British Journal of Nutrition (2013), **109**, 1573–1589
doi:10.1017/S000711451200579X

Review Article

Relationships between dietary macronutrients and adult neurogenesis in the regulation of energy metabolism

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(Submitted 3 August 2012 – Final revision received 27 November 2012 – Accepted 30 November 2012 – First published online 25 February 2013)

Abstract

Of the environmental factors which have an impact on body weight, nutrients are most influential. Within normal limits, hypothalamic and related neuronal populations correct perturbations in energy metabolism, to return the body to its nutritional set-point, either through direct response to nutrients or indirectly via peripheral appetite signals. Excessive intake of certain macronutrients, such as simple carbohydrates and SFA, can lead to obesity and attendant metabolic dysfunction, also reflected in alterations in structural plasticity, and, intriguingly, neurogenesis, in some of these brain regions. Neurogenesis, previously thought to occur only in the embryo, is now known to take place in the adult brain, dependent on numerous stimulating and inhibiting factors, including dietary components. Because of classic associations between neurogenesis and the hippocampus, in learning and cognition, this brain region has also been the focus of attention in the study of links between diet and neurogenesis. Recently, however, a more complete picture of this relationship has been building: not only has the hypothalamus been shown to satisfy the criteria for a neurogenic niche, but appetite-related mediators, including circulating hormones, such as leptin and ghrelin, pro-inflammatory cytokines and the endocannabinoid intracellular messengers, are also being examined for their potential role in mediating neurogenic responses to macronutrients. The present review draws together these observations and investigates whether PUFA may exert their attenuating effects on body weight through the stimulation of adult neurogenesis. Exploration of the effects of nutraceuticals on neurogenic brain regions may encourage the development of new rational therapies in the fight against obesity.

Key words: Macronutrients: Adult neurogenesis: High-fat diets: PUFA

Maintenance of a healthy body weight and composition is important for the achievement of lifelong health and well-being[1]. It occurs through the successful balancing of energy expenditure and energy intake within a normal range, which is controlled by several complex regulatory systems[2], themselves being governed by the interaction with both internal and external environmental factors. Internal factors include circulating metabolic and hormonal signals, whereas the nutrients that we consume are the most influential external factors. Their effects on body weight depend not only on the amount consumed, but also on their type. Thus, a diet high in carbohydrates and/or fat will encourage weight gain[3]; however, genetic contribution notwithstanding[4] the nature of that gain – how much adipose tissue accrues and where it is deposited in the body – will depend on whether carbohydrates are simple or complex, and whether fats are saturated or polyunsaturated[5,6]. The current obesity epidemic is thought to be largely attributable to excessive consumption of palatable foods, high in refined (simple) sugars and saturated fats[3]. As part of a complex causation, including reduced physical activity[7], this contributes to a range of cardiovascular and metabolic disturbances (metabolic syndrome), including insulin resistance, hyperlipidaemia and type 2 diabetes. Other attendant disorders include cancers and dementia, which also threaten the quality of life and shorten lifespan[3,8].

Within normal limits, neuronal populations in the brain, connected by circuitry both inside and outside the hypothalamus, correct perturbations in energy metabolism to return the

Abbreviations: BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CNTF, ciliary neurotrophic factor; DG, dentate gyrus; FA, fatty acid; GPR, G-protein-coupled receptor; HFD, high-fat diet; NPC, neural progenitor cell; NSC, neural stem cell; PACAP, pituitary adenylate cyclase-activating polypeptide; pCREB, phosphorylated cyclic AMP response element-binding protein; RAR, retinoic acid receptor; SVZ, subventricular zone.

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body to its nutritional set-point, either through direct response to circulating nutrients, such as glucose[9] and fatty acids (FA)[10], or indirectly via changing levels of peripheral adiposity and appetite-regulating hormones, such as the adipokine leptin and the gastric peptide ghrelin[11]. Palatable foods are thought to stimulate the brain's hedonistic reward (dopaminergic, opioid and endocannabinoid) pathways to override these homeostatic signals within the hypothalamus that would normally curb appetite[2,12]. This supports a primary role for the brain in the regulation of energy metabolism[13,14], alongside growing knowledge of important peripheral drivers such as lean mass[15].

Neuroplastic changes in the hypothalamus, including altered neurochemical phenotype, neuronal activation, synaptic connections, and dendritic growth and pruning, can be stimulated by dietary factors, not only during critical periods of development, but also in adulthood[16–20]. This is also true of neurogenesis[21–25], the process by which neurons are born, proliferate, differentiate and integrate into established circuitry. This phenomenon, previously thought to occur only in the embryo, has now been demonstrated in the adult brain of most animals, including humans[26,27], and can be influenced by a range of factors including age, sex, olfaction, stress, environmental enrichment, and animal species and strain[26,28–32]. The most proliferative neurogenic regions have been identified as the dentate gyrus (DG) of the hippocampus and the olfactory bulb, their new neurons originating from precursor cells in the subgranular zone of the DG and the subventricular zone (SVZ), respectively[26]. Because of the traditional associations between neurogenesis in the hippocampus and learning and other forms of cognition, this brain region has also been the focus of attention in the study of links between neurogenesis and diet, including manipulation of feeding regimen, energy restriction and dietary nutrients[33–35]. This is not unreasonable, as healthy hippocampal function is also required for normal feeding behaviour[36]. Recently, however, the hypothalamus has also been shown to satisfy the criteria for a neurogenic niche in adult mammals, having similar characteristics as these classical neurogenic zones[37,38]. It has the requisite capability of generating new neurons and expresses phenotypic markers of cell proliferation and neuronal fate, including the cell cycle protein Ki-67 and uptake of the thymidine analogue bromodeoxyuridine. Its newly formed cells migrate to appropriate areas of the parenchyma[39], express a range of neurohormones and specific markers related to energy metabolism[40,41], acquire leptin responsiveness[22,42] and become functionally mature for neuropeptide secretion[22]. Hypothalamic neurogenesis is thought to be a compensatory mechanism that regulates energy balance by replacing dead neurons[42]. It is also impaired by high-fat diet (HFD)-induced and genetic forms of obesity, but can be restored by energy restriction in the former[25]. However, it is only recently, primarily over the last 4 years, that researchers have begun to identify the factors that may mediate the relationship between diet composition, obesity and neurogenesis (either hippocampal or hypothalamic) in the adult. It is reasonable to think that these factors might include a wide range of metabolic signals known to indicate changing energy supply by controlling its different facets, including adiposity, nutrient sensing and satiety.

If these relationships are directly linked mechanistically, this presupposes that neural stem or progenitor cells (NSC and NPC, respectively) in brain regions involved in energy metabolism are responsive to these signals, being equipped with the requisite cellular machinery. Certainly, this has been shown in the principal populations of adult NSC *in vivo* (SVZ and DG) and *in vitro*. Several lines of evidence show that energy metabolism plays a role in determining NSC fate. NSC are not only regulated by immediate signalling due to alterations in intracellular energy metabolism, for instance, via insulin/insulin-like growth factor 1–mammalian target of rapamycin signalling and its multiple downstream pathways, but they are also influenced by changes in systemic energy availability and subsequent response by the whole organism, under both physiological (e.g. dietary restriction and exercise) and disease conditions (e.g. diabetes)[43]. Thus, it remains to expand these findings to the hypothalamus and other regions more closely associated with feeding regulation, such as those in the brainstem which regulate meal size, identifying the metabolites, hormones and other signals involved which cross the blood–brain barrier (BBB) to influence neuronal activity in these areas.

The field of cognition can also be drawn upon to suggest likely candidates. Obesity is becoming increasingly linked with depressed mood, impaired memory and learning abilities, and executive functioning, as well as with neurodegenerative diseases including Alzheimer's disease. All these impairments are also underpinned by neuroplastic changes[3,44–50]. These changes include impaired neurogenesis, as will be shown in the following sections of the present review. Indeed, the link between obesity and central neuropathology has been substantiated by showing that weight reduction improves cognition[51,52]. It has been proposed that adult hippocampal neurogenesis may link energy metabolism and cognition in order to regulate body weight[34], functioning as an 'interface' between the two[53].

Because of the pertinence of simple carbohydrates and SFA to obesity induction, the present review focuses on the influence of these particular macronutrients on neurogenesis. However, just as there are 'bad' nutrients that can cause body-weight dysregulation, there are 'good' nutrients with potentially therapeutic effects that can offset these. The prospect that PUFA may treat obesity by restoration of normal levels of neurogenesis will be examined. PUFA have mechanisms of action relevant to maintaining normal body-weight regulation and cognition, and independent lines of evidence for both will be examined for points of overlap that might apply to the regulation of neurogenesis.

Table 1 summarises the findings from the key whole-animal research publications reviewed. As far as possible, it highlights the main components of the diets used, based on the information provided by the study authors. This is most complete where diets have been manufactured by Research Diets, Inc. According to the OpenSource Diets® policy of this company, the composition of these diets is made fully available.

Table 1. Key findings on the relationships between dietary macronutrients and adult neurogenesis *in vivo**

Macronutrient			Model			Phenotype		
	Main source	Duration (weeks)	Species	Strain	Sex	Energy intake	Body weight	Adiposity
Simple carbohydrates								
Concentration (%, w/v)								
23 (11·5 fructose)	Sucrose (fructose)	4	Rat	Sprague–Dawley	M	↑	(–)	↑
10 (5 fructose)	Sucrose (fructose)	6	Rat	Wistar	M	(–)	(–)	NR
SFA								
Energy (%)								
58	Coconut oil	8	Mouse	C57BL/6	M	NR	↑	NR
58	Coconut oil	16	Mouse	C57BL/6	M	NR	NR	NR
60	Lard	4 (after exposure *in utero*)	Mouse	C57BL/6	NR	NR	NR	NR
42	Coconut butter and maize oil	4	Rat	Sprague–Dawley	M and F	NR	(–) (M) ↑ (F)	(–) (M) ↑ (F)
60	Lard	4, 8 and 12	Mouse	C57BL/6N, 6J	M	NR	↑	NR
45	Lard	7	Mouse	C57BL/6	M	↑	↑	↑
45	Lard	17	Mouse	C57BL/6J	M	↑	↑	NR
60	Lard	12	Rat	Wistar	M	↑	↑	NR
Cholesterol								
Concentration (%, w/w)								
1·25	Cocoa butter and coconut oil	12	Mouse	B6	?	NR	NR	NR
PUFA								
Concentration (%, w/w)								
41·5 or 45·1	Brine shrimp enriched with *n*-3 FA or *Spirulina*	3·5	Lobster	N/A	NR	NR	NR	NR
9·27	LMN cream (PUFA and polyphenols)	6	Mouse	129S1/SvImJ	M	NR	–	NR
1·8–2·0	Marine oil concentrates (commercially supplied)	12	Rat (aged)	Wistar	M	–	–	NR
N/A (300 mg/kg per d)	Ethyl-ester-DHA (commercially purified)	6	Rat	Wistar	M	NR	NR	NR

Macronutrient	Mediating factors		Neurogenesis				
	Circulating	Central	Cell proliferation	Differentiation	Region	Niche	References
Simple carbohydrates							
Concentration (%, w/v)							
23 (11·5 fructose)	↑ Leptin, ghrelin, TAG, TNF-α (–) Glucose, insulin, NEFA, CORT, IGF-1, IL-6, IL-1β	NR	↑ Ki-67 +	↓ BrdU + /NeuN +	Hippocampus	DG	van der Borght *et al.*[61]
10 (5 fructose)	(–) BDNF	(–) BDNF	(–) Ki-67 +	NR	Brainstem	DVC	Zeeni *et al.*[74]
SFA							
Energy (%)							
58	↑ Glucose, insulin	NR	↓ BrdU + , Ki-67 +	(–) BrdU + /HuC/D +	Hypothalamus	ARC	McNay *et al.*[25]
58	NR	NR	↓ BrdU +	↓ BrdU + /Tuj1 +	Hypothalamus Hippocampus Lateral ventricle	MBH/3v DG SVZ	Li *et al.*[24]
				↓ BrdU + /NeuN +	Hypothalamus	ARC	
60	NR	NR	↑ BrdU +	↑ BrdU + /Hu +	Hypothalamus	ME	Lee *et al.*[23]

Table 1. *Continued*

Macronutrient	Mediating factors		Neurogenesis				
	Circulating	Central	Cell proliferation	Differentiation	Region	Niche	References
42	↑ CORT (M) (−) CORT (F)	NR	↓ BrdU + (M) (−) BrdU + (F)	(−) BrdU + /NeuN + (M and F)	Hippocampus	DG	Lindqvist *et al.*[82]
60	NR	↓ BDNF, GAD67, pCREB↑ MDA	↓ Ki-67 +	↓ DCX +	Hippocampus	DG	Hwang *et al.*[85], Yoo *et al.*[88]
45	↑ Glucose, total cholesterol, NEFA (−) TAG	↓ BDNF↑ MDA	↓ BrdU +	(−) DCX +	Hippocampus	DG	Park *et al.*[90]
45	↑ Leptin, insulin, CORT, cholesterol (−) Glucose, TAG	NR	NR	(−) DCX +	Hippocampus	DG	Boitard *et al.*[92]
60	↓ Glucose, TAG (−) Leptin, adiponectin, insulin, cholesterol	NR	(−) BrdU +	(−) BrdU + / βIII-tubulin +	Hippocampus Hypothalamus Lateral ventricle	DG ARC−ME SVZ	Rivera *et al.*[93]
Cholesterol							
Concentration (%, w/w)							
1·25	NR	NR	↓ Ki-67 +	↓ DCX +	Hippocampus	DG	Kim *et al.*[104]
PUFA							
Concentration (%, w/w)							
41·5 or 45·1	NR	NR	↑ BrdU +	NR	Cluster 10	N/A	Beltz *et al.*[128]
9·27	NR	NR	↑ BrdU + , PCNA +	↑ DCX + , BrdU + /NeuN +	Lateral ventricle	SVZ−RMS−OB	Valente *et al.*[135]
1·8−2·0	NR	↑ RAR-α, RXR-α,-β, PPAR-γ	NR	↑ DCX +	Hippocampus	DG	Dyall *et al.*[115]
N/A (300 mg/kg per d)	NR	NR	NR	↑BrdU + /NeuN +	Hippocampus	DG	Kawakita *et al.*[139]

M, male; ↑, increased; (−), no change; CORT, corticosterone; IGF-1, insulin-like growth factor 1; NR, not reported; Ki-67, cell cycle protein (proliferation marker); + , positive immunoreactivity; ↓, decreased; BrdU, 5-bromo-2-deoxyuridine (thymidine analogue, proliferation tracer); NeuN, nuclear protein (pan-neuronal marker); DG, dentate gyrus; BDNF, brain-derived neurotrophic factor; DVC, dorsal vagal complex; HuC/D, nuclear proteins (early neuronal markers); ARC, arcuate nucleus; Tuj1, class III tubulin (neuron-specific microtubule, pan-neuronal marker; early neuronal commitment marker); MBH, mediobasal hypothalamus; 3v, wall of the third ventricle (ependymal cells therein); SVZ, subventricular zone; Hu, nuclear protein (pan-neuronal marker); ME, median eminence; F, female; GAD67, glutamic acid decarboxylase, isoform 67; pCREB, phosphorylated cyclic AMP response element-binding protein; MDA, malondialdehyde; DCX, doublecortin (microtubule-associated protein, immature neuronal marker); βIII-tubulin, class III tubulin (neuron-specific microtubule, pan-neuronal marker; early neuronal commitment marker); ?, indeterminate (manuscript typographical error); FA, fatty acid; N/A, not applicable; PCNA, proliferating cell nuclear antigen (proliferation marker); RMS, rostral migratory stream; OB, olfactory bulb; RAR-α, retinoic acid receptor-α; RXR-α,-β, retinoid X receptor, α and β.

* Information is listed according to its order of discussion in the main text. Diets are identified by their main energy sources. The metabolic and neurogenic findings displayed represent those in response to diet exposure only, without any concurrent intervention that may also have been carried out (e.g. drug administration). Neuronal differentiation was sometimes confirmed by the co-expression of multiple immunoreactive markers in the same cell; these are separated by a forward slash. In contrast, cell proliferation was sometimes confirmed by the expression of immunoreactive markers in separate tissue sections; these are separated by a comma. Note that cell proliferation does not necessarily indicate neurogenesis, as progenitor cells may also develop into glia. Thus, where authors have quantified the proportion of proliferating cells co-expressing neuronal markers in high-fat diet (HFD)-fed animals and found it to be the same as that in control diet-fed animals, this confirms that a HFD-induced reduction in proliferation is a reduction in neurogenesis *per se* (see McNay *et al.*[25] and Lindqvist *et al.*[82]).

Immunocytochemical markers distinguishing the stages of neurogenesis, from cell proliferation to maturity, are by now well established[54], and are also listed in Table 1.

Simple carbohydrates

One theory put forward to explain the relatively recent development of obesity epidemic in the West is the over-consumption of sugar-sweetened beverages. The patterns of development of the two phenomena have overlapped over the last few decades[55]. High-fructose corn syrup has been identified as the ingredient that may be particularly detrimental in this regard[5,56]. It is commonly assumed that high-fructose corn syrup contains 42–55% fructose[57], but one study has found the mean content of high-fructose corn syrup in several major soft drink brands to be 65%[58].

Rodent models have been used to investigate the mechanisms that might explain the link between weight gain and the chronic ingestion of simple sugars in liquid form. Interestingly, markers of the metabolic syndrome, such as high serum TAG, impaired glucose metabolism and increased abdominal fat pad mass, have correlated with the consumption of much lower concentrations of sugars (10%), including fructose. Importantly, in some cases, these associations have been observed in the absence of body-weight gain[59,60].

Indeed, van der Borght *et al.*[61] found that rats allowed to consume liquid sucrose, glucose or fructose, at a concentration of 23% (w/v) for 4 weeks (along with *ad libitum* normal chow), showed no increase in body weight compared with control animals consuming water. This was despite becoming hyperphagic (consuming less solid food, but more of their respective solutions than did the controls) and having heavier gonadal fat depots. Terminal serum concentrations of TAG, leptin, ghrelin and the pro-inflammatory cytokine TNF-α were elevated in sucrose- and fructose-fed rats. Of these circulating parameters, only leptin was elevated in glucose-fed rats. The former also showed that the numbers of newly mature neurons in the DG were reduced by almost 50%, while the numbers of apoptotic cells were significantly increased. However, enhanced proliferation of newborn cells was also observed, and in all groups, presumably to compensate for apoptosis. The authors proposed that elevated TNF-α was responsible for this failure of newborn hippocampal cells to survive, through both a direct apoptotic effect and the impairment of the BBB. In addition to inflammatory cytokines, raised TAG are also known to compromise the integrity of the BBB[62]. Therefore, it was suggested that combined damage by TNF-α and TAG prevented leptin and ghrelin from crossing the BBB, thereby depriving the hippocampus of their neuroprotective effects. *In vivo* and *in vitro* studies have shown that both hormones stimulate adult neurogenesis through direct receptor activation on newly formed neurons: leptin in the hippocampus[63] and hypothalamus[22,25,37,42,64]; ghrelin also in the hippocampus[65] and brainstem regions that regulate feeding, the dorsal motor nucleus of the vagus nerve and the nucleus of the solitary tract[66,67].

On the other hand, circulating levels of glucose, insulin, insulin-like growth factor 1 and corticosterone were unchanged in all test groups, suggesting that down-regulation of hippocampal neurogenesis by sucrose and fructose is independent of these factors. This is in contrast to the findings from *in vitro* NSC biology and *in vivo* disease pathology, which have suggested roles for these factors: In addition to insulin-like growth factor 1 and other neurotrophins, insulin acts as a growth factor in the brain, crossing the BBB to bind to its receptor expressed on NSC. It appears to be required for NSC survival, as its withdrawal from NSC culture medium leads to autophagic cell death. At high concentrations, it stimulates the differentiation of embryonic and postnatal NSC, but its role in regulating adult NSC *in vivo* remains to be directly explored. So far, hippocampal neurogenesis has been shown to be impaired in rodent models of both type 1 and type 2 diabetes[43,68–70], an effect thought to be mediated by glucocorticoid dysfunction, as the impairment is reversed when elevated levels of circulating corticosterone are normalised[68,70]. Neurogenesis in the SVZ may also be supported by insulin, as its impairment is observed in type 1 diabetic mice, where it also appears to be mediated by glucocorticoids and the brain-derived neurotrophic factor (BDNF)[68]. The BDNF is another in the range of growth factors, including insulin-like growth factor 1 and ciliary neurotrophic factor (CNTF), which regulate body weight through central mechanisms, including hippocampal neurogenesis[33,53,71–73]. Although the relationship between circulating levels of BDNF and body mass is unclear, reduced central expression is associated with obesity[72].

Significantly, the simple study design by van der Borght's group lends critical support to the scrutiny currently afforded to fructose, as opposed to the other two simple sugars. Because sucrose comprises equal concentrations of glucose and fructose, and similar changes were observed in sucrose- and fructose-fed, but not glucose-fed, animals, the authors were able to attribute these effects to fructose alone. By the same rationale, these effects were therefore stimulated by a concentration of only 11–12% fructose (w/v).

In contrast, Zeeni *et al.*[74] found in rats that there was no effect of 6-week ingestion of a high-carbohydrate liquid diet, containing 10% (w/v) sucrose, on cell proliferation in the dorsal vagal complex of the brainstem. This could have been due to the lower concentration of fructose therein, less than 50% of that used by van der Borght's group[61] (5% *v.* 11–12%). Interestingly, however, they also did not observe an effect of isoenergetic high fat intake, suggesting that, in general, the dorsal vagal complex may be less sensitive to macronutrient challenge than the DG examined by van der Borght's group. However, consistent with this lack of central effect, the authors observed no significant dietary effect on body weight, or on circulating or brain levels of BDNF.

In summary, in rats, appetite-related and inflammatory signals appear to mediate impaired hippocampal neurogenesis resulting from the chronic intake of fructose, at concentrations much lower than those consumed by humans, and these effects are independent of obesity. Whether or not this phenomenon extends to brainstem regions of feeding regulation may depend on fructose concentration and the duration of consumption (the longer, the more detrimental) interacting

with the site of the neurogenic niche. About 10 % (w/v) of fructose appears sufficient to impair hippocampal neurogenesis in rodents. There is now growing evidence to challenge the view that fructose metabolism occurs primarily in the liver and kidney, suggesting that its role in the brain may have important implications for neuronal function[75]. The findings of van der Borght's group raise the possibility that there is at least some neurobiological evidence for the detrimental effect of high fructose consumption on cognition.

SFA

Effects on hypothalamic neurogenesis

Although evidence had been growing over the early part of the last decade to qualify the hypothalamus as a neurogenic niche[76,77], it was not until the seminal work of Flier's[22] group that this property was finally linked with its key role in feeding regulation. They found that neurogenesis in the arcuate nucleus was suppressed in obese mice. The arcuate nucleus is the key region, along with the nearby median eminence, where leptin and other peripheral hormones access the hypothalamus through a weakened BBB. These mice consumed a HFD, providing 58 % of energy from fat, for 8 weeks. (For the purposes of the present review, and in common with much of the literature, HFD refers to a high content of saturated, rather than unsaturated, FA.) Specifically, this was due not to an absence of stem cells in the region, but to apoptosis of newly proliferating cells. The causative role of obesity was confirmed by showing that neurogenesis was partially restored by energy restriction[25]. Earlier, they had determined that centrally infused CNTF stimulates proliferation in these mice, and, furthermore, by using the mitotic inhibitor cytosine-b-D-arabinofuranoside, they also showed that this proliferation was the mechanism by which CNTF causes sustained weight loss[22]. Many of the new cells expressed neuronal markers and functional phenotypes relevant to energy balance control, such as leptin responsiveness[22]. Thus, the involvement of CNTF in hypothalamic neurogenesis was clear, but the mechanisms that might explain how a HFD inhibits neurogenesis remained unresolved. The authors did confirm, however, that mice were both obese and diabetic, showing hyperglycaemia and hyperinsulinaemia, although data were not shown. This suggests that the mice were insulin-resistant, and therefore resistant to the central effects of insulin, including its neuroprotective properties.

Furthermore, there is now evidence to suggest that the observed inhibition of hypothalamic neurogenesis persists with continued exposure to HFD. Recently, Li *et al.*[24] fed adult mice for twice as long as did Flier's group (16 *v.* 8 weeks), with a diet providing the same amount of energy from fat[25]. Although they found that proliferation and neurogenesis were reduced in the mediobasal hypothalamus and the nearby third ventricular lining, regions adjacent to the arcuate nucleus, they discovered that this was, in fact, due to a reduction in the number of stem cells, as identified by the expression of two key NSC genes, nestin (*Nes*) and SRY-box 2 (*Sox2*), as well as in their ability to make new neurons. This highlights the differing consequences on hypothalamic neurogenesis of dietary timescale, composition (fat sources from lard *v.* coconut oil; see Table 1) and the compartmentalisation of neurogenic niches into several discrete subregions with different dietary responsiveness.

In contrast, young adult mice fed a HFD, providing a similar amount of energy from fat (60 %), have recently been shown to display active neurogenesis in the median eminence. Lee *et al.*[23] fed mice up to 2·5 months of age (between postnatal days 5 and 75) for 1-month periods, after the diet had been supplied to their mothers. Specifically, β2-tanycytes were identified as the proliferating cell type and were suggested, by CRE technology, to give rise to neurons, thus confirming the median eminence as a true neurogenic niche. When proliferation of these cells was selectively inhibited by focal irradiation, weight gain was attenuated, and energy expenditure, as measured by V_{O2} and total activity, increased[23]. This suggested that adult neurogenesis in this region has a functional role in body-weight regulation. These metabolic changes suggest that corresponding changes in circulating appetite-related factors would have occurred, though no measurements were reported. Interestingly, the rate of this neurogenesis had quadrupled by postnatal day 75, indicating that HFD activation persists into adulthood and suggesting that it might modulate hypothalamic neural circuitry later in life[23]. This notion is supported by earlier work by Chang *et al.*[21] who observed that offspring of rat dams fed a HFD, providing 50 % of energy from fat, displayed increased proliferation of neuroepithelial cells and NPC in widespread areas of the hypothalamus, including the median eminence, as well as increased food intake and body weight that prevailed at least until postnatal day 70 (when the animals were terminated). Moreover, enhanced differentiation and migration towards hypothalamic areas, where these neurons ultimately expressed orexigenic peptides, was also observed. This was linked with a marked increase in circulating lipids (TAG and NEFA) in dams and offspring. Although a precise mechanism had not been determined, it was proposed that the purpose of this neurogenesis was to prepare juveniles for the increased food intake and a HFD preference they would show after weaning[21].

Lee *et al.*[23] also performed lineage analysis, necessary to confirm stem cell commitment to either a glial or neural fate, and showed that few cells in other hypothalamic regions were derived from the tanycytes, suggesting that other progenitor cell populations may exist in the hypothalamus. Therefore, it may be that these populations were observed to be inhibited by HFD feeding in the other studies outlined above, explaining their opposing findings. The findings of Li *et al.*[24] on HFD-induced neurogenic inhibition in the nearby mediobasal hypothalamus strongly support this.

Thus, although the focus of the present review is adult neurogenesis, it would be remiss not to consider that its sensitivity to HFD feeding exists before birth, and that this early remodelling may determine further responses to HFD exposure in adulthood. In real-world terms, this fetal programming is an important target mechanism for the prevention of childhood obesity, a growing problem which population-based and animal studies have now clearly shown is linked to maternal overconsumption of high-energy, palatable foods[78,79].

Effects on hippocampal neurogenesis

The effects of HFD on neurogenesis in the adult hippocampus have been more extensively studied and, as with those in the hypothalamus, are consistent with the effects observed in the offspring of HFD-fed mothers[80,81]. Lindqvist *et al.*[82] found that 4-week exposure to a HFD providing 42% of energy from fat inhibited hippocampal neurogenesis in rats in a way that was sex-dependent, but obesity-independent. Although male rats gained fat pad mass, this was not significant and did not result in overall body-weight gain. However, neurogenesis was reduced by almost 50%. Thus, it appears that dietary fat *per se*, rather than adiposity, impairs hippocampal neurogenesis. This fits with the recent findings of Thaler *et al.*[83], where HFD-fed rats and mice receiving 60% of energy from fat, for periods ranging from 1 d to 8 months, displayed hypothalamic injury. This was reflected in gliosis and mRNA expression of the inflammatory cytokines IL-6 and TNF-α, and the intracellular inflammatory signalling molecule Iκ kinase β as early as 24 h after exposure to the diet, long before the onset of an obese phenotype. In addition, impaired neurogenesis observed by Lindqvist's group correlated with raised circulating levels of corticosterone in these rats, consistent with the later observations in diabetic and insulin-resistant mice referred to above[70]. These effects were observed only in male rats, suggesting that females are protected by oestrogen. Indeed, it has been documented that oestrogen and glucocorticoids combine in protecting pre-menopausal women against the metabolic syndrome[84].

Similar results were found to be strain-dependent in mice fed a HFD providing 60% of energy from fat for 4 or 12 weeks[85]. C57BL/6N mice were more vulnerable to HFD-induced obesity, as reflected in increased body-weight gain, than C3H/HeN mice. This was associated with reduced cell proliferation and differentiation in the DG. The authors have suggested the strain-specific difference to be associated with HDL, stating that this would agree with previous findings that the efficacy of cholesterol absorption in mice is also strain-dependent[86,87]. The same group has recently gone on to confirm their findings, extending them to show HFD-sensitive (C57BL/6J) mice to be hyperglycaemic[88]. They followed up on a previously proposed relationship in developing neurons between BDNF induction by the excitatory neurotransmitter γ-amino butyric acid and the activation of phosphorylated cyclic AMP response element-binding protein (pCREB)[89]. Indeed, they found reduced levels of BDNF, the γ-amino butyric acid synthetic enzyme, glutamic acid decarboxylase, isoform 67, and pCREB in the DG of HFD-fed mice, but elevated levels of the lipid peroxidation marker malondialdehyde.

Park *et al.*[90] also showed impaired hippocampal cell proliferation (though not differentiation) in mice made obese through 7 weeks' consumption of a HFD providing 45% of energy from fat. This was also found to occur through enhanced lipid peroxidation, reflected in elevated malondialdehyde levels and mediated by reduced levels of BDNF. *In vitro* studies by the same authors confirmed a normally protective role for BDNF, which, they proposed, when disrupted, could provide the mechanism for cognitive dysfunction and learning and memory impairment observed with a high dietary intake of SFA; that is, as measured by performance in prospective memory tasks in human subjects and appetitive operant conditioning tasks in rats[3]. Mansouri *et al.*[91] modelled this lipotoxicity *in vitro* by exposing adult NSC to the SFA palmitate. They found that pre-incubation with the neuroprotective peptide pituitary adenylate cyclase-activating polypeptide (PACAP), a member of the vasoactive intestinal polypeptide/secretin/glucagon family, counteracted the impairment of NSC viability. This occurred through the activation of the PACAP receptors PAC-1 (formerly PACAP receptor subtype I) and VPAC-2 (formerly vasoactive intestinal polypeptide receptor subtype 2), up-regulated in NSC by the palmitate treatment, and through the activation of PAC-1, VPAC-1 and VPAC-2, up-regulated in the SVZ/striatum of *ob/ob* mice. The authors proposed a protective role for PACAP in NSC lipotoxicity and a potential therapeutic role for PACAP receptor agonists in the treatment of premature development of neurological disorders in diabetes and obesity, both characterised by hyperlipidaemia which can lead to this toxicity.

Using the same diet and strain as Park's[90] group, Boitard *et al.*[92] also found that hippocampal neuronal differentiation was unaffected by HFD consumption in adult mice (they did not examine proliferation), even after induction of obesity and metabolic dysfunction by a much longer exposure to the diet (17 *v.* 7 weeks). In contrast, juvenile animals, exposed to the diet for the same duration, but from weaning, showed reduced hippocampal differentiation when compared with standard chow-fed control juveniles. The authors have suggested that this underpins impaired relational memory also displayed by the juvenile but not by adult mice, pointing to a vulnerability to the detrimental effects of HFD consumption on cognition in early life. Juveniles showed weight gain associated with elevated plasma levels of leptin, insulin, corticosterone and cholesterol. However, TAG and glucose levels remained unchanged, suggesting that the observed cognitive and neurogenic impairments were mediated by the former, but not the latter, circulating factors. Comparison of control-fed adults with their juvenile counterparts revealed that impairment of hippocampal neuronal differentiation does indeed occur in adults[92], suggesting that this impairment reaches a nadir with age, which cannot be exacerbated further by HFD feeding.

Interaction with the endocannabinoid system in neurogenesis

Rivera *et al.*[93] also found no effect of chronic HFD feeding on cell proliferation or neurogenesis. They fed rats a diet providing 60% of energy from fat for 12 weeks and compared them with control rats fed a low-fat diet, providing 10% of energy from fat. Despite induction of obesity (assumed from significantly higher body weight) in the HFD-fed group, they found no difference between the two groups in the levels of neurogenesis in the subgranular zone, SVZ or hypothalamus.

This was consistent with largely similar metabolism between the groups, reflected in similar levels of circulating markers[93]. The lack of effect could have been due to the study design. Sucrose and a small amount of lard were also present in the low-fat diet. This may have led to a degree of metabolic dysfunction in control animals, such that levels of their metabolic markers failed to separate from those in HFD-fed animals; for example, our laboratory has found that rats fed the same low-fat diet become hyperinsulinaemic, suggesting insulin resistance (MA Yon and LC Pickavance, unpublished results).

Nevertheless, Rivera's group attempted, for the first time, to investigate a functional link between the endocannabinoid system and cell proliferation in a model of diet-induced obesity[93]. The endocannabinoids, intracellular signalling lipid-related molecules, are well known to stimulate feeding[94] and, through *in vitro* work and the use of cannabinoid receptor knockout mice, had been known for some time to regulate neurogenesis in both the developing and adult nervous systems[95–99]. However, how the two phenomena are linked was unknown. Rivera's HFD-fed rats and their low-fat diet-fed controls were treated with the cannabinoid-1 receptor inverse agonist AM251. This reduced food intake, stimulated weight loss and improved metabolism in both groups, as expected. However, accompanying reductions in circulating cholesterol, TAG and glucose levels were more pronounced in the HFD-fed group and, intriguingly, neurogenic change was stimulated only in this group. Adding another layer of complexity, the direction of this change was site-specific, with raised levels in the subgranular zone, but reduced levels in the SVZ and, contrasting with the previous findings of Flier's group, the hypothalamus[25,93]. However, it is difficult to meaningfully compare between studies employing different species (mice *v.* rats), diets and means of inducing weight loss (energy restriction with and without exogenous challenge of the endocannabinoid system). The authors suggested that the endocannabinoid system is sensitised by high fat feeding, enabling the cannabinoid-1 signalling system to adapt, in order to limit obesity-induced functional impairment in the brain. In addition, this adaptation is mediated by appetite-related signals. Overall, they concluded that cannabinoid modulation of cell proliferation in adult neurogenic regions is obesity-dependent, despite the fact that body-weight gain induced in their animals was not proved to be associated with an abnormal metabolic phenotype[93]. What these results may indicate, more precisely, is that a threshold exists at which specific nutrients in the HFD, at certain minimum concentrations, sensitise the cannabinoid system for neurogenic modulation, and that this threshold may not necessarily coincide with frank obesity.

Cholesterol effects on hippocampal neurogenesis

It is worth expanding briefly on the role of cholesterol in HFD effects, as it has been shown to have an impact on neuroplasticity and neurogenesis. Some dietary SFA disturb cholesterol homeostasis, raising circulating levels of 'bad' cholesterol (LDL) in relation to those of 'good' cholesterol (HDL)[100]. This is associated with atherosclerosis and amyloid-β plaque formation, both of which may contribute to the aetiology of Alzheimer's disease[101,102]. Diet-induced elevated serum cholesterol has been associated with hippocampal neurodegeneration[92,103], but its effects on cell proliferation and differentiation have been investigated directly in only one study. Kim *et al.*[104] fed mice isoenergetic diets high or low in cholesterol (1·25 *v.* 0·03 % by weight) to isolate their effects on hippocampal neurogenesis. They showed that 12-week consumption of a high-cholesterol diet inhibited both cell proliferation and differentiation in the DG, but that this effect was dependent on sensitivity to hypercholesterolaemia; that is, this impairment was observed only in B6 mice which are sensitive to the high-cholesterol diet, and not in C3H mice that are resistant[104]. However, in adult macaques, post-mortem hippocampal neurogenesis, but not initial cell proliferation, was recently found to correlate positively with pre-mortem lipid ratio (total cholesterol:HDL)[105], suggesting that the exact nature of the relationship between cholesterol and neurogenesis may be complex, and possibly species-dependent. Neither research group speculates on the possible mechanisms behind these changes[104,105], but it would appear likely that impairment of hippocampal neurogenesis is related to cholesterol accumulation in the hippocampus and associated oxidative stress[103].

Summary

In summary, under most experimental paradigms using adult rodents, consumption of diets high in SFA stimulates change in neurogenesis that may be more nutrient- than obesity-dependent. Even in the pre-obese state, SFA-induced oxidative stress may alter neurogenesis in both the hypothalamus and hippocampus, an effect which appears to be mediated by changes in a range of metabolic signals. Although the findings are not always consistent, the candidates identified so far appear to include cholesterol, corticosterone, TAG, glucose and the trophic factors CNTF and BDNF. The full extent of at least some of their effects may depend on the interaction with PACAP and endocannabinoid systems, although these relationships do not appear to have been explored yet. Neuroinflammation, which, as described above, can also precede obesity or develop independently of increased adiposity, during high SFA consumption, is another phenomenon known to impair neurogenesis[83,106–108]. Whether it, in turn, is mediated by these same factors in this context remains to be tested. So far, chronic high SFA consumption has been associated primarily with the inhibition of neurogenesis, but the probable complexity of this relationship requires the careful design of studies comparing time course, FA composition and concentration, model species, strain, age and neurogenic site.

PUFA

Overview of health benefits and mechanisms of action

PUFA include *n*-3 and *n*-6 FA, found primarily in fish and seed oils, respectively. In contrast to SFA, they have wide-ranging health benefits. Dietary interventions with *n*-3 FA, in

particular, have been shown to counteract, attenuate or prevent dysfunction in energy metabolism, cardiovascular health and cognition, through their anti-inflammatory properties or direct control of gene expression[109–113]. PUFA are natural ligands at the key transcription factors, the retinoic acid receptors (RAR), retinoid X receptors and PPAR, and, in this way, directly regulate gene transcription related to a range of functions, including energy metabolism and cognition[114–116]. By this mechanism, they act at the level of the adipocyte to attenuate the accumulation of adipose tissue by inhibiting the expression of lipogenic genes and stimulating the transcription of those involved in lipid oxidation[5]. Although not all the underlying mechanisms are clear, centrally, *n*-3 FA are thought to improve the metabolic syndrome through alterations in insulin receptors and ventromedial hypothalamic dysfunction. That is to say that (1) incorporation of *n*-3 FA into synaptic membranes in adequate amounts maintains membrane fluidity, enhancing the number of insulin receptors and the affinity of insulin to their receptors, resulting in improved insulin sensitivity, and (2) *n*-3 FA potently inhibit the pro-inflammatory cytokines IL-1 and -2, and TNF-α, which cause neuronal damage in the ventromedial hypothalamus that manifests, in animal models, as the metabolic syndrome[13]. PUFA are thought to normalise appetite, through restoration of hypothalamic neuropeptide levels[117], and to reduce reward associated with food, through the effects on dopaminergic transmission and endocannabinoid levels[118]. These changes at the cellular level are manifested behaviourally, as PUFA consumption attenuates weight gain by suppressing appetite, thereby enhancing satiety. These findings are somewhat inconsistent, however, and in trials of human consumption, only short-term effects have been examined, and only in the form of supplementation[109], rather than long-term consumption of PUFA incorporated into foodstuffs. Despite this, epidemiological studies and intervention trials have indicated that *n*-3 FA treatment may be applied in clinical practice and used to prevent the metabolic syndrome[13].

Overview of n-3 fatty acid function

Studies modelling the central effects of PUFA supplementation in animals have focused mainly on impairments in central nervous system development, resulting from maternal dietary deficiency[119], and the potential for repair in traumatic brain injury[120] and neurodegenerative disorders[113]. There are two *n*-3 FA, DHA and EPA, that cannot be synthesised by mammals and so must be obtained from the diet, either directly or via their parent compound, the essential FA α-linolenic acid. DHA is required for correct development of the embryonic nervous system and normal central nervous system function throughout life[119]. The molecular underpinnings of neuroprotection by *n*-3 FA are extensively linked with neural physiology, including ion channel activity, membrane fluidity, neurotransmission, enzyme modulation and gene expression[121]. Indeed, a third to one-half of FA in the brain are long-chain PUFA, predominantly *n*-3 FA, which are incorporated into cell membrane phospholipids[13]. Although still somewhat contentious, the benefits of dietary supplementation have been shown, in both human subjects and animal models, to manifest as improved mood[122,123] and cognition, the latter in both healthy subjects and those with neurodegenerative disease, including Alzheimer's disease[113,124,125]. It has been suggested that this can occur through the stimulation of neurogenesis[123,126,127].

n-3 Fatty acid effects on non-mammalian neurogenesis

EPA was first shown to up-regulate neurogenesis in a non-mammalian species, the lobster[128]. Crustaceans, like fish, have inherently high levels of neurogenesis and so make convenient models for the study of highly conserved neurogenic regulatory mechanisms[128,129]. It was hypothesised that *n*-3 FA would be involved in these regulatory processes, such that changes in their dietary intake would correlate with the extent of neurogenesis. The diets used varied in their content of α-linolenic acid and in their ratios of *n*-6:*n*-3[128]. This is an important nutritional consideration when modelling human supplementation, as ratios exceeding 2:1 can inhibit the conversion of α-linolenic acid to EPA and DHA[130]. Lobsters were incubated in bromodeoxyuridine added to artificial seawater and their brains dissected and examined for altered cell proliferation in cluster 10 of the brain, a population of interneurons innervating the olfactory bulb. Increased proliferation was observed with diets enriched with PUFA sourced from either brine shrimp or the cyanobacterium *Spirulina*. The increase was due to a rise in the overall basal level, as well as a small increase in the maximal rate seen at dusk, indicating that PUFA influence the circadian rhythmicity of neurogenesis. Correlational analysis suggested that the increased proliferation resulted from a favourable *n*-6:*n*-3 ratio, brought about by the increased α-linolenic acid present in the enriched diets. Thus, the authors were able to conclude that the adult nervous system benefits from this nutritional enhancement. As no metabolic parameters were measured, it is impossible to suggest whether this enhancement was stimulated directly by PUFA or via mediators of energy metabolism. In addition, proliferation in homologous equivalents of the hypothalamus or hippocampus was not reported[128], limiting extrapolation to mammals. Moreover, it is the enormous potential for central regeneration in non-mammalian species that sets them apart from mammals[129], further limiting cross-species comparison.

EPA/DHA effects on hippocampal neurogenesis in models of Alzheimer's disease

Nevertheless, extensive findings from psychiatric research confirm that PUFA may remodel brain cells[131,132]. Work with models of Alzheimer's disease showed that DHA, in particular, protects against neuronal apoptosis[133]. Recently, it has been shown that chronic consumption of a high-*n*-3 diet prevents the impairment of hippocampal neurogenesis in transgenic mouse models of autoimmune disease, in addition to preventing neuroinflammation and deficits in hippocampal synaptic plasticity[134].

The LMN diet, a diet rich in PUFA and polyphenols derived from dried fruits and cocoa, has been shown to not only

enhance neurogenesis in the SVZ and subgranular zone of normal adult mice, but also to ameliorate the cognitive decline seen in normal aged mice[135], and a mouse model of Alzheimer's disease. Furthermore, the diet is thought to delay the onset of hippocampal amyloid-β plaque formation induced by oxidative stress[136]. The nutritional breakdown of the patented LMN diet is not revealed, precluding comment on the relative contributions of PUFA and polyphenols to these effects. The authors reported that there was no diet-specific effect on body weight and did not report on any metabolic changes[135]. Thus, we cannot comment on their potential role in mediating the relationship between the LMN PUFA and neurogenic change.

Comparing adult and old rats, Dyall *et al.*[115] further explored the putative mechanisms behind the neuroprotective effects of *n*-3 FA on the decline in learning and memory observed with ageing. Dietary supplementation with EPA and DHA in combination (at a ratio of 1·5:1) partially reversed the decreased hippocampal neurogenesis observed in old rats and fully reversed the decline in some forebrain and hippocampal nuclear receptors, leading the authors to speculate that the two phenomena are linked[115]. Indeed, RAR-α signalling has been implicated in the differentiation of NPC[137]. DHA supplementation alone only partially increased RAR expression in these regions, suggesting that EPA may be required for the full reversal effect, and the authors conceded that a more comprehensive analysis of neurogenesis is required to ascertain fully the effects of EPA and DHA, alone and in combination[115]. However, not only does it remain to be established whether the effect of *n*-3 FA on neurogenesis is directly linked to the restoration of retinoid signalling, but also whether it is mediated by changes in energy metabolism. The authors did not explore in detail the energy metabolism effects of the PUFA-enriched diets, and therefore could not comment on whether they may have mediated the improvements in ageing-related change in the brain. Although they did monitor food intake and body weight of the animals throughout the studies, they did not present the data. They stated that animals on both diets (high DHA and high EPA/DHA) consumed similar amounts to controls, and that PUFA-fed animals showed only a small, non-significant increase in body weight. The authors suggested that at least this rules out a confounding effect of reduced energy intake[115], which could have contributed to the observed increase in neurogenesis, as occurs with dietary restriction[33,43]. They speculated that a likely mediating candidate would be BDNF[115], as its expression has been shown to be enhanced by both *n*-3 supplementation and RAR-α/-β agonists[123,138].

Mechanisms of DHA action in neurogenesis

Kawakita *et al.*[139] proved the link between DHA and adult neurogenesis, showing that dietary DHA supplementation stimulates hippocampal neurogenesis in rats, and confirming this through complementary *in vitro* studies of NSC. Using primary culture of rat forebrain cortices, they discovered the direct mechanism of DHA action on neurons, showing it to be an essential molecule for neuronal differentiation. Its effects were shown to be dependent on the stage of neurogenesis, whereby DHA inhibits cell proliferation but promotes neuronal differentiation by promoting cell cycle exit and suppressing cell death[139]. They later expanded on this mechanism by showing that promotion of cell cycle exit occurs through the control of the expression of basic helix-loop-helix transcription factors[140]. Based on these findings, and the fact that DHA acts at the retinoid X receptor[141], which is expressed at high levels only in differentiated NSC and primary hippocampal cells[142,143], they hypothesised that DHA differentially affects NSC and intermediate NPC. Furthermore, DHA's effects were shown to be concentration-dependent, whereby high concentrations reduce survival by inducing apoptosis leading to neuronal death[140].

PUFA interaction with G-protein-coupled receptors in hippocampal neurogenesis

In addition to nuclear receptors, PUFA activate a range of fat-sensing G-protein-coupled receptors (GPR) in peripheral tissues, which are involved in regulating energy metabolism and inflammation[144,145]. These include GPR120 and GPR40, which have been localised centrally and studied there for their direct roles in PUFA-mediated alleviation of SFA-induced hypothalamic inflammation[110] and hippocampal neurogenesis, respectively[146–149]. DHA acts at GPR40, expressed ubiquitously in the primate brain. Supported by extensive circumferential data, researchers have proposed that this interaction, even at low concentrations of DHA, up-regulates hippocampal neurogenesis required for improved memory function[147–149], and does so through induction of the phospholipase C/inositol triphosphate signalling pathway, which modulates intracellular Ca^{2+} mobilisation[148]. A primate model of transient global ischaemia has further shown that the signalling mechanism of PUFA, once bound to GPR40 in the neurogenic niche, involves an interaction with pCREB and BDNF, expressed in hippocampal newborn neurons 9 d after ischaemia induction[146]. This is consistent with the dysregulation of this pathway in response to high-level consumption of SFA[88], as described above, and, intriguingly, suggests the mechanistic level at which PUFA may counteract the inhibitory SFA effects on neurogenesis.

Summary

In summary, evidence continues to build for the stimulation of adult neurogenesis, in brain regions associated with cognition, by chronic consumption of PUFA-enriched diets. The degree of enhancement may depend on the ratio of *n*-6:*n*-3 FA, and determination of the relative contributions of EPA and DHA will require direct investigation. Mechanisms of this stimulation probably involve GPR40 and RAR located on hippocampal and forebrain neuroblasts, and may also involve neuroprotective systems that prevent stress induced by oxidative damage. Further work is required to define where these actions of PUFA might intersect with those at work in energy metabolism systems. Clues may arise from growing evidence of an interface between metabolism and other

forms of neuroplasticity. For example, *n*-3 FA have been proposed to exert their effects on cognitive enhancement by affecting molecular events related to both energy metabolism and synaptic plasticity, sharing mechanisms with, and sometimes complementing the action of, exercise. BDNF is thought to act at this interface[150]. It would therefore be interesting to determine whether PUFA exert their effects on body weight through changes in hypothalamic neurogenesis, and whether these are mediated by the BDNF. This would provide a neurobiological basis for the positive health benefits of dietary PUFA, enhancing their profile as potential nutraceuticals. The slow turnover of hypothalamic neurons[40], combined with technical issues surrounding bromodeoxyuridine use[24,151,152], may explain why this has not yet been observed.

Future considerations

Interactions between PUFA and intrinsic factors regulating body weight

The aim of the present review was to bring together recent evidence of the means by which dietary carbohydrates and FA might influence neurogenesis in the adult brain to control body weight. They would do this either directly, crossing the BBB to act at receptors located on NSC or NPC, or indirectly, through alteration of circulating levels of appetite-related intermediates, which themselves cross the BBB. In general, simple carbohydrates and SFA have been studied for their indirect effects, and PUFA for their direct effects, although primarily in the context of their potential for cognitive and mood enhancement and brain repair. In their capacity to improve energy metabolism, however, the evidence gathered so far suggests that, rather than directly stimulating neurogenesis, PUFA may act indirectly by counteracting the impairment of neurogenesis imposed by simple carbohydrates and SFA.

In the case of both of these macronutrient types, most evidence suggests that this impairment is mediated by circulating metabolic factors, but is generally independent of obesity, indicating the direct importance of these macronutrients in adult neurogenesis. Their shared mechanisms include BBB compromise, inflammation and glucocorticoid dysregulation. Indeed, elevation of both TAG and inflammatory cytokines impairs BBB integrity, blocking the neuroprotection normally afforded by leptin, ghrelin and insulin, and possibly other adipokines or gut hormones not yet examined in relation to neurogenesis. Future work should investigate the role of other possible candidates, such as glucagon-like peptide-1, an insulinotrophic intestinal peptide. *In vitro* and *in vivo* pharmacological intervention studies of control, obese and type 2 diabetes models have shown that it stimulates both hippocampal[153–157] and hypothalamic neurogenesis, and that CNTF mediates this latter relationship[64]. The neurogenic capacity of glucagon-like peptide-1 and its therapeutic analogues may, indeed, come from their ability to facilitate insulin release[158], as insulin has been implicated in NSC biology[43].

Elevated levels of TNF-α and IL-6, observed both peripherally and centrally in obesity[159–162] and Alzheimer's disease[163,164], have implicated inflammatory cytokines in the aetiology of both disorders. Combined with the findings from non-dietary studies that NSC are disabled by inflammatory cytokines[165], considerable indirect evidence converges on their key role in mediating impaired hippocampal neurogenesis in response to high-sugar/HFD. Future work should confirm their role in impaired hypothalamic neurogenesis in response to such diets. PUFA are likely to restore access to the brain of neurogenic factors through their well-established suppression of TAG[166] and inflammatory cytokines[124], as well as their direct improvements to BBB function[167,168].

Further investigation is required to determine whether or not the link between glucocorticoid dysregulation, impaired neurogenesis and high SFA consumption can be extended to high sugar intake. So far, the findings are inconsistent; whereas, in some cases, diets high in simple sugars, particularly fructose, have been linked to altered glucocorticoid metabolism[169], in others, there appears to be no relationship; for example, van der Borght's group found no change in circulating levels of corticosterone in response to the ingestion of high-glucose, -sucrose or -fructose solutions. Thus, the observed down-regulation of hippocampal neurogenesis which they linked to fructose consumption could not be associated with a corticosterone-dependent pathway[61]. Nevertheless, all of the mechanisms so far shown to underpin SFA-induced neurogenic impairment are associated with blocked expression and reduced levels of BDNF in the hippocampus and need to be confirmed in association with high-sugar diets, as well as with altered hypothalamic neurogenesis. PUFA enhance synthesis, secretion and intracellular signalling of BDNF[122,125], and therefore may restore neurogenesis by this means.

It is less clear how PUFA may act via the endocannabinoid system to enhance neurogenesis. Although this system is observed to be neuroprotective under conditions of brain repair[107], and, as we have seen, high fat feeding[93], its neurogenic responsiveness is generally inconsistent[98,170]. Increased dietary intake of *n*-3 FA decreases the synthesis of endogenous endocannabinoids, improving energy metabolism[118,171], but work is required to determine whether this may also occur through a neurogenic mechanism.

Potential role of PUFA in hypothalamic neurogenesis

Although SFA inhibit hypothalamic neurogenesis, it remains to be seen whether, conversely, PUFA exert their attenuating effects on weight gain through its stimulation. This will depend on the precise role of neurogenesis in the hypothalamus. If it is to redress apoptotic loss resulting from hypothalamic inflammation[172], then PUFA may only stimulate neurogenesis where required, i.e. in obese, rather than healthy, animals. Through the activation of GPR120 in key appetite areas of the hypothalamus, PUFA correct neurotransmitter expression, hypothalamic inflammation and impaired leptin and insulin signalling in obesity[110]. Combined with their robust peripheral effects, this may mean that these functions make a neurogenic effect superfluous. A related question is whether the putative mechanisms by which PUFA regulate hippocampal neurogenesis are also likely to

control hypothalamic neurogenesis. This may depend on whether the complex microenvironment on which neurogenesis depends is subject to control by the same extrinsic and intrinsic factors in both regions[120]. Aside from the extrinsic factors discussed above, there is the potential for PUFA to regulate hypothalamic neurogenesis through other local signals which also affect hippocampal neurogenesis, including glutamate receptor activation. These receptors are also expressed by the median eminence tanycytes[173], which we now know to be neurogenic[23], and have been shown to be regulated by PUFA in the hippocampus[174]. Studies similar to those of Katakura *et al.*[140] will have to be carried out on hypothalamic cells to confirm whether the key intrinsic factors at play include alteration of the balance of basic helix-loop-helix transcription factors by *n*-3 FA, as they do in the hippocampus.

Modelling the neurogenic interface to test therapeutic potential

Understanding how dietary PUFA regulate neurogenesis under conditions of altered energy metabolism is essential to fully harnessing their therapeutic benefits. Modulation of hippocampal neurogenesis has been viewed as a potential target in the development of novel treatments for neurodegenerative disorders[175], including those associated with disorders of energy metabolism, such as diabetes[26]. Dietary management is being increasingly viewed as a non-invasive and effective strategy by which to counteract neuronal injury and cognitive disorder; for example, (1) the inclusion in the diet of sources of *n*-3 FA, such as oily fish, and of antioxidant polyphenols, such as curcumin, and the flavonoids found in some fruits, green tea and red wine, and (2) the avoidance of 'junk food' high in SFA and refined carbohydrates, which decrease brain levels of BDNF[111]. It may transpire that it also modulates hippocampal and hypothalamic neurogenesis to effectively prevent or attenuate obesity development. Greater understanding of how these relationships are mediated may lead to nutraceutical approaches that encourage greater patient compliance than do pharmaceutical interventions. This potential is important to consider, as no dietary, lifestyle or pharmacological interventions have so far shown long-term success in the fight against obesity[176,177]. The putative neurogenic interface between cognition and energy metabolism may turn out to be a viable therapeutic target, if it can be shown to respond to a diet in a way that (1) demonstrates a differential sensitivity to variable macronutrient components and energy contents, and (2) is modulated by appetite-related signals. Determining whether this interface meets these criteria will be possible when studies are designed along parameters that adequately control key influences:

(1) *Dietary energy content*. Use of isoenergetic diets will remove the potentially confounding effects of different energy contents on neurogenic levels, allowing direct comparison of different macronutrients *per se*.
(2) *Precise dietary macronutrient composition*. Macronutrients should be tested in isolation as far as possible. For example, a number of the HFD reviewed here[21–25,83,85,88,92,93,104] include sucrose, which promotes insulin resistance in addition to saturated fats alone. Although perhaps a better replica of the Western diet that induces obesity in humans, combined ingredients confound the ability to map individual nutrients to the levels of neurogenesis. Researchers must work closely with commercial suppliers to balance this need against practical considerations of diet formulation, such as palatability and shelf life. The relative importance of high sugar and high fat, as well as the properties of carbohydrate and FA classes derived from different food sources and administered in different forms (solid *v.* liquid), could also be disentangled this way. This would also allow the macronutrient survey to be properly completed, first, with studies of diets high in complex carbohydrates. These are associated with a low glycaemic index and the prevention and mitigation of type 2 diabetes through the maintenance of steady blood sugar levels and better body-weight control[178,179]. Second, the neurogenic effects of altered proteins could be examined. These have not yet been reported; however, work with *Drosophila* has shown that dietary amino acids are key regulators of stem cell behaviour in cell cycle transitions[180,181].
(3) *Neurogenic impact*. Studies should begin to control for the myriad of external influences on adult neurogenesis, including exercise, environmental enrichment and stress, including that produced by social isolation[182]. This is a particular concern for feeding studies, where single housing is often the norm. All of these influences, in turn, interact with other important choices for animal model design, including species, strain, age and sex, all of which differentially affect neurogenesis[26,28–32,183].

    In addition, the potential impact of differential sensitivity to HFD-induced obesity on neurogenesis should be examined. The degree of sensitivity present at birth, as discussed above[21,23,92], may continue to be expressed in adults as the degree of proneness or resistance to weight gain and adiposity, modelled, for instance, in Sprague–Dawley rats[184]. It has been suggested to explain the variation in adverse effects induced by HFD feeding on hippocampal-dependent cognitive functioning[185], and this may be underpinned by variable degrees of neurogenic inhibition.
(4) *Outcome measures*. Experimenters should carry out behavioural tests of cognitive ability (e.g. learning and memory) and energy metabolism (e.g. feeding and activity) in the same animal model. We will not know fully which factors mediate the links between cognition, neurogenesis and diet until we establish a unified model. In this model, direct and indirect effects of macronutrients could be more clearly delineated by comparing the neurogenic effects of the central infusion of macronutrients with those of their consumption.
(5) *Functional significance*. Most findings so far have been phenomenological, showing that levels of neurogenesis alter in response to changes in macronutrient intake. The unified model could be used to show that the

corollary is also true; that is, that the manipulation of neurogenesis results in alterations in macronutrient intake. Ablation methods, or administration of mitogenic inhibitors, followed by measurement of changes in feeding behaviour, for example, as manifested by altered dietary preference or meal patterns, would demonstrate the functional requirement for new neurons.

In summary, a great deal more work is required to fully define the relationships between individual macronutrients and neurogenesis. Table 1 shows how there are presently too many differences between experimental approaches to tease out more than general associations. Once a more systematic approach to dietary intervention is adopted and more is learned about the unique properties of the hypothalamic neurogenic niche, in particular, researchers can begin to consider possible mechanisms of action and translation to functional relevance in humans.

Acknowledgements

There are no conflicts of interest with respect to any of the authors. All authors contributed to the literature review as well as the preparation of the manuscript at various stages. M. A. Y.'s studentship was supported by a BBSRC-funded Capacity Building Award in Integrative Mammalian Biology. L. C. P.'s lectureship is HEFCE-funded. We thank Professors J. Quinn and J. Wilding for their helpful feedback on the draft manuscript, and Dr L. Leiter of Research Diets, Inc. for the clarification on diet composition.

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