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# Introductory Chapter: Feed Your Mind - How Does Nutrition Modulate Brain Function throughout Life?

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## 1. Introduction

Nutrition is a transdisciplinary science that aims at studying the role of food and physical exercise on health and diseases. It includes notably biochemistry, metabolism, behavioural and social studies. Nutrition science is highly diverse and constantly evolving for several reasons:

- The control of energy balance is a primary need for humans and for all animals, which implies it is of high importance.
- A high diversity of dietary models throughout the world exists, which is closely related to the diversity of culture, even in one single country.
- In human societies, alimentation participates to social behaviour.
- Modern societies have been hugely transformed since food industrialization.

The last point has critically changed the way of life for people in industrialised countries. Food industrialisation was originally designed to ease life and feed the growing population following the First and Second World Wars. Unexpectedly, industrialisation has engendered a profound dietary imbalance.

For the first time in history, people with industrialised diet are facing food with high quantities of sugar and saturated fats. This diet can also lead to deficiency in essential nutrients, such as vitamins, minerals and polyunsaturated fatty acids. This change in diet has been paralleled by an increase in sedentariness, which contributes to energy imbalance. This change in the last 70 years leads to global epidemics as obesity, cardiovascular disorders and depressive disorders.

In this context, the brain appears as a structure highly sensitive to dietary imbalance [1]. In addition, the brain can participate to dietary imbalance by controlling feeding behaviours and through its interaction with peripheral organs and hormones involved in the control of energy balance. Thus, the impact of nutrition on brain function is a specific field of research that has gained interest in the recent years, and the role of the brain appears central in nutrition. Nutrition will impact the brain from early-developmental stages to adolescence, when the brain tissue is built and modelled. Nutrition also appears critical at adult age, to maintain optimal brain function. Finally, nutrition appears as an important environmental factor that

should be controlled through ageing, to prevent neurodegenerative processes. In this introductory chapter, we will take the example of vitamin A, which is a nutrient that has been demonstrated as critical for brain function throughout life [2–5].

## 2. Vitamin A and its active metabolite: retinoic acid

Vitamin A is a lipophilic vitamin that cannot be synthesised *de novo* by organism. Food sources are animal products for the preformed vitamin A and vegetables for provitamin A. Preformed vitamin A and provitamin A are found in sufficient quantities in most diets, but strong deficiency may occur in undernourished populations, mainly in sub-Saharan Africa. Vitamin A deficiency in children can cause blindness and growth retardation and can ultimately lead to death. Besides, vitamin A deficiency may occur with ageing, since its bioavailability can be reduced. In both cases, vitamin A supplementation can reverse this deficiency, which emphasises the need to study the impact of vitamin A supplementation for pregnant women and children, as well as for elderly.

The active metabolite of vitamin A in the brain is the all-*trans* retinoic acid (*atRA*), synthesised from vitamin A (retinol) by aldehyde dehydrogenase enzymes [6, 7]. Retinoic acid and its derivatives bind to nuclear receptors, namely, RAR and RXR. These receptors act as homo- or heterodimers to control gene transcription [3, 6]. Therefore, retinoic acid is a powerful morphogen factor, highly involved in embryonic development and growth [8].

## 3. The role of vitamin A during brain development

During brain development, retinoic acid synthesised from dietary vitamin A binds to nuclear receptors to drive transcription of hundreds of genes. Retinoic acid is a morphogen that acts through a concentration gradient [8]. To carry out the precision of retinoic acid gradient during embryonic development, metabolism and signalling pathways for retinoic acid are multiple and highly robust [8]. Remarkably, retinoic acid is the only morphogen that comes from dietary sources, which highlights the importance of vitamin A intake during pregnancy. Through its action on nuclear receptors, retinoic acid is implicated in the patterning of neural axis along the dorsoventral and anteroposterior axes [2].

In addition to development and growth, retinoic acid in the brain is critical for neuronal differentiation and neurite outgrowth. This is particularly true in the basal ganglia network, which is a group of brain structures involved in the control of action. Indeed, retinoic acid is key in the differentiation of specific subpopulations of neurons, such as the medium size spiny neurons in the striatum, or the dopaminergic neurons from the substantia nigra pars compacta [9–13].

## 4. The role of vitamin A in the adult brain

At adult age, vitamin A-derived retinoic acid has two remarkable roles; it is involved in homeostatic plasticity and in neurogenesis [3, 5, 14, 15]. First, retinoic acid induces molecular and morphological changes in neuronal network, to maintain overall synaptic activity constant, despite synaptic plasticity, a process named homeostatic synaptic plasticity [16]. For this, retinoic acid binds to nuclear RAR and RXR receptors, but evidence suggests that non-genomic mechanisms are also

involved [17–19]. Changes induced by retinoic acid to produce homeostatic plasticity include transcription of synaptic proteins, such as AMPA receptors, but also modulation of neuronal morphology, through outgrowth or retraction of synapse boutons and dendrites.

Second, retinoic acid controls neurogenesis. In rodent deficient for vitamin A, neurogenesis in the hippocampus is strongly dampened and can be restored by replenishment with vitamin A or derivatives [20–23]. However, in physiological conditions, retinoic acid applied exogenously can inhibit neurogenesis in the hippocampus and facilitate cell differentiation [3]. The apparent discrepancy between physiological and deficient states may be explained by the finely tuned concentration and timing of retinoic acid that is needed for its control of neurogenesis. In the hypothalamus, neurogenesis is highly dynamic to orchestrate circadian rhythms that govern several hypothalamic functions. In this structure, a similar role has been demonstrated for retinoic acid, inhibiting proliferation of cells and thus neurogenesis [5].

## **5. The role of vitamin A in the ageing brain**

Ageing process is a physiological and unavoidable phenomenon involving the whole body. Related to brain function, ageing is characterised by a cognitive decline, which comprises all molecular and cellular alterations that lead ultimately to decreased performance in cognitive and executive functions [24]. Evidence suggests that bioavailability of retinoic acid in the brain reduces with ageing, likely due to peripheral alterations [4]. Yet several studies have highlighted the parallel between ageing, decrease in brain retinoid signalling and cognitive decline [4, 25–27]. Mechanisms linking retinoid metabolism and cognitive decline are not yet completely unravelled, but evidence suggests the involvement of glucocorticoids [20] and morphological changes of neuronal trees (unpublished data).

Beyond normal ageing, decreased retinoid signalling in the brain with ageing may be involved in neurodegenerative processes, such as in Alzheimer's and Parkinson's diseases. For Alzheimer's disease, accumulating evidence suggests that the lack of retinoic acid in the hippocampus is a risk factor that precipitates the deposition of  $\beta$ -amyloid plaques, a histological landmark of the disease [28–31]. Therefore, vitamin A and retinoids appear as potential therapeutics [30, 32]. However, mechanisms are not yet sufficiently understood to elaborate such therapeutics. Additionally, retinoids are lipophilic molecules that oxidise rapidly, which render their pharmacological use challenging.

In the context of Parkinson's disease, a similar process has been proposed. Reduced signalling of retinoids in the brain, and particularly in the substantia nigra compacta, may be a risk factor that accelerates the degeneration of dopaminergic neurons [33, 34]. This hypothesis is supported by the fact that rodents deficient for vitamin A or for retinoid receptors display motor impairments close to Parkinson's models [35, 36]. Some studies revealed encouraging results with retinoid supplementation to prevent neurodegeneration in cell culture or in vivo [37, 38], but research is still preliminary to envisage soon vitamin A-based treatments for this disease.

## **6. Conclusion**

Through the solely example of vitamin A, we can appreciate the importance of nutrition for brain physiology, from development to adult age. Remarkably, a same

nutrient can have different roles depending on the timing, the brain structure and even the cell type. The field of research on nutrition applied to neurosciences is growing, to better encompass the impact of industrialised diet on brain function and also to consider nutrients and their derivatives as potential therapeutic strategies. In this way, it is to expect that nutritional approaches will give rise in the future to new therapeutics to prevent, and in some case cure, neurological disorders.

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