Dynamic Immunonutritional Interplay in Cognitive Function

José Moisés Laparra Llopis[*]

Department of Molecular Immunonutrition, Instituto Madrileño de Estudios Avanzados en Alimentación, Spain

[*]**Corresponding author:** José Moisés Laparra Llopis, Director, Department of Molecular Immunonutrition, Instituto Madrileño de Estudios Avanzados en Alimentación, Spain, Tel: (+34) 625141128; E-mail: J.Moises.Laparra@uv.es

Introduction

Western lifestyle, mainly the lack of physical activity coupled with over-nutrition, is considered the major contributor to the development of distinct immunometabolic-based diseases (i.e., type 2 diabetes, obesity and non-alcoholic fatty liver disease). While it has become evident that there exists a close association between the microbiome and immunometabolic-based diseases, physiological dysfunctions may either precede or be the consequence of alterations in gut microbiota. The intestinal microbiota in health and disease is increasingly perceived as an external organ that modulates the metabolism of its host and conversely responds to cues from the host. The microbiome is shaped by both endogenous and environmental factors, such as genetics and nutrients, but in turn influences host biology either in health and disease.

Emerging evidences have established complex and varied interactions between the gut microbiota and neuroinflammatory processes and link imbalances in the gut microbiota to neurological diseases and cognitive function [1]. Compelling evidence for the microbiome's role as either trigger or driver within the neuroimmune axis [2]. The possible mechanisms underlying the microbiota's signaling to the brain are diverse including the immune system, the vagus nerve or other endocrine and metabolic host-microbe interactions. It is well-known that diet can affect the gut microbiome both in a beneficial and in a detrimental way. Moreover, sustained high-fat diet causes not only obesity/insulin resistance, but also microglial hyperactivity and impairs cognition [3]. Consumption of high fat diet is associated with altered microbial diversity and reduced synaptic plasticity thus leading to cognitive decline.

There is evidence of the relevance of pre- and postnatal nutrition to developmental programming towards health or disease. Exposure to inflammatory products can impair perinatal brain development predisposing, among other, to cognitive disorders. Here, it has been evidenced the effect of acute systemic inflammatory insults on brain injury [4]. In this context, food composition rather than calorie intake comes to some principal place as defined food components act as strong activators of intestinal innate immunity contributing to high fat diet-associated systemic inflammation. Dietary triggers of innate immune signals associated to toll-like receptors (TLR) [5] engage neurostimulatory signals through the endocannabinoid system that could favor the impairment in synaptic plasticity [6]. TLRs have been identified as mediators interfering the adenosine A2A receptor signaling to correct autism [7]. Macrophages are key mediators of innate immunity. Macrophages that can result activated by systemic inflammation can infiltrate the brain parenchyma to induce microglial activation and neuroinflammation. In a feed-back loop, neuroinflammatory processes contribute to aggravate hepatic dysfunction, for example, via alterations in neurotransmitters signaling on liver 5-HT7 receptors [8]. This scenario highlights the need to identify immunonutritional activators of TLR4, as well as to improve our knowledge about shifting downstream pathways associated to TLR4 for the regulation of immune responses. The curtail or selective modulation for retrieval of TLR4 appears as a key process giving rise or preventing alterations of immune homeostasis. Many exogenous agonists of TLR4 have been proposed; however, the molecular mechanisms by which they activate (magnitude and intensity) TLR4-driven response(s) are not completely understood.

Activation of aryl hydrocarbon receptor (Ahr) has been identified as derived from high fat diet consumption. Activation of TLR4 converges in downstream signaling of Ahr. The promoter activity of the cyclooxygenase-2 gene is induced by Ahr ligands. Neuroinflammation and cyclooxygenase-2 enzyme have gained increased interest as key factors involved early in Alzheimer's disease, although the signaling pathways and pathophysiologic mechanisms underlying a link between sAß-induced neurotoxicity and inflammation are still unclear [9]. Excessive activation of AhR signaling has been shown to disrupt neuronal migration in the hippocampal CA1 region in the developing mouse [10].

Modulation of bacterial composition can contribute positively improving insulin resistance by interaction with innate immune signaling through TLR4 and LPS receptor CD14 and/or nucleotide oligomerization domain (NOD)-1 and -2 proteins [11]. Recent findings showed that immunonutritional strategies based on prebiotics, probiotics and synbiotics resulted effective to restore cognition in obese-insulin resistant animals through gut-brain axis [12]. Notably, immunonutritional intervention improved hippocampal plasticity, brain mitochondrial function, and decreased microglial activation in high fat diet fed animals.

In summary, cognitive impairment results as comorbidity in obese patients with metabolic syndrome where over-nutrition, together with sedentary lifestyles, is considered major contributors. There is increasing evidence for a correlation between intestinal dysbiosis and imbalances in intestinal

microbiota with the development of neurodevelopmental disorders. Animal and human data demonstrate that phylogenetic changes occur in the microbiota of obese versus lean individuals, been characterized by an increased Firmicutes to Bacteroidetes ratio. Evidence for the role of gut microbiota concerning energy harvest, but also its immunomodulatory and anti-inflammatory influence started to appear indicating that positively influences pathological condition and complications of liver disease. The latter effects appear to be mediated not only specie-, but strain-specific and point out the potential use of gut microbiota as predictive/therapeutic tool, although, this needs to be further studied. In addition, dietary immunonutritional innate immune activators, particularly via TLR4, deserve special attention since TLR4-driven response(s) are not completely understood. Therefore, novel immunonutritional strategies based on the use of probiotics acquire growing importance because of their proven positive effects on inflammation and immune response(s).

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