# Modulating adult neurogenesis through dietary interventions

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### Abstract

Three areas in the brain continuously generate new neurons throughout life: the subventricular zone lining the lateral ventricles, the dentate gyrus in the hippocampus and the median eminence in the hypothalamus. These areas harbour neural stem cells, which contribute to neural repair by generating daughter cells that then become functional neurons or glia. Impaired neurogenesis leads to detrimental consequences, such as depression, decline of cognitive abilities and obesity. Adult neurogenesis is a versatile process that can be modulated either positively or negatively by many effectors, external or endogenous. Diet can modify neurogenesis both ways, either directly by ways of food-borne molecules, or possibly by the modifications induced on gut microbiota composition. It is therefore critical to define dietary strategies optimal for the maintenance of the stem cell pools.

**Key words: Neurogenesis: Neural stem cells: Brain**

## Introduction

Like any other organ, the brain possesses regenerative capacities, and the process of adult neurogenesis, since its existence was proven, has been the subject of intense investigation. The discovery of neural stem cells (NSC) has also instigated new hopes for neuronal repair in regenerative medicine, and inspired studies designed to better understand the events and regulations involved in neurogenesis. Even if the understanding of this complex process is still uncompleted, the knowledge of the factors influencing neuron generation is more and more precise and detailed, and the ensemble of neurogenesis-related studies shows that neurogenesis is a highly malleable process, in which diet can play an important part.

## Neurogenesis is restricted to specific areas

Compared with high-rate turnover tissues such as the intestine for example, the brain presents limited regenerative capacities, in terms of intensity as well as in terms of location. The stem cells in the brain comply with the requirements defining stem cells: they self-renew, and are multipotent, i.e. they can differentiate into functional neurons, astrocytes and oligodendrocytes. The NSC are localised in three areas: the subventricular zone (SVZ) lining the lateral ventricle, the subgranular zone of the dentate gyrus (DG) in the hippocampus and a recently acknowledged area of the hypothalamus, the median eminence (ME). In the parenchyma, some scattered dividing cells have also been described, but these dividing cells are progenitors and not stem cells, in the sense that they do not self-renew, and that their *in vivo* fate is limited to the glial lineage. They will not be considered here.

The NSC of the SVZ give rise to neuroblasts migrating to the olfactory bulb, where they differentiate into GABAergic olfactory bulb interneurons and integrate the existing neuronal networks[1]. They take part in the maintenance of the network, the incorporation of new olfactory stimuli, or the olfactory memory. The fate of the NSC has been precisely documented in the SVZ: NSC (type B cells) derived from the embryonic radial glial cells divide slowly and give rise to transient-amplifying cells (type C cells), precursors of the neuroblasts (type A cells) which migrate into the rostral migratory stream to reach the olfactory bulb[1–3]. NSC have also the possibility to differentiate into astrocytes and oligodendrocytes[4,5].

In the DG of the hippocampus, the NSC are designated by different names, but the successive events are very similar: the NSC are named radial and horizontal type 1 NSC. They divide slowly into type 2 neuronal precursors, which cycle more intensely. The precursors differentiate into neuroblasts and are finally integrated into the network of the granular zone after 4 weeks of maturation as glutamatergic granule cells. The difference in this structure resides in the fact that the neuroblasts migrate shorter distances, and differentiate in the layer of subgranular cells. They establish connections with the pyramidal layer of cornu Ammonis (CA) 3 zone of the hippocampus[6,7]. Correlative studies by ablation and deletion have established that the new neurons are involved in the

maintenance of spatial memory, learning capacities, and the retention of new memories[8]. There seems to be a correlation between the survival of newborn cells and spatial-memory performances[9,10]. DG neurogenesis has also been linked with anxiety and depression or depression susceptibility in humans. This aspect has been under intense focus after the ground-breaking studies showing that the anti-depressant fluoxetine could increase cell division in the DG, and that this effect could correspond to the time needed for the treatment to have an impact in the patients[11,12].

If the existence of neurogenesis is now firmly established in rodents' brains, the relevance of these observations in humans has been debated. In humans, SVZ neurogenesis is very active until 2 years of age, with large numbers of immature neuroblasts migrating in the rostral migratory stream, but is nearly extinct in adulthood[13]. A similar observation has been made in non-human primates[14]. By contrast, human DG neurogenesis remains very active in adults: it has been estimated that 700 neurons/d are added in the DG[15].

Another very important role of neurogenesis in both areas is that the generation of new neurons is involved in neuronal repair after ischaemic stroke. Neuroblasts from the SVZ migrate to the damaged areas such as the cortex and the striatum and serve as a replacement of the dead neurons[16,17] and ischaemic stroke enhances also neurogenesis in the DG[18]. NSC transplants can survive and migrate into the ischaemic area[19] and neuroblast transplantation helps the restoration of behaviour and motor skills in rodents[20–22].

There is a great similarity in the markers of the NSC and progenitors from both areas: nestin and Sox2 are the classical markers for the NSC, and are not expressed anymore along the line of differentiation, polysialylated neuronal cell adhesion molecule (PSA-NCAM) and doublecortin are the most commonly used markers for neuroblasts, which once fully differentiated into neurons, can be labelled with NeuN or HuC/D. Using these markers enables to trace the fate of the newly generated cells *in vivo*.

The hypothalamus has been less studied. There have been reports showing the existence of dividing cells for long[23]; but this structure has recently gained further interest because studies have pointed out that the neurogenesis in this area is modulated by high-fat diets, a point that will be discussed below. Tanycytes are glial cells that line the third ventricle. Four different types have been characterised, α 1 and 2, and β 1 and 2, the function and properties of which differ with their location along the ventricle[24]. The β2 tanycytes, at the bottom of the third ventricle in the ME region and the α2 subtype, bordering the lateral walls of the third ventricle in the paraventricular and arcuate nuclei, are now considered as NSC, because they proliferate and display markers such as nestin and Sox2[25]. They migrate under intermediate differentiation into the arcuate nucleus (ARC) of the hypothalamus, and differentiate fully into pro-opiomelanocortin (POMC) neurons. POMC neurons are anorexigenic neurons; they decrease food intake through αMSH release, a proteolytic product of POMC. A fraction of these new neurons differentiate in a second wave into NPY and Agouti-related peptide (AgRP) neurons, which are orexigenic, and increase food intake[26,27]. The origin of the feeding circuitry lies in the embryonic period, and the

remodelling is very intense postnatally, and up until adolescence in the rodent[18] but persists into adulthood[28]. Disruption of the neurogenic process leads to modifications of food intake: an acute degeneration of AgRP neurons leads to a severe anorexia in mice, while a slow and progressive deletion does not have a significant effect on food intake, because neurogenesis can compensate and replace the degenerated neurons[29]. Therefore, the loss of POMC neurons in ARC could favour the development of obesity.

The neurogeneses in the three areas present similarities on several aspects: (1) the stem cells display markers specific to the glial lineage[30–32]; (2) the succession of events involved, i.e. proliferation followed by migration and differentiation; and (3) the nature of the markers. Yet, because each area is also a particular niche, their regulations can present some differences.

## Regulation and effectors

As mentioned above, NSC are not scattered in the parenchyma, but are concentrated in particular areas named 'niches' which provides the environment necessary to protect and preserve the cell pool. The niches are localised in proximity to ventricles (SVZ and ME) and/or capillaries (DG). Therefore, they are in close contact with effectors and the NSC pool can react to signalling modifications, either by dividing or staying quiescent. The signals can be endogenous; they include hormones, growth factors or neurotrophins. They can also be external, and that is how diet and nutrition can influence the process.

Neurotrophins and growth factors are positive regulators of neurogenesis: brain-derived neurotrophic factor (BDNF), insulin-like growth factor or vascular endothelial growth factor all increase cell proliferation, and/or promote cell survival or cell differentiation in the DG[33,34]. A broad range of hormones can also act on neurogenesis: oestrogen, progesterone and dehydroepiandrosterone promote DG neurogenesis[35,36], while corticosteroids, the last messengers of the hypothalamic–pituitary–adrenal axis, diminish cell proliferation and differentiation[37]. Peptide hormones can also modify neurogenesis: leptin promotes cell proliferation in the DG[38] and insulin promotes neuronal differentiation[39]. Gut peptides can modify cell renewal: ghrelin, peptide YY and cholecystokinin can increase cell proliferation in the DG and ghrelin acts positively on all steps of neurogenesis in the SVZ[40,41]. Chronic injections of glucagon-like peptide-1 increased neurogenesis in a model of Alzheimer's disease[42]; the effect of satiety peptides have been described on DG neurogenesis so far, and their effect on the proliferation and differentiation of β2 tanycytes is not known. It would be interesting to examine this point. Indeed, although the mechanisms involved in the three areas unroll very similarly, they are not necessarily modified by the same factors: significant differences in the length and importance of the successive steps may be responsible for the differences in sensitivity towards effectors. For instance, prolactin enhances SVZ neurogenesis and thereby increases the olfactory potential of the mother in preparation for maternal behaviour but DG neurogenesis is not modified by prolactin[43]. Conversely, BDNF increases cell proliferation in the DG, but does not affect cell proliferation in the SVZ[44].

A common feature of neurogenesis in the three areas is the vulnerability to the ageing process. Following embryonic neurogenesis, proliferation is very active in the postnatal period and decreases significantly until mid-age, then keeps decreasing at a slower pace during senescence in the hippocampus[45,46]. Recently, a study by Zhang *et al.*[47] showed that inflammation in the hypothalamus increases with age, as measured by NF-κB activation in the microglia; this ageing process negatively regulated gonadotropin-releasing hormone (GnRH) synthesis, and GnRH delivery into the third ventricle could reverse age-induced neurogenesis decline.

## Dietary influences

Environmental factors are efficient actors in the regulation of neurogenesis and diet or dietary intakes take an important part in these interactions. Several aspects can be considered: the quantity of ingested food or its composition, as developed below, and even its texture: rat hippocampus proliferation was decreased in animals fed soft food, and after being fed a powdered diet for 1 year, mice had lower counts of pyramidal neurons in the CA1 and CA3 regions of the hippocampus than mice fed a solid diet[48,49].

### Energy restriction v. overnutrition

Dietary restriction achieved by a reduction of 20–40 % of energy intake is reported to promote many health benefits, and to extend lifespan in many organisms, including mammals. The mechanism involved is thought to be linked to a reduction in oxidative stress[50–52]. In the brain, dietary restriction increases the number of newborn neurons in the DG of male rats fed every other day. A similar observation has been made in mice fed according to the same schedule: proliferation in the DG was not modified, but the rate of the survival of the new neurons was increased. This has been put in relation with higher levels of BDNF in the CA1 of the hippocampus[53,54].

Conversely, in male adult rats, overnutrition resulting from the ingestion of high-sugar[55] or high-fat/high-energy diets leads to a reduction of NSC proliferation and neuron generation in the DG[56] and ARC[20]. However, a high-fat diet and obesity make an impact on cell proliferation in the brain selectively[57,58]. In the ME, the consequences of a high-fat diet seem less consistent: a study showed a decrease in cell generation only after a long-term ingestion of a high-fat diet (4 months) in male adult rats. Another group, after a much more limited period of high-fat feeding (1 month), showed an opposite effect on cell proliferation, but this group studied young rats right after weaning[59]. The 4-month feeding resulted in a diminution of cell proliferation, diminution of cell survival, with a decrease more important in the neuronal lineage, compared with the glial lineage; the effect on neurogenesis was connected with an increase in TNFα and IL-1β concentrations, resulting from an activation of the NF-κB pathway. This activation promoted a higher rate of apoptosis in the ARC, leading to a moderate loss of POMC neurons, while NPY neurons remained unchanged[20]. In young adult mice, a high-fat diet (60 % fat) resulted in a decrease in both sexes in ARC neurogenesis, but enhanced ME neurogenesis in female mice[60]. A maternal diet rich in lipids and energy (32 % fat) also impairs the hippocampal and hypothalamic neurogenesis of young mouse offspring, with negative consequences on learning abilities and energy intake control[61]. A concordant result has been established in patients, linking the Western diet and a smaller left hippocampus[62].

It is interesting to underscore that the results obtained after long-term high-fat feeding paralleled the consequences of the ageing effect: very similarly, ageing results in cytokine elevation and NF-κB activation in the hypothalamus[36].

Consequently, food-borne molecules known for their anti-inflammatory and antioxidative properties could be considered valuable in view of dietary strategies aimed at restoring neurogenesis capacities.

### Dietary interventions

The present paragraph will discuss the possibility of dietary strategies or supplementations using food-borne molecules with a focus on their role on neurogenesis, knowing that the effects of these molecules cover a more complex and much broader field than mere neuron generation.

Polyphenols are such compounds. They are known for their antioxidant and anti-inflammatory properties[63]. Flavonoids are a class of polyphenols which have attracted a considerable interest. Dietary supplements of compounds such as oroxylin A, baicalin or heptamethoxyflavone, a citrus flavone, can increase cell proliferation in the hippocampus of mice following global cerebral ischaemia[64–66], and baicalein reduces the impairment provoked by γ-ray irradiation[67]. They can also play a neuro-protective role, favouring neurite outgrowth and neural differentiation *in vitro*[68,69]. Resveratrol, a phenol present in wine, red grapes and groundnuts, can increase cell proliferation in prenatal stress or in mice with chronic fatigue syndrome[70,71], and the supplementation also led to a decrease in inflammation and improvement of cognitive functions. Low intakes of curcumin, a phenol present in curry powder, increased cell proliferation in the hippocampus[72]. Curcumin also has neuroprotective properties, as shown in aged rats: it can reverse the effects of age and ischaemia, and promote cell repair in spinal cord injury[73,74].

*n*-3 PUFA have also generated much interest, being a major constituent of brain structures. Insufficient brain DHA, the main *n*-3 PUFA in cell membranes, has been associated with memory impairment, emotional disturbances and altered brain processes in experimental studies. Epidemiological studies have revealed that low *n*-3 PUFA is correlated with cognitive or behavioural defects during early development[75], adulthood and ageing[76]. Among many other roles, *n*-3 PUFA can improve hippocampal neurogenesis by enhancing cell proliferation and differentiation in adult rats[77–79], and reverse the decline observed in aged rats under a short supplementation[80]. In 19-month-old mice, 8 weeks of *n*-3 supplementation led to an increase in hippocampal neurogenesis and in arborisation of newborn neurons[81]. They also affect deeply the physiology of rat NSC, by enhancing their proliferation and differentiation, and modifying their trancriptome[82].

Most of the studies described above refer to hippocampal neurogenesis, because until now, this aspect was the most

relevant to the human situation. It would be now interesting to test these compounds on hypothalamic neurogenesis, particularly to check if they could reverse some of the aspects resulting from obesity, for instance.

## Mechanisms involved

From the examples, a general outline can be drawn, showing that molecules or events that increase inflammation tend to lower neurogenesis, while anti-inflammatory molecules or pathways restore it. Therefore, the mediators of the inflammatory pathway represent the central targets and the balance upon which the different effectors can impinge. We will develop here some examples of these targets, such as the cAMP response element binding protein (CREB), BDNF, NF-κB, sirtuin 1 (Sirt1), and the energy-sensing kinase AMP-activated protein kinase (AMPK), and we will show how they all inter-relate.

### Brain-derived neurotrophic factor and cAMP response element binding protein. 
BDNF is a well-recognised effector of neurogenesis. This neurotrophin is involved in brain development and neural plasticity. It mediates its effect through binding to the membrane receptor tropomyosin receptor kinase B (TrkB). The variations of BDNF in the hippocampus induced by environmental modifications and dietary interventions are directly correlated with the variations noted in neurogenesis: dietary restriction, which increases neurogenesis, and increases BDNF mRNA expression and protein[83]. On the other hand, overnutrition decreases BDNF levels. It is here interesting to underline that BDNF, apart from its role on neurogenesis, acts also on food intake, since knock-out mice deficient in *bdnf* display hyperphagia and develop obesity[84]. Very similarly, the effects of flavonoids on neurogenesis have been connected with parallel modifications of BDNF in whole brain or hippocampus: ingestion of naringin, oroxylin A or blueberry extracts leads to a significant increase in BDNF levels[85–87]. Resveratrol promotes BDNF synthesis from astroglia[88] and in the hippocampus[89], and by promoting BDNF synthesis reverses hippocampal atrophy in chronic fatigue mice and reverses the effect of mild stress on cognition[90,91].

The effects of *n*-3 PUFA supplementation are similar: a large body of studies has unanimously shown that, in experimental models, the dietary supplementation of DHA or a mixture of *n*-3 PUFA could increase BDNF levels, or normalise them after mild brain injury in rats[92]. DHA supplementation at 1·25 % could increase the effects of voluntary exercise in mice, with a parallel increase in BDNF in the brain. Quite interestingly, the benefits of *n*-3 PUFA were also transmitted by the maternal diet since prenatal *n*-3 PUFA supplementation to a micronutrient-imbalanced diet protected brain neurotrophins in both the cortex and hippocampus in the adult rat offspring[93].

In most cases the similarity of actions on BDNF synthesis could be related to the effects on synthesis of CREB and its phosphorylation. CREB is an ubiquitous transcription factor, highly expressed in the brain in which it is involved in many signalling pathways serving many functions, ranging from neuronal survival to memory formation[94]. Its activation through phosphorylation is the result of the action of the mitogen-activated protein kinases, or protein kinase C kinase. Once phosphorylated, CREB enters the nucleus where it binds to the CREB response element. One of its target gene is *Bdnf*. Experimental data showed that *n*-3 PUFA supplementation after traumatic brain injury enhanced CREB protein contents[95] and reduced oxidative damage in injured rats. Curcumin enhanced CREB expression in rat brain[96,97], and resveratrol increased the phosphorylated state of CREB after ischaemia[98].

### Inflammatory NF-κB v. anti-inflammatory Sirt1 and AMP kinase. 
Another factor affecting neurogenesis is the balance between pro- and anti-inflammatory pathways.

Ageing, depression and obesity have all been related to low-grade neuroinflammation and its oxidative stress companion[99,100]. NF-κB is the major and central mediator of inflammation. This transcription factor, once activated, can induce the transcription of the inflammatory cytokines such as TNFα, *monocyte chemoattractant protein-1* and IL-1β or IL-6[101]. NF-κB activation has also been cited in the different situations leading to an increase or decrease of neurogenesis: all the signals, either endogenous such as age and stress, or external such as overnutrition, lead to an activation of NF-κB in the brain, either in the hippocampus or the hypothalamus, and decrease neurogenesis in these areas.

An endogenous inhibitor of NF-κB is Sirt1. Sirt1 is a deacetylase enzyme regulating energy metabolism and cell survival. Among other targets, the RelA/p65 component of the NF-κB complex is deacetylated by Sirt1 on Lys130, which inhibits the transcription ability of NF-κB[102]. By this mechanism, Sirt1 can prevent the deleterious effects of a high-fat diet and protect from hepatic steatosis[103]. Therefore, Sirt1 activators could also be valuable in preventing the inflammatory pathway. Dietary restriction is a strong inducer of Sirt1 expression and activity. The first compound detected among a screening of small molecules to be an inhibitor of Sirt1 was resveratrol[104], and it was later demonstrated that resveratrol could mimic the effects of energy restriction and delay the ageing process through its up-regulation of Sirt1[105]. It is now well admitted that nutrients can modulate inflammation through Sirt1 involvement. Other flavonoids, such as quercetin or rutin for instance, can also up-regulate Sirt1 expression[106,107]. Because of its broad enzymic activity, Sirt1 can take part in many pathways. It has been demonstrated that Sirt1 activity could modify the differentiation fate of NSC, favouring astrogliosis to the expense of neurogenesis under oxidative stress[108]. Sirt1 is also essential for cognition and neuronal plasticity[109]. It is interesting to mention that the overexpression of Sirt1 stimulates BDNF expression[110], and is neuroprotective in a model of Huntington's disease[111]. By its deacylating activity, Sirt1 is involved in a large range of effects. Among the numerous Sirt1 targets, we will focus on AMPK, because its involvement in NSC physiology and its regulation by dietary factors attract increasing interest.

AMPK is a fuel-sensing kinase that drives the cellular metabolism from catabolic to anabolic depending on the energy level of the cell. Its activity is up-regulated when the ATP levels of the cell are low. AMPK and Sirt1 share many cellular targets, are activated by the same stimuli, and also regulate each

other[112]. Experimental evidence from transgenic mice lacking the AMPKβ1 subunit demonstrates that this kinase is involved in NSC proliferation, since the mice display cerebral atrophy. AMPK could also improve neuronal survival under low energy conditions[113]. Several studies have shown that bioflavonoids can induce, *in vitro* and *in vivo*, an activation of the AMPK pathway. Naringenin, quercetin and quercetin 3-*O*-glycosides extracted from plants in muscle cells, or in the brain of old mice, up-regulate AMPK activity. Apigenin induces the activation in human keratinocytes and its activity is also up-regulated by resveratrol in mouse primary neurons[114–118]. Similarly, *n*-3 PUFA exert their protective and anti-inflammatory effects through the up-regulation of AMPK[95]. The implication of Sirt1 has not been extensively investigated in these studies, but has been demonstrated in others[119,120].

For clarity we have described the two pathways under two distinct paragraphs, but they actually are also intertwined and it is interesting here to notice that the mediators susceptible to act on neurogenesis are also found at the intersection of the fields of inflammation, energy homeostasis and neuronal plasticity, as recapitulated in Fig. 1.

Rodent experimentation has amply demonstrated the disadvantages/benefits of diets/molecules on neurogenesis and



**Fig. 1.** Adult neurogenesis is a flexible process, which can be modified by positive or negative influences. Pro-inflammatory molecules or mechanisms activate NF-κB, which induces the transcription of pro-inflammatory cytokines, while anti-inflammatory molecules by their action on sirtuin 1 (Sirt1) activate cAMP response element binding protein (CREB), brain-derived neurotrophic factor (BDNF) and AMP-activated protein kinase (AMPK) and restore cell renewal in the brain. The influence of gut microbiota is here hypothetical. For a colour figure, see the online version.

their functional consequences such as the effects on learning, mood or energy homeostasis. The relevance of these studies to the human situation is hampered by the difficulty in measuring human neurogenesis so this point is mainly based on correlations: for instance, a recent study tested the supplementation of resveratrol in elderly and proved it efficient in protecting memory and glucose metabolism[121]. Similarly, components of the Mediterranean diet improved cognition in elderly[122]. So data generated from animal experimentation have opened the way to many more studies on the usage of diets or natural compounds as therapeutic agents.

## Gut microbiota: a possible effector?

Gut microbiota is now considered as a major factor in the modulation of the host's physiology, including neural functions through the gut–brain axis. Seminal data obtained from the comparison of germ-free (GF) mice with their conventional counterparts have shown that the absence of intestinal microbiota was associated with a decreased anxiety but a stronger response to stress[123], but GF male F344 rats exhibited increased anxiety compared with SPF counterparts[124]. The genetic background of the animals has been proposed as an important factor[124]. GF mice display a lower abundance of BDNF in the hippocampus, and an increased monoamine turnover in the striatum[123]. Another group has shown higher hippocampal concentrations of 5-hydroxytryptamine in male GF mice[125].

A robust body of evidence has shown that gut microbiota composition differs between fat and lean animals, with a higher proportion of Firmicutes and a lower presence of Bacteroidetes in obese animals[126]. The modifications pointed out in animals are consistent with the modifications of the gut microbiota detected in obese patients[127]. Moreover, microbiota alone seems able to modify the host's metabolism, as exemplified by the recent clinical observation, resulting from a faecal transfer[128]. The mechanisms involved are still under clarification, but hypotheses suggest that microbiota composition could either promote a more efficient energy harvest from the nutrients, or act through the lowering of the systemic inflammation level associated with obesity. Indeed, the inflammation develops with different kinetics in the organs, and the brain is the first one to be harmed, since a low level of inflammation is perceived after only 7 d of a high-fat diet[18]. Furthermore, the installation of obesity is accompanied with a deregulation of numerous hormones levels, such as insulin, leptin, adiponectin[129] and the gut satiety peptides such as glucagon-like peptide-1. We have seen in the paragraph above that these factors can positively modify neurogenesis, and, therefore, their deregulation could contribute to the development of a downward spiral aggravated by an impairment of neuronal repair. Recent data from obese and non-obese patients show that gut microbiota and brain microstructure are associated[130]. Whether 'obese' or 'non-obese' microbiota can modulate neuroinflammation or act directly through bacterial metabolites would be interesting questions to study, particularly in the hypothalamus, but also in the hippocampus, with regard to depression or decline of the cognitive abilities linked
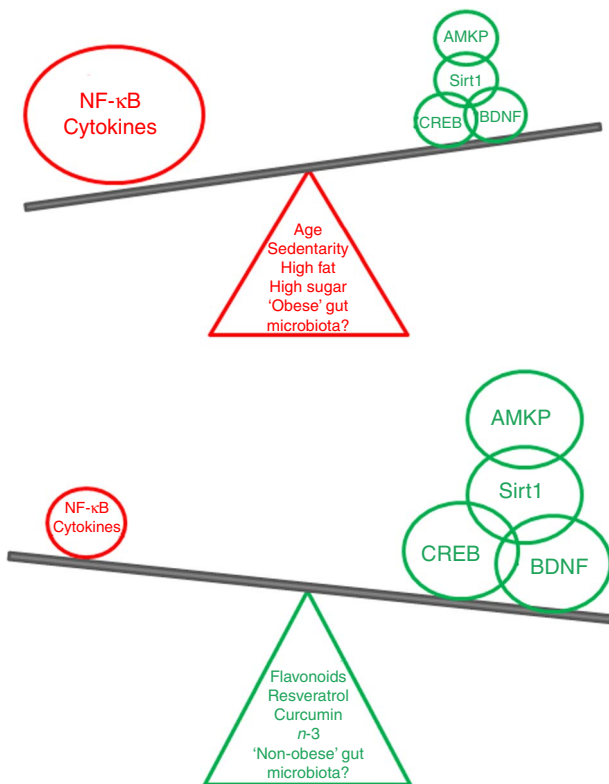
with obesity. Moreover, since the characteristics of the diet (for example, animal *v.* plant proteins) themselves can modify the composition of gut microbiota[131], dietary recommendations should be made to drive the intestinal microbes' mass to beneficial and optimal proportions.

## Conclusion

Neurogenesis is an active component of brain physiology, and its malfunctioning can lead to adverse consequences such as depression, decline of learning abilities, and obesity. It is also a versatile and very sensitive process that can be modulated by many factors: if it can be impaired very easily, it can also be restored. Modifications in lifestyle can help keep the stem cell pools under optimal conditions, and nutrition is particularly helpful on this point. We have established here that most of the pernicious effects on neurogenesis are interrelated, and come from neuroinflammation. Keeping this inflammation down could help contribute to restore cell renewal; Fig. 1 sums up the detrimental effectors, and the possible solutions to counteract them. The experimental data have pointed out the favourable role of food components or molecules. A deeper knowledge of the possibilities linked with gut microbiota could also open new possibilities, and this could provide interesting alternatives to pharmaceutical treatments.

## Acknowledgements

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