippocampal neurogenesis. It has been proposed that adverse effects of sleep disruption may be mediated by stress and glucocorticoids. However, a number of studies clearly show that prolonged sleep loss can inhibit hippocampal neurogenesis independently of adrenal stress hormones (reviewed in [77]). Interestingly, sleep deprivation also disturbs memory formation (reviewed in [105]) and this suggests that promoting AHN may be a mechanism by which sleep supports learning and memory processes. Social isolation is a stressful experience in rodents and has been shown to be another negative regulator of AHN that correlates with learning abilities [69]. Pregnancy [95] and maternal experiences [64] in rodent also have a negative impact on AHN. These are associated with a decline in performance in hippocampus-dependent tasks during pregnancy and the reduced AHN may be an outcome of pregnancy-induced changes in the immune response rather than of hormonal changes [95]. During the postpartum period, the decrease in AHN is dependent on elevated basal glucocorticoid levels [64]. Decreases in AHN during the postpartum period could be linked to postpartum depression experienced by some women.

In contrast, running and enriched environment promote AHN and enhanced spatial learning abilities. Running increases the proliferation [117], whereas enriched environment increases the survival rate of newborn neurons [52, 109]. Both enriched environment and exercise lead to increased synaptic formation and up-regulation of neurotrophins (e.g. BDNF); however, they most likely act via dissociable pathways. Olson et al. [88] suggest that exercise leads to the convergence of key somatic and cerebral factors in the dentate gyrus to induce cell proliferation, whereas enriched environment induces cell survival by cortical restructuring as a means of promoting survival. The regulation of AHN by neural activity suggests that learning might also induce the activation of newborn neurons and enhance their survival and incorporation into circuits. Indeed, AHN is increased upon learning, but only by learning tasks that depend on the hippocampus (reviewed in [63]).

The deleterious effect of many negative regulators of AHN, including ageing [50], stress/depression (reviewed in [10]) and pregnancy [95], can be offset by running or providing an enriched environment in rodents. However, the molecular mechanisms by which physiological and environmental changes influence AHN remain to be fully understood.

Dietary modulation of adult hippocampal neurogenesis

Diet is another important environmental factor that can influence AHN. Diet can impact on AHN from four different levels: calorie intake, meal frequency, meal texture and meal content (Fig. 3). Not only do these four parameters modulate AHN in rodents (Table 1), but independent rodent studies and intervention or epidemiological studies in human have shown that they also modulate cognitive performance and mood (Table 2).

Calorie restriction can extend lifespan, improve behavioural outcomes in some experimental animal models of neurodegenerative disorders and enhance spatial learning (reviewed in [76]). It was shown more recently that a reduction in calorie intake of 30–40% increases AHN in rodents, and that this effect is partly mediated by BDNF [61, 62]. We have also found that independent of calorie intake, meal frequency is a key player in modulating AHN. Indeed, without reducing calorie intake, extending the time between meals increases AHN. It also changes hippocampal gene expression and correlates with performance in hippocampus-dependent tasks and mood (S. Thuret, unpublished data). However, further studies are ongoing to understand the mechanisms by which calorie restriction and meal

Fig. 2 Overview of physiological and environmental modulation of adult hippocampal neurogenesis and its impact on learning and memory abilities and mood. The *dotted square* contains the enlarged hippocampus. The *red dots* symbolize newborn neurons in the dentate gyrus (*DG*)
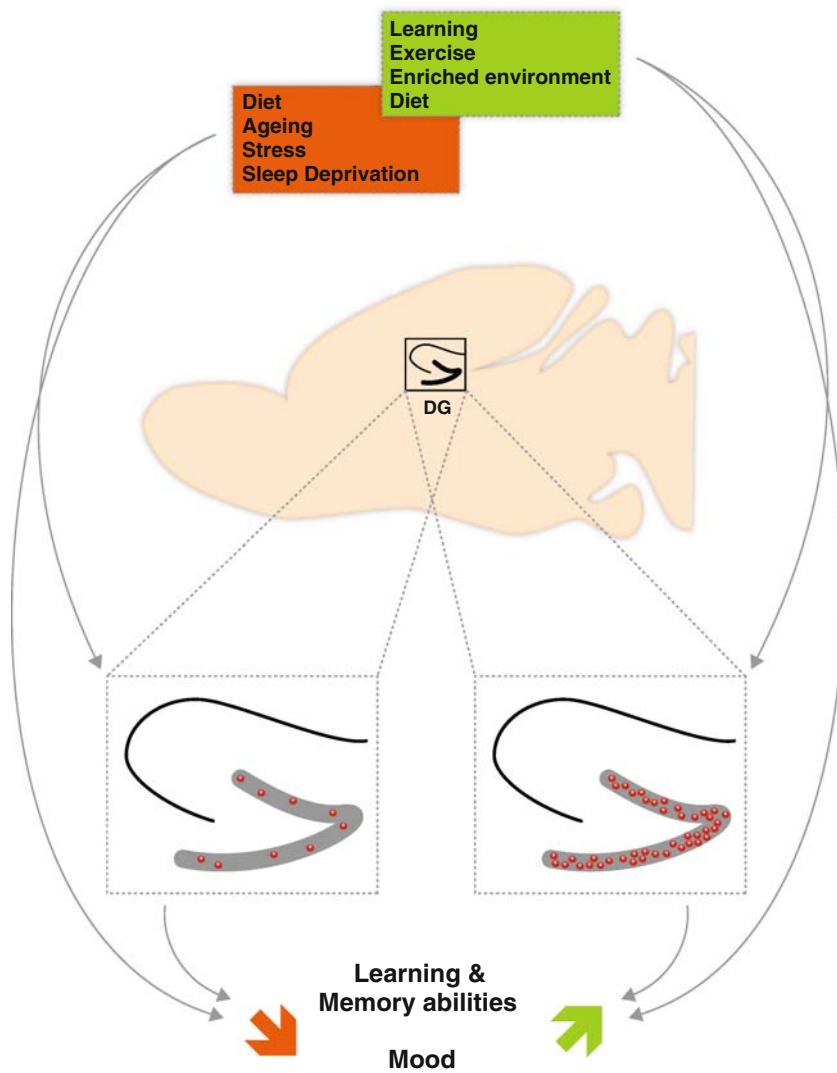
Fig. 3 Overview of the impact of diet on adult hippocampal neurogenesis. The *red dots* symbolize newborn neurons in the dentate gyrus of the hippocampus
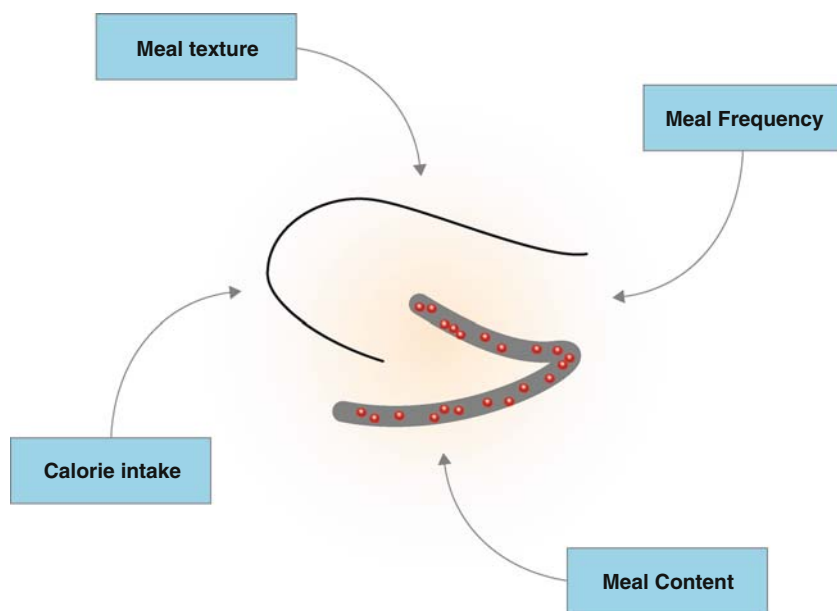
Table 1 Modulation of adult hippocampal neurogenesis (AHN) by diet

Diet	Study models	Effect on AHN	References
Caloric restriction/dietary restriction	Rat	Increased survival	[60]
	Mouse	Increased survival	[62], [61], [54], [8]
Omega 3 fatty acids	Rat	Increased (DHA)	[46]
Flavonoids	Rat, chronically stressed	Increased proliferation	[3]
Blueberry	Rat	Increased proliferation	[12]
Curcumin low concentrations	Mouse	Increased proliferation	[53]
Retinoic acid excess	Mouse	Decreased proliferation	[16]
Vitamin A deficiency	Rat	Decreased proliferation (rescued with retinoic acid)	[9]
Thiamine deficiency	Mouse	Decreased proliferation/survival	[128]
Zinc deficiency	Rat male	Decreased proliferation/survival	[14]
Folate deficiency	Mouse	Inhibited proliferation	[56]
Increased homocysteine	Mouse	Inhibited proliferation	[93]
			[57]
High fat	Male rat	Decreased proliferation	[67]
	Female rat	No change	
Soft diet	Rat	Decreased proliferation	[4]
Caffeine			
At physiologically relevant doses	Mouse	Decreased proliferation	[121]
At supraphysiological doses	Mouse	Increased proliferation/decreased survival	[121]
Low doses, chronically	Rat	Decreased proliferation	[36]
Ethanol	Rat	Decreased proliferation	[84], [37]
	Mouse	Decreased proliferation	[103]

DHA docosahexaenoic acid

frequency modulate AHN and mental health. Interestingly, food texture also has an impact on AHN; rats fed with a soft diet, as opposed to a solid/hard diet, exhibit decreased hippocampal progenitor cell proliferation. The authors hypothesize that chewing resulting in cell proliferation is related to corticosterone levels [4]. Interestingly, independent studies have shown impairment in learning and memory abilities with similar soft diets [59, 114]. If chewing plays a role in AHN, these data could be particularly relevant to the ageing population with cognitive decline where dental weakening might limit the chewing ability.

Meal content offers the most flexibility to regulate AHN, as a variety of bioactives/nutrients have been identified as potential modulators. For example flavonoids, which are enriched in foods such as cocoa and blueberries, have been shown to increase AHN in chronically stressed rats [3], and the authors hypothesized that this effect might be mediated by BDNF. Moreover, independent studies have shown that treatment with flavonoids improves symptoms of depression [18] and improves spatial working memory in ageing rats [122]. Interestingly Williams et al. [122] have also identified BDNF as a potential mediator of the effect of flavonoids on cognition. Deficiency in zinc inhibits AHN [14] and induces depression in rodents [110], whereas independent intervention studies have shown the

efficacy of zinc supplements in improving symptoms of depression (for review [108]). Corniola et al. [14] hypothesized that zinc plays a role in AHN by regulating p53-dependent molecular mechanisms that control neuronal precursor cell proliferation and survival.

Some bioactives act in a dose-dependent manner on AHN. Some can induce AHN at low doses or at a very precise physiological dosage and inhibit AHN at high doses. For example, excess retinoic acid decreases AHN and leads to depressive behaviour and impaired spatial learning in rodents [16, 86]. A deficiency in retinoic acid will lead to similar effects on AHN and mental health, but its effects are reversed by re-establishing a normal level [9]. Caffeine is another dose-dependent bioactive. Indeed, consumed at low doses chronically, Han et al. [36] have shown that it decreases AHN and performance in hippocampus-dependent learning tasks in rodents. Interestingly, at supraphysiological doses, there is an increase in proliferation of neuronal precursors. However, neurons induced in response to supra-physiological levels of caffeine have a lower survival rate than control cells and increased proliferation does not yield an increase in AHN [121]. Curcumin is a natural phenolic component of yellow curry spice that increases AHN in rodents [53] and epidemiological studies have reported better cognitive performance from curry

Table 2 Modulation of learning and memory and depressive behaviour by diet

Diet	Effect on learning and memory	Effect on depressive behaviour	Study models	References
Caloric/dietary restriction	Enhanced spatial learning in aged rats		Rat	[104]
	Enhanced cognitive performance in females only		Rat	[74]
	Increased learning and motor performance		Mouse	[40]
	Increased learning consolidation		Mouse	[28]
Omega 3 fatty acids		Improved (EPA)	Human	[42]
		Delayed onset of depressive periods	Human (bipolar)	[106]
		Decreased	Human (bipolar)	[89]
		No benefit 6 g/day EPA	Human (bipolar)	[47]
		Improvement with 1 g/day EPA	Human (bipolar)	[30]
		Various effects with various concentrations of various fatty acids	Human	For review: [5]
	Improved spatial memory		Mouse Alzheimer model	[38]
	Improved acquisition and retention in a T-maze foot shock avoidance test		Mouse Senescence-Accelerated	[92]
Flavonoids		Improved	Rat	[18]
	Improved			For review: [119]
Blueberry	Increased spatial memory		Rat	[122]
Polyphenol/flavonoids/berry	Positive impact		Various animals	For review: [123]
		Improved	Rat	[78]
Curcumin	Improved cognitive performance		Human	[83]
Retinoic acid excess		Increased	Mouse adult	[86]
Vitamin A/retinoid deficiency	Impaired spatial learning and memory		Rat adult	[13]
	Impaired relational memory		Mouse adult	[25]
Zinc		Improved	Rodents	For review: [108]
		Improved	Human	For review: [108]
		Improved	Human	[85]
High fat	Decreased spatial learning		Rat	[80]
	Decreased learning and memory and Increased risk for dementia		Rat	[124]
High sugar	Impaired spatial learning		Rat	[107]
Low glucose (extracellular)	Impaired memory		Rat aged	[34]
Soft diet	Impairment of learning ability and memory		Rat Alzheimer model	[59]
Caffeine	Improved object recognition		Mouse	[15]
		Reduced risk	Human	[101]
Ethanol	Improved associative learning with moderate chronic consumption		Mouse male	[94]
	Deficits		Human	[91]

EPA eicosapentaenoic acid

consumption in ageing populations [83]. Moreover, in vitro studies have shown that curcumin exerted biphasic effects on progenitor cells; low concentrations stimulated cell proliferation, whereas high concentrations were cytotoxic.

Curcumin activates extracellular signal-regulated kinases (ERKs) and p38 kinases, cellular signal transduction pathways known to be involved in the regulation of neuronal plasticity and stress responses [53].

Finally, it is important to note that independent of calorie intake, diets with high-fat content are detrimental and impair AHN in male rats. The authors hypothesize that high dietary fat intake disrupts AHN through an increase in serum corticosterone levels, and that males are more susceptible than females [67].

BDNF and corticosterone levels appear to be common protagonists of dietary modulated AHN; however, they are unlikely to be the only mediators. For example, further studies will need to be done to investigate if dietary factors modulate AHN by modifying the neurogenic niche. The vasculature [90] and astrocytes [102] are important constituents of the neurogenic niche and interestingly flavanol-rich foods can positively enhance cortical blood flow [27, 29] and are regulators of astrocytic signalling pathways and gene expression [6]. Such changes in the neurogenic niche in response to flavanols might underpin neuro-cognitive improvements through the concurrent promotion of adult hippocampal neurogenesis. Forthcoming studies will not only need to refine the molecular mechanisms by which food intake influences AHN, but also consider the role of epigenetic mechanisms. Indeed, there is increasing evidence that epigenetic mechanisms underlie both AHN [44] and changes in gene expression in response to diet [75]. Future research will need to investigate if diet can modulate AHN through epigenetic changes.

Conclusion and perspectives

It is now getting clearer that AHN affects cognition and mood. It is also firmly established that nutrition has an impact on cognition and mood. Therefore, AHN is emerging as a possible mediator of the effect of certain food on cognition and mood. Consequently, modulating AHN by diet could be a target of choice to prevent cognitive decline during ageing, as well as to counteract the effect of stress and prevent depression. However, further studies are needed to confirm that AHN does mediate the effect of certain diet on mental health, and additional investigations are essential to understand the mechanisms by which diet modulates AHN.

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