Chapter

Serotonin Pathway in Neuroimmune Network

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Abstract

Once considered merely as a neurotransmitter, serotonin (5-HT) now enjoys a renewed reputation as an interlocutor in the dense and continuous dialogue between neuroendocrine and immune systems. In the last decades, a role has been depicted for serotonin and its derivatives as modulators of several immunological events, due to the expression of specific receptors or enzymes controlling 5-HT metabolism in diverse immune cell types. A growing body of evidence suggests that the effects of molecules belonging to the 5-HT pathways on the neuroimmune communication may be relevant in the clinical outcome of autoimmune/inflammatory pathologies of the central nervous system (CNS), such as multiple sclerosis, but also in Alzheimer's disease, or in mood disorders and major depression. Moreover, since the predominance of 5-HT is produced by enterochromaffin cells of the gastrointestinal tract, where 5-HT and its derivatives are important mucosal signalling molecules giving rise to the so-called "brain-gut axis", alterations in brain-gut communication are also involved in the pathogenesis and pathophysiology of several psychiatric and neurologic disorders. Here we illustrate how functional interactions between immune and neuronal cells are crucial to orchestrate tissue homeostasis and integrity, and the role of serotonin pathway components as pillars of the neuroimmune system.

Keywords: neuroimmune system, tryptophan metabolism, serotonin, N-acetylserotonin, melatonin, indoleamine 2,3-dioxygenase

1. Introduction

It's now widely accepted that the immune system and neuroendocrine system function in close association of each other, to such an extent that it's possible to refer to them as "neuroimmune system" [1]. The interactions that take place within the neuroimmune system involve the production and use of immune factors, as well as neuroendocrine mediators, in a role-playing game where it's impossible to trace the belonging of specific molecules exclusively in one of the two systems. The constant dialogue between the participants to the neuroimmune communication in the CNS and in the periphery not only allows the fine tuning of the immune response, but also the synaptic plasticity, and alterations in the propagation of neuroimmune messages may account for several immune-mediated and psychiatric diseases.

Here we examine the role of serotonin and its derivatives in the neuroimmune communication and we highlight the importance of an appropriate balance between the production of tryptophan metabolites for the maintenance of the neuroimmune

homeostasis. Moreover, we give a perspective on how the regulation of the metabolic pathways leading to different tryptophan metabolites, including serotonin and derived molecules, could represent a significant pharmacological target for the treatment of various CNS diseases.

2. Serotonin pathway in the neuroimmune system: an overview

Under physiological conditions, the majority of Tryptophan (Trp) is degraded along the kynurenine pathway (KP) and only about 1% is metabolized into serotonin (5-HT) in the so-called methoxyindoles pathway (**Figure 1**). This metabolic route begins with the transformation of Trp into 5-hydroxytryptophan and then into serotonin through two consecutive reactions catalyzed by the enzymes tryptophan hydroxylase (TPH) and 5-hydroxytryptophan decarboxylase (AADC). Subsequently, the rate-limiting enzyme arylalkylamine N-acetyltransferase (AANAT) promotes the acetylation of serotonin into N-acetylserotonin (NAS), which, in turn, serves as a substrate for the hydroxyindole-O-methyl transferase (HIOMT or acetylserotonin O-methyltransferase, ASMT) to generate melatonin. Then, melatonin can be cleaved by indoleamine 2,3-dioxygenase 1 (IDO1) in a non-specific reaction and transformed into N-acetyl-N-formyl-5-methoxykynurenamine (AFMK). Additional enzymatic or oxidative pathways other than IDO1 are responsible for the generation of AFMK from the common precursor. Specifically, AFMK can arise from reaction of melatonin with hydroxyl radical and the subsequent interaction of the new-born melatonyl species with superoxide anion [2]. Moreover,

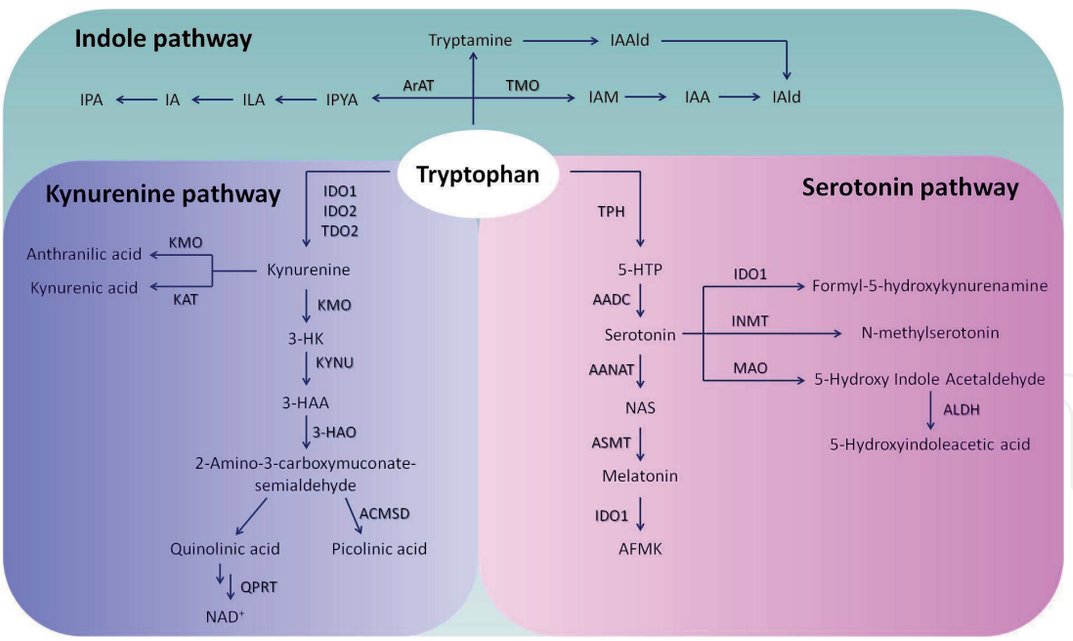

Figure 1.
Tryptophan metabolism along the kynurenine, serotonin and indole pathways. The majority of tryptophan is converted into kynurenine, whereas only about 1% is metabolized into serotonin. A small amount of tryptophan is used by the gut microbiota to produce indole derivatives. AADC, aromatic amino acid decarboxylase; AANAT, arylalkylamine N-acetyltransferase; ALDH, aldehyde dehydrogenase; AFMK, acetyl-N-formyl-5-methoxykynurenamine; ArAT, acromatic amino acid aminotransferase; ASMT, N-acetylserotonin O-methyltransferase; 3-HAA, 3-hydroxyanthranilic acid; 3-HK, 3-hydroxykynurenine; 5-HTTP, 5-hydroxytryptophan; IA, indoleacrylic acid; IAA, indoleacetic acid; Iald, indole-3-aldehyde; IAAld, indole-3-acetaldehyde; IAM, indole-3-acetamide; IDO1, indoleamine 2–3-dioxygenase 1; ILA, indolelactic acid; INMT, indolethylamine-N-methyltransferase; IPA, indole-3-propionic acid; IPYA, Indole-3-pyruvate; KAT, kynurenine aminotransferase; KMO, kynurenine-3-monooxygenase; KYNU, kynureninase; MAO, monoamine oxidase; NAD+, nicotinamide adenine dinucleotide; NAS, Nacetylserotonin; TDO2, tryptophan 2,3-dioxygenase; TMO, tryptophan 2-monooxygenase; TPH, tryptophan hydroxylase.

melatonin can yield to AFMK either by directly scavenging hydrogen peroxide or serving as a substrate of neutrophils' myeloperoxidase [3, 4].

Serotonin is a double life metabolite acting as neurotransmitter and peripheral hormone [5]. As a matter of fact, about 5% of the total serotonin is synthesized by serotoninergic neurons and operates within the CNS, while the majority of human body's serotonin is produced by enterochromaffin cells (EC) located in the gastrointestinal tract (GI). A significant amount of gut serotonin is released in the bloodstream where it is rapidly absorbed and stored by platelets and, to a lesser extent, by immune cells [6]. Although both TPH and AADC are necessary for the production of serotonin, TPH is the rate-limiting enzyme, as demonstrated by its weak affinity for any other amino acid and by the reduced serotonin levels upon pharmacologic or genetic ablation of the enzyme [7]. TPH exists into two isoforms that mainly differ in terms of cellular localization, i.e. TPH1- expressed by EC cells - and TPH2, found in central neurones [8].

The balance between the biosynthesis and the metabolism affects the bioavailability of serotonin. Indeed, besides the main branch of methoxyindoles pathway that yields to AFMK as end product, three additional catabolic reactions are responsible for the biotransformation of serotonin into metabolites mainly excreted with the urine [9]. In particular, through the catalysis mediated by IDO1, monoamine oxidases (MAO) or indolethylamine-N-methyltransferase (INMT), serotonin is converted into formyl-5-hydroxykynurenamine, 5-hydroxyindoleacetic acid and N-methylserotonin, respectively. Although rapidly metabolized, serotonin can be taken up by serotonin reuptake transporters (SERT) expressed in the CNS, platelets, GI and peripheral vasculature; once in the cytosol, the metabolite is immediately packaged into vesicles by vesicular monoamine transporter (VMAT) that prevents further degradation by mitochondrial MAO. Calcium-dependent exocytosis, such as that triggered during an inflammatory response or vascular injury, is responsible for the release of serotonin from the storing vesicles.

As an archetype of chronobiological hormone, melatonin is mainly produced by the pineal gland in response to circadian rhythm, i.e. the concentration of melatonin rises in the darkness and decreases in the daytime [10]. Along with melatonin, pineal NAS levels are higher at night than during the day, as opposed to pineal serotonin whose concentration peaks with the lightering. The rhythmic rotation between daily and nightly profiles of pineal indoles is controlled by the circadian clock located in the suprachiasmatic nuclei of the hypothalamus [11]. In homeostatic conditions during the darkness, the norepinephrine-mediated activation of adrenergic receptors results in an increase of cytosolic calcium and cAMP, which activate the protein kinase A (PKA) with the consequent phosphorylation of the cAMP response element binding protein (CREB). Phosphorylated CREB migrates into the nucleus and induces the transcription of *Aanat* gene, thus fuelling the synthesis of NAS and melatonin. Moreover, PKA phosphorylates AANAT, protecting the enzyme from the proteasomal degradation.

This central clock not only ensures the adaptation of living organisms to the cyclic and seasonal environmental changes, but also allows the efficient handling of immune responses [12]. If on one hand, pineal melatonin can regulate the immune responses and rhythmically vary the immune system's components, on the other hand signals sent by immune cells can be perceived by pineal gland as feedback for the regulation of melatonin production [13, 14]. This back and forward switch in melatonin biosynthesis, namely immune-pineal axis, is considered the cornerstone of the neuroendocrine-immune network that allows the communication between immune, nervous and endocrine systems [15].

Pathogen-associated molecular patterns (PAMPs, such as bacterial lipopolysaccharide and viral double stranded RNA) as well as danger-associated molecular

patterns (DAMPs; including tissue debris and amyloid β peptide) trigger the shift between pineal and extra-pineal melatonin synthesis. By interacting with their cognate receptors, PAMPs and DAMPs promote the nuclear translocation of the transcription factor nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), which binds to the promoter of target genes coding for pro-inflammatory mediators as well as of anti-inflammatory factors involved in the later recovery phase. *Aanat* is one of the genes whose transcription is regulated by NF-κB either positively or negatively, depending on cellular microenvironment. Specific NF-κB dimers allow the activation of the immune system in synch with the relocation of melatonin production from the pineal gland to the activated immune cells and vice versa. In the pinealocytes, the homodimer p50/p50 inhibits *Aanat* transcription, while in macrophages the heterodimer RelA/c-Rel induces Aanat gene expression and thus fuels the local melatonin production [16]. Whilst macrophages-derived melatonin promotes their migration to damaged tissue and enhances their phagocytic capacity, it is the indole metabolite itself that directly ends the process through the inhibition of NF-κB activity [17, 18]. The blockage of NF-κB re-establishes the homeostatic conditions and shifts the synthesis of melatonin from immune cells to pinealocytes. Moreover, during the recovery phase, melatonin is assisted by the adrenal cortex hormones (namely corticosteroids) in reducing the nuclear content of pineal p50/p50 homodimer, leading to an increase of *Aanat* transcription and thus more feed for melatonin synthesis [19].

3. Serotonin and its metabolites in immune cells

In the guise of both neurotransmitter and hormone, serotonin contributes to the regulation of several physiologic processes, such as central and peripheral functions, including sleep, mood and appetite as well as heart functionality, intestinal mobility and vascular tone among the most relevant. Accumulating evidences suggest that non-neuronal serotonin is also endowed with immunoregulatory properties. As a matter of fact, several immune cells possess the machinery to synthesize, store, respond to and take serotonin up from the microenvironment [20]. Changes in serotonin levels have been reported in patients with chronic inflammation and autoimmune dysfunctions, including multiple sclerosis (MS), rheumatoid arthritis and inflammatory bowel disease [21]. Drugs that modulate serotonin signalling, such as the selective serotonin reuptake inhibitors (SSRIs), appear to affect peripheral immunity. By blocking the reuptake of serotonin, SSRIs have found a place as anti-depressant in the clinical practice and only recently their ability to influence T lymphocytes proliferation, apoptosis and cytokines' production has emerged [22].

3.1 Serotonin receptors expression in cells of the innate immune system

In mammals, seven families of serotonin receptor (5-HTRs) have been identified (**Table 1**) [23]. All 5-HTRs belong to the G-protein coupled receptor (GPCR) superfamily, with the exception of 5-HT_3R, which is a ligand-gated ion channel permeable to calcium, sodium and potassium, whose activation leads to a rapid depolarization of the plasma membrane. The members of the GPCR-like serotonin receptors activate an intracellular signaling cascade that involves Adenylyl cyclase (AC) and phospholipase C (PLC) as effector systems [23]. 5-HT_1R and 5-HT_5R are negatively coupled with AC and thus their activation results in a reduced cAMP. Conversely, 5-HTRs 4, 6 and 7 are positively associated with AC with the consequent raise of cAMP levels. Upon serotonin binding, 5-HT_2R signals through

Target	Subtype	Ligand	Type of immune cells expressed on
5-HT_1R	A	Serotonin	Mast cells, Monocytes, Macrophages, NK cells, T and B cells
	B		Immature DCs, T cells
	E		Immature DCs, Monocytes
5-HT_2R	A		Monocytes, Macrophages, Eosinophils, T and B cells
	B		Monocytes, Macrophages, immature DCs
	C		Macrophages
5-HT_3R			Monocytes, Macrophages, DCs, T and B cells
5-HT_4R			Monocytes, Macrophages, mature DCs
5-HT_5R			Unknown
5-HT_6R			Unknown
5-HT_7R			Monocytes, Macrophages, mature DCs, T and B cells
MT1		Melatonin	Monocytes, Macrophages, Nk cells, T cells
MT2			
MT3		Melatonin, NAS	Neutrophils
RORα/RORβ		Melatonin	T cells
Free radicals		Melatonin, AFMK	Macrophages, Neutrophil
COX-2			
iNOS			
TrKB		NAS	Neutrophils, Macrophages, DCs
IDO1			DCs

Table 1.
Molecular targets of serotonin and metabolites thereof, and their expression on immune cells.

PLC-mediated release of inositol triphosphate and diacylglycerol, which increases intracellular calcium levels.

By virtue of the ubiquitous expression of the 5-HTRs and the different intracellular pathways activated, the biology of serotonin appears to be somewhat intricate and this accounts for its pleiotropic functions. 5-HTRs have been identified on murine and human innate immune cells, including neutrophils, monocytes, macrophages, dendritic cells (DCs), mast cells and natural killer cells [24]. The modulatory effects of serotonin on DCs depends on their maturity state, as 5-HTRs are differentially located on mature (mainly expressing 5-HT_4R and 5-HT_7R) and immature (expressing 5-HT_1BR and 5-HT_2BR) cells [25]. The overall literature agrees on the role of serotonin in modulating migration, morphology and cytokines' production by human and murine DCs. Through the activation of 5-HT_4R and 5-HT_7R, indeed, the monoamine affects the differentiation capacity of human monocytes to DCs, and increases the release of the anti-inflammatory cytokine IL-10, meanwhile the engagement of 5-HT_7R results in increased expression of C-C chemokine receptor type 7 (CCR7), an important receptor involved in DCs migration [25, 26].

Although the expression of several 5-HTRs has been described in both human macrophages (5-HT_1AR, 5-HT_2AR, 5-HT_2BR, 5-HT_3R and 5-HT_7R) and monocytes (5-HT_2AR, 5-HT_3R, 5-HT_4R and 5-HT_7R) at transcriptional level, only specific

subtypes have been confirmed by molecular and functional studies. Indeed, through 5-HT_1AR, serotonin can induce the secretion of pro-inflammatory cytokines by peritoneal macrophages as well as boosts their phagocytic activity. Contrarily, by the engagement of 5-HT_2BR and 5HT_7R, serotonin promotes the polarization of human macrophages toward the anti-inflammatory phenotype [27]. The 5-HT_1AR is the prevailing receptor involved in inducing mast cells adhesion to fibronectin and thus in promoting their recruitment to the inflammatory bed. Unlike to other innate immune cells, mast cells express TPH1 enzyme, thus they are able to deplete Trp from the microenvironment and de novo synthesise serotonin [28]. Thanks to the presence of SERT, mast cells, macrophages and DCs are able to take serotonin up, store it in vesicles and subsequently release it in a calcium-dependent manner, in response to danger signals and inflammatory stimuli.

3.2 Serotonin receptors expression in cells of the adaptive immune system

Serotonin can shape the course of not only innate, but also adaptive immune responses, as demonstrated by its co-stimulatory role in the immunological synapse between DCs and T lymphocytes. By activating the 5-HT_2BR expressed on inflammatory monocyte-derived DCs (moDCs), serotonin alters their cytokines' profile and thus interferes with the differentiation of moDCs primed-$CD4^+$ T cells toward the inflammatory Th1 and Th17 lymphocytes [29]. Besides indirectly affecting the activation of T cells, serotonin can activate the 5-HTRs expressed on T and B cells and thus directly influence their phenotype and functions. Pioneering studies have proposed that the stimulation of 5-HT_1AR and 5-HT_3R promotes T cells proliferation, while the blockage of 5-HT_1BR with a specific antagonist decreases the cytokines' production by T lymphocytes and their cell-mediated immunity [30]. In naive-T cells, signalling through the 5-HT_7R induces the phosphorylation of the kinase ERK1/2 and activates the transcription factor NF-κB, converging in IL-2 synthesis and T-cell proliferation [31].

In addition to 5-HTRs, T cells express the high affinity transporter SERT, whose modulation with the selective inhibitors (SSRIs) suppresses T cells proliferation and induces apoptosis [32]. Moreover, T lymphocytes possess all the machinery to store, produce and degrade serotonin, suggesting an autocrine and paracrine role of the monoamine in modulating T cells proliferation and function [33]. As in platelets, the secretory ability of T cells can be affected by intracellular serotonin via a process known as serotonylation, which is the covalent linking of serotonin to glutamine residues of small intracellular GTPases involved in the exocytosis. This process occurs right after the monoamine transport into the cell, involves the enzyme transglutaminase for the creation of glutamyl-amide bonds, and results into a constitutive activation of the G-protein dependent signalling cascade [34].

The complexity of peripheral serotonin has emerged since 1999, i.e. since, when applied to intestinal preparations, opposite effects appeared depending on the conditions [35]. The variety of serotonin functions outside the CNS seems to apply also to the role of the monoamine in the regulation of immune responses. Although numerous investigations have attempted to fill the gaps in such direction, the knowledge in this field remains yet incomplete [20].

3.3 Distribution of receptors for serotonin-derived metabolites in immune cells

Likewise serotonin, melatonin exhibits a functional versatility as it regulates several biologic processes, ranging from sleep and circadian rhythm to oxidative stress, age and immune function [10, 36, 37]. Mechanistically, the physiologic effects of melatonin can be achieved through the binding of membrane and nuclear

receptor as well as via receptor-independent pathways; the latter involving the interaction with cytoplasmic and mitochondrial proteins [38]. Three different subtypes of membrane receptor have been identified, i.e. melatonin receptor type 1a (MT1), type 1b (MT2) and type 1c (MT3) (**Table 1**). With the exception of MT3 (which is quinone reductase-2 enzyme), the melatonin membrane receptors belong to the GPCRs superfamily and are distributed in the CNS and, to a less extent, in cardiovascular system, colon, skin and immune cells. MT1 and MT2 are negatively coupled with AC and thus their activation results in a reduced production of cAMP and the consequent failure of PKA activation. The nuclear receptor signalling of melatonin is mediated via the transcription factor retinoid Z receptors and retinoid orphan receptors (RZR/ROR). RZR/ROR is an orphan member of the nuclear receptor superfamily, which encompasses the product of three genes: RORα, RORβ and RORγ. In immunocompetent cells, specific nuclear melatonin-binding sites have been reported, including RORα and RORβ in human lymphocytes, and RORα in both thymus and spleen of mice [39, 40].

Whilst the MT1/MT2 receptors are mainly responsible for the neuronal functions of melatonin, the activation of both nuclear and membrane receptors appears to be primarily involved in the imunomodulatory and anti-tumor effects of the hormone [41]. The exogenous administration of melatonin stimulates monocyte as well as macrophage production in both bone marrow and spleen of mice, by activating MT receptor and increasing the sensitivity of progenitors to stimulants such as IL-4 and GM-CSF [42]. Human monocytes express both membrane and nuclear melatonin receptor, whose activation stimulates the production of the pro-inflammatory cytokines IL-1β, IL-6 and TNF-α, while decreases IL-10 [42]. By engaging MT1/MT2 receptor, melatonin activates a mitogenic signal that counteracts the spontaneous apoptosis of circulating monocytes. The activity of melatonin with regard to macrophages translates into the inhibition of inducible nitric oxide synthase (iNOS) expression and blockage of COX-2 activity, with the consequent decrease of inflammatory mediators [43].

T lymphocytes express both membrane and nuclear receptors for melatonin, as well as all the machinery required for the synthesis and secretion of the hormone. Thus, is not surprising that melatonin impacts T cell biology, from the differentiation to the functional activation, as demonstrated by the blunted proliferation of splenic lymphocytes in response to mitogenic signal when both the nuclear and the MT1/MT2 receptors are inhibited [44]. Melatonin, by directly interacting with RORα and promoting its degradation, regulates the expression of IL-2 [45]. Meanwhile, through the activation of MT1-dependent signalling pathway restrains the constitutive activity of RORα, thus further stimulating the IL-2 production [46]. Such a redundancy of the membrane and nuclear receptor is at the service of T cell differentiation as well. Although RORγt is the well-known lineage specific transcription factor for Th17 cells, it synergizes with RORα to enhance Th17 differentiation. On one side, melatonin induces the degradation of nuclear RORα, while on the other, by binding MT1, it activates an intracellular signalling cascade that ends with the repression of the Rora and Rorc gene expression [47]. Depending on the immunological context, melatonin differentially controls T cells effector functions, i.e. under immunosuppressive condition, melatonin stimulates the immune system, while it inhibits exacerbated immune responses. For instance, melatonin increases the number of regulatory T cells in both human and murine model of inflammatory/autoimmune diseases, such as systemic lupus erythematosus or MS; meanwhile it reduces the frequency of IFN-γ and IL-17 producing T lymphocytes [48–50].

For many years, NAS was thought to be merely an intermediate product in melatonin biosynthesis. However, a series of non-overlapping activities of NAS as well

as different brain distribution of the metabolite - when compared to melatonin and serotonin - has given a precise biologic identity to this indole derivative. NAS, but not serotonin or melatonin, is an agonist of the tyrosine kinase B (TrkB) receptor of the brain-derived neurotrophic factor (BDNF), whose activation contributes to the antidepressant, cognition-enhancing and anti-apoptotic effect of NAS (**Table 1**) [51, 52]. TrkB receptors are transmembrane proteins with an extracellular BDNF-binding domain and an intracellular tyrosine kinase domain that, once activated, undergoes autophosphorylation and subsequent coupling to intracellular signalling pathways. Through the activation of TrkB, NAS offers neuroprotection in experimental models of neurological injury and MS, which at least in part occurs by the mitigation of apoptosis and autophagic dysfunction [53, 54]. Additionally, NAS-mediated neuro-immune modulatory effects can arise from the allosteric activation of the enzyme IDO1 [55]. The direct binding of NAS to a previously unknown allosteric site on IDO1 enhances the production of the immunoregulatory metabolite L-Kynurenine, which, in turn, by re-educating the immune system, ameliorates the disease symptoms in a mouse model of MS. Moreover, NAS displays a high affinity for the melatonin MT3 receptor, which is a quinone reductase-2 enzyme and through which NAS exerts additional anti-oxidant and anti-depressant effects [56].

The metabolic product of melatonin, i.e. AFMK, is considered a potent tissue protector as it efficiently neutralizes reactive molecules and reduces lipid peroxidation and DNA damage [57]. AFMK acts as a reducing agent able to donate two electrons, in contrast with other physiological antioxidants that donate a single electron to neutralize free radicals. Increased formation of AFMK is associated with inflammatory conditions, as the concentration of this kynuramine increases in the cerebrospinal fluid of patients with meningitis and the human epidermal keratinocytes exposed to UVB radiation [58, 59]. The raised levels of AFMK are consistent with its role as tissue protector and immune modulator. Indeed, AFMK is capable to attenuate the severity of acute pancreatic inflammation, by reducing pancreatic tissue damage and TNF-α serum concentration, and by increasing the activity of anti-oxidant enzymes [60]. Likewise melatonin, AFMK prevents COX-2 and iNOS activation induced by LPS in macrophages, and the production of TNF-α and IL-8 in activated neutrophils, thus exerts anti-inflammatory and immunomodulatory effects [61, 62].

No longer considered as merely neuronal mediators, the methoxyindoles metabolites are now emerging as key modulators of immune responses. Given the intrinsic complexity of the biological systems, the evolution has conserved and specialized the functions of each serotonin derivatives, making them able to work in the same direction or independently.

4. Role of serotonin in the gut-brain axis

Is "*Butterflies in the stomach*", a metaphor or a real experience? From a physiological point of view, butterflies are authentic visceral sensations coming from an unexpected source, which is the *second* brain. Hidden in the walls of the digestive system, this intestinal brain is also known as enteric nervous system (ENS). It's generally thought that the ENS is the original nervous system that developed in the first vertebrates more than 500 million years ago and that has been conserved during the evolution to link digestion with mood and general organism's fitness [63]. The human ENS contains more than 200 million neurons, distributed in many thousands of small ganglia, the great majority of which are found in two plexuses, the myenteric and submucosal plexuses. Its main role is controlling all the digestive process from the swallowing to the nutrient absorption and elimination. It does not

seem capable of common thoughts, but it can communicate back and forth with our big brain, creating the otherwise known "gut-brain axis".

The bidirectional communication underlying the gut-brain axis includes the CNS, the autonomic nervous system, the ENS and the hypothalamic pituitary adrenal (HPA) axis. On one side, the autonomic nervous system drives both afferent and efferent signals arisen from the GI and the CNS, respectively. For its part, the HPA axis is activated by environmental stressors and promotes the cortisol release from the adrenal glands. Thus, by means of hormones and neurotransmitters, the brain controls the activity of intestinal effector cells, including epithelial cells, neurons, smooth muscle, enterochromaffin and immune cells. Recently, the gut microbiome has emerged as critical component of the gut-brain axis, handling not only the local intestinal functions, but also the distant CNS activities [64, 65].

Trp and its metabolite serotonin are the main nexus for the gut-brain-microbiome axis. This link builds on the principles that (*i*) the manipulation of the microbiota composition across lifespan influences the Trp availability, (*ii*) the gut microbes can directly or indirectly affect the Trp metabolism and serotonergic signaling at the level of CNS to modulate behaviour, and (*iii*) serotonin influences the development of both ENS and CNS. Indeed, the gut microbiota can indirectly influence Trp availability by balancing the amino acid metabolism along the serotonin or the kynurenine pathway. Germ-free animals (i.e., microbiota-deficient mice raised in a sterile environment) exhibit a reduced IDO1 activity (as measured by the kyn/Trp ratio) as well as an increased central serotonin turnover, which both normalize following microbiota colonization immediately post-weaning [66, 67]. The gut microbiome can also directly affect the local and circulating Trp availability for the host, as some bacterial strains harbour the enzymes that can either utilize Trp to produce indole-derivatives (such as indole 3-acetic acid and indole-3-carboxaldehyde) or synthesize the amino acid on their own [68, 69].

Although mainly formed before the mid-gestation in the foetus, the central neuronal circuitry is continuously subjected to genetic and environmental-mediated modifications until puberty. Serotonin is considered one of the signaling molecule that can regulate the development of CNS, among many other organs, as the lack of brain serotonin results into reduced body growth and improper central circuitry formation [70]. Changes in the serotonergic system occurs across the lifespan and a decreased uptake of the metabolite follows the aging [71]. Although, in the human brain, the levels of serotonin remain fairly stable, the overall serotonin receptors reduce by about 30–50% over the lifespan. Developmental changes of serotonergic system are mirrored by the variation of gut microbiota composition during the lifetime, as the infant gut microbiota tends to reach a stable adult-like configuration in the childhood - while completely changes in elderly subjects - and the early colonization of the GI tract is fundamental for the proper development of the central serotonergic system [66].

Likewise the CNS, the ENS is capable of neurogenesis in post-natal and adult life. Such an intrinsic plasticity is mainly related to the exposure of the ENS to microbial, diet and inflammatory challenges that populate the intestinal lumen. Moreover, the normal process of aging contributes to such variability by increasing the neuronal degeneration and cell death. In mice, the post-natal neurogenesis depends on the activation of 5-HT_4Rs, whose expression affects the abundance of ENS neurons, while the differentiation of enteric nerve cells is conditioned by the activation of 5-HT_2BR [72, 73]. In addition, stimulation of 5- HT_4R inhibits inflammatory reactions, protects enteric neurons from apoptosis and promotes the mobilisation of adult stem cells to form new neurons that may replace damaged or dead ones [72].

By involving neuronal, immune and endocrine mediators, the gut-brain-microbiome axis ensures the gut homeostasis as well as integrates the peripheral intestinal activities with emotions, cognitive functions and immune activation. As a matter of fact, people coping with inflammatory bowel disease or other intestinal issues (such as constipation, diarrhoea and abdominal pain) experience depression and anxiety, as a consequence of danger signals sent by an altered GI to the CNS. Noteworthy, these people receive benefit from antidepressants and mind–body therapies that help in smoothing negative signals coming from the GI tract. It is thus clear that not only the big brain is conscious of the ENS and of the gut microbiome, but the intestine as a whole can influence the perception of the world and alter human behaviour. Therefore, in coming years, physicians will need to expand their drugs pool to treat the "mental illness" of the big brain alongside of the second brain, in order to reach therapeutic profits in both behavioural and gastrointestinal diseases.

5. Balancing act between Trp degradation pathways as a pharmacological target for CNS diseases

Serotonin biosynthesis is strictly related to tryptophan availability; in fact, Trp is metabolized not only along the serotonin pathway (SP), but also the kynurenine pathway (KP). The importance of the maintenance of a homeostatic balance between KP and SP of Trp metabolism is underlined by the hypothesis that, in the CNS, some diseases, such as depression [74], Alzheimer's [75] and Parkinson's [76] are triggered by a shift of this equilibrium towards the KP; however, little is still known between the interplay between the two Trp metabolic pathways.

As mentioned above, the very existence of serotonin in different organs and tissues is strongly conditioned by the expression and enzymatic activity of molecules belonging to the tryptophan-metabolizing family, which includes IDO1, tryptophan 2,3-dioxygenase (TDO) and, according to much of the literature to date, IDO2 [77]. Nevertheless, the role of IDO2 as an enzyme capable of initiating the degradation of Trp along the KP probably derives from the erroneous interpretation of the structural analogy between IDO1 and IDO2; recently, this concept is being progressively revisited, and now the idea is emerging that IDO2 functions are linked to an activity other than the enzymatic one [78], which is almost negligible [79]. Thus, IDO1 and TDO represent the two key players determining the fate of Trp.

Trp depletion by TDO and IDO1 occurs via a mechanism that is well studied and has rather clear consequences: as a matter of fact, the catabolism of Trp to immunosuppressive and neuroactive kynurenines is a key metabolic pathway regulating immune responses and neurotoxicity.

The KP initiated by IDO1 or TDO has two main branches (**Figure 1**). Under physiological conditions, Kyn is preferentially converted into 3-hydroxykynurenine (3HK) and then 3-hydroxyanthranilic acid (3HAA), quinolinic acid (QA), and ultimately NAD^+. Alternatively, Kyn can be converted into kynurenic acid (KynA) by the kynurenine aminotransferase (KAT) enzymes [80].

KynA is generally considered to be neuroprotective; it competitively inhibits ionotropic glutamate receptors at high concentrations, and acts as a negative allosteric modulator at the α7-nicotinic receptor [81]. Moreover, KynA has also been shown to act as an agonist at an orphan G-protein-coupled receptor in neurons and astrocytes, leading to a suppression of several inflammatory pathways [82]. KynA also regulates the immune response through its agonistic effects on the aryl hydrocarbon receptor (AhR), a transcription factor involved in the metabolism of xenobiotics. Numerous compounds have been proposed as putative endogenous AhR ligands, many of which are generated through pathways involved in the metabolism

of tryptophan and indole. Among them, besides the already mentioned KynA, Kyn, xanthurenic acid, cinnabarinic acid can also be counted, as well as indole derivatives mainly produced in the gut by microbial metabolism, such as indole-3-acetic acid (IAA), indole-3-aldeyde (IAld) and tryptamine; the activation of AhR by metabolites produced downstream IDO1 or TDO may contribute to the modulation of the immune response both in periphery and CNS [83].

QA is an NMDA receptor agonist that can also inhibit the reuptake of glutamate by astrocytes leading to excitotoxicity, and exerts neurotoxic effects via several different mechanisms, including the generation of reactive oxygen species and the disruption of the blood brain barrier. In astrocytes, QA also potentiates the inflammatory response by inducing the production of proinflammatory mediators; moreover, QA may also activate microglia through NMDA receptors, a pathway that triggers neuronal cell death [81].

The two enzymes leading to the activation of the KP, TDO and IDO1 are localized in different cells and tissues and are used in different physiological processes. Hepatic TDO regulates blood homeostasis of Trp and neuronal TDO influences neurogenesis. TDO-deficient mice show no peculiar phenotypes, but display alterations in neurogenesis and anxiety-related behaviour. Moreover, TDO-deficiency or inhibition is neuroprotective in a murine model of MS, suggesting a role for TDO in the production of byproducts involved in the pathogenesis of neurological autoimmune diseases [84].

IDO1 is expressed in most tissues at low levels, including cells of the central nervous system (CNS) and cells of the immune system, but not in the liver. The activity of IDO1 is more closely related to the modulation of the immune response than to the regulation of dietary levels of Trp, and, as in the case of TDO, is decisive in the production of neuroactive metabolites. The effects of Trp metabolism by IDO1 (or TDO) in immunity are complex, and can be shortly explained by four mechanisms: (i) by means of the so-called "Trp starvation", that is, locally depleting Trp, which deprives tryptophan-dependent cells, such as proliferating T cells, of an essential amino acid; (ii) by the production of bioactive kynurenines; (iii) by regulating immune cell metabolism, for example, by feeding de novo NAD^+ biosynthesis; and (iv) by means of a recently discovered signalling activity, through which IDO1 becomes phosphorylated in its immunoreceptor tyrosine-based inhibitory motifs (ITIMs), so to mediate intracellular signalling events in a self-sustaining feedforward loop leading to durable immunoregulatory effects [85]. All these mechanisms are involved on the potential development of neuropsychiatric disorders [83], since, as previously said, many kynurenines are neuroactive, modulating neuroplasticity and/or exerting neurotoxic effects. Thus, it is not surprising that KP is considered implicated in psychiatric illness in the context of inflammation, such as mood disorders (i.e., major depressive disorder - MDD), psychosis, schizophrenia, as well as in neurodegenerative disorders such as Alzheimer's and Parkinson's disease (all reviewed in [81]) and autoimmune diseases, such as MS.

Many efforts in drug development for neurodegenerative and neuropsychiatric diseases have focused on altering the overall balance of neuroactive KP metabolites production through inhibition of enzymes involved in the formation of either QA or KA, or by means of synthetic molecules mimicking the effects of the endogenous compounds. The first clinical trials for MDD are currently ongoing, assessing the effects of an analogous of KynA, AV-101 (NCT02484456 and NCT03078322). AV-101 is a selective antagonist at the glycine-binding site of the NMDA receptor [86].

Since Trp, Kyn, and 3HK can be transported across the blood brain barrier (BBB), and other KP metabolites possibly share the same feature [81], another potential target is the carrier facilitating the passage through the BBB, that is the

large amino acid transporter (LAT1). It has been recently demonstrated that leucine treatment is a feasible method of competitively blocking LAT1 to prevent exogenous Kyn from entering into the brain [87]; on the basis of this observation, a phase 2 clinical trial to test the anti-depressant effects of leucine in individuals with MDD is currently ongoing (NCT03079297). Nevertheless, recent findings suggest that several established treatments for depression also alter KP metabolism, as in case of the electro-convulsive therapy, which significantly increases circulating levels of KynA and KynA/3HK in depressed patients [88]. Another example is represented by Ketamine, used as treatment for MDD in selected population of patients, that was shown to acutely decrease circulating kyn and the Kyn/Trp [89].

However, besides the overt involvement of KP in the pathogenesis of several CNS diseases, how the production of kynurenines and the shift of the Trp metabolism from SP towards KP affect the production of serotonin to date it is not clear, and it's also a subject of intense investigation whether the reduced production of serotonin, and the molecules thereof, is involved in the pathogenesis of certain diseases. In the specific case of MDD, the Trp metabolism is considered to explain the aetiology and pathogenesis of depression. More specifically, the aetiology of MDD seems to rely on the concomitant manifestation of an imbalance between the Kyn pathway induced by IDO1 and the serotonin pathway, the neurotoxic effects of Kyn pathway metabolites and the persistent activation of the KP due to exposure to repeated and consistent stress. A further example of the close connection of neuronal and immune systems, and of the importance of a balance between the two branches of Trp metabolism for the maintenance of a health status, can be represented by depression related to cancer. A simplistic and nowadays outdated vision of the immunological asset of cancer patients proposed that one of the major causes of depression in cancer patients could be related to their apparent immunosuppressive general status; today this perspective is gradually undermined by the awareness that in many types of cancer, chronic inflammation is a common feature. Trp breakdown, and the subsequent reduction of the production of serotonin and metabolites thereof, due to the enhanced activation of enzymes of the KP, seems to be related to the prevalence of depressive disorders in cancer patients, since many patients often show decreased plasma Trp levels and increased kyn concentrations [90]. In line with this hypothesis, and with the identification of IDO1 as an authentic immune checkpoint target for the immunopharmacological treatment of cancer [91], inhibition of IDO1 and/or TDO seems to be a promising strategy for the treatment of cancer-related fatigue and depression, with the aim of restoring the physiological balance between the KP and the SP [92].

Moreover, there is an additional factor to consider: not only the functional activity of IDO1/TDO can push the balance towards a decreased production of serotonin, but also the production of specific serotonin metabolites can, in turn, affect this balance, in favour of a sustained production of kynurenines. This is the case of NAS. As previously mentioned, a consistent part of the antidepressant and neurotrophic actions of NAS is due to its capability to activate the TrkB receptor; nevertheless, very recently, additional exciting mechanisms of action of NAS have been demonstrated, unveiling its role as an immunomodulatory molecule. In fact, NAS and melatonin have potent anti-oxidant, anti-inflammatory and neuroprotective properties in several animal models of neurological injury and disease, including MS [53]. When administered in vivo in a murine model of multiple sclerosis, experimental autoimmune encephalomyelitis (EAE), melatonin and NAS reduced the loss of mature oligodendrocytes, demyelination and axonal injury, significatively ameliorating the disease symptoms and progression. Both compounds also significantly attenuated iNOS induction and reactive oxygen species (ROS) generation in lipopolysaccharide-activated microglia in culture [53].

Moreover, NAS is capable of inducing DCs to acquire an immunosuppressive phenotype, which requires the presence and functional activity of the enzyme IDO1. Very interestingly, NAS has been demonstrated to function as a positive allosteric modulator of the enzyme IDO1 binding a recently identified allosteric site thus increasing the catalytic efficacy, but not the binding affinity of IDO1 toward its substrate Trp [55]. Moreover, the effects of NAS have been demonstrated not only in murine DCs, but also in peripheral blood mononuclear cells from a specific subset of MS patients, that is RR-MS patients, opening the possibility for the identification of an innovative and safe immunomodulating therapy for MS. NAS is the first-identified indole derivative of the SP acting as an endogenous IDO1 positive allosteric modulator (PAM). It is noteworthy that Trp shows an opposite behaviour, acting as an IDO1 negative allosteric modulator (NAM) when present at high concentrations [93]. Therefore, although kynurenines acting as endogenous PAMs for the enzymes of the serotonin pathway have not been identified yet, it is possible to speculate that products downstream of the KP and the SP might guarantee an appropriate equilibrium between the two main metabolic routes of Trp metabolism by allosteric mechanisms. This hypothesis may have important relevance for the design of innovative therapeutic strategies not only for the treatment of inflammatory/autoimmune CNS diseases, such as MS, but also for diseases involving an altered regulation of Trp metabolism. As an example, the therapeutic use of potent orthosteric inhibitors of IDO1 for the cancer immunotherapy could be hampered by the induction of a skewing toward the serotonin pathway and thus an excess production of immunoregulatory NAS. Regarding the possibility of rethinking the therapeutic approach for CNS inflammatory/autoimmune diseases, such as MS, that is immunosuppression, the development of PAMs selective for the IDO1 enzyme and therapeutically active in vivo may provide unprecedented opportunities to develop therapeutic agents with a considerably more limited number of undesirable effects than the conventional immunosuppressive therapy.

A cross-regulation of the two metabolic pathways of Trp degradation is performed not only by NAS, but also by its derivative melatonin. As previously said, melatonin can be used by the enzyme IDO1 as a substrate, giving rise to the production of AFMK, a metabolite endowed with anti-inflammatory properties. The effects of AFMK on expression and functional activity of Trp metabolizing enzymes are still unknown, if there are any. Melatonin not only can be metabolized by IDO1, but is capable of inducing the expression of the IDO1 gene in fibroblasts, melanocytes and in adrenal pheochromocytoma cells. In the latter model, silencing of IDO1 gene triggered the up-regulation of the expression of AANAT gene [94], and the overexpression of IDO1, in turns, led to the down-regulation of AANAT, meaning that, in specific cellular subsets, a strictly interconnection occurs between the two Trp degradation pathways. In the same study, melatonin induced an up-regulation of the IDO1 expression, through the JAK-STAT2 signaling pathway, and of its enzymatic activity.

Moreover, melatonin is a competitive inhibitor, whereas serotonin is an allosteric inhibitor of the enzyme TDO [95] and although the biological significance of this effects has not been unveiled, it can be speculated that, in the CNS, inhibition of TDO by two metabolites of the SP could contribute to a shift of the balance of Trp consumption through the SP, depending on microenvironmental factors.

Overall, a huge number of pharmacological interventions for CNS diseases targeting Trp metabolism have been developed or are currently under investigation (reviewed in [96]), ranging from the inhibition of specific enzymes along the KP to the modulation of AhR signalling or administration of KYNA and its derivatives [96]; nevertheless, the interconnections between the major pathways of Trp metabolism remain an open question.

6. Concluding remarks

Bidirectional interactions between the nervous system and immune system, known as the "neuroimmune system", regulate a wide range of physiological and pathological processes [1] and there is a huge literature linking general neuroinflammation to neuropsychiatric disorders, such as depression [97], schizophrenia [98], but also MS [99], Alzheimer's [100] and Parkinson's disease [101]. Specific neuroimmune factors, such as Trp derivatives, have been shown to modulate neuronal activity and complex behavioral processes and to create a functional bridge connecting the neuroendocrine and the immune systems. For this reason, serotonin and its derivatives, and the metabolic processes leading to the production of serotonin rather than kyn, are involved in the pathogenesis of various CNS diseases. Thus, it's easy to imagine how Trp metabolism, and mostly the pursuit of an optimal balance between the two Trp metabolic pathways, may be a promising therapeutic target for a manifold spectrum of CNS pathologies. However, there is need for an in-depth knowledge of the mechanisms leading to one or the other Trp metabolic fate, and it's also necessary to unveil their interconnections to define the appropriate intervention for each specific disease, and to have the ability to precisely act on the targeted metabolite or enzyme.

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Conflict of interest

The authors declare no conflict of interest.

List of abbreviations

3HAA	3-hydroxyanthranilic acid
3HK	3-hydroxykynurenine
5-HT	serotonin
5-HTRs	serotonin receptor
AADC	5-hydroxytryptophan decarboxylase
AANAT	arylalkylamine N-acetyltransferase
AC	Adenylyl cyclase
AFMK	N-acetyl-N-formyl-5-methoxykynurenamine
AhR	aryl hydrocarbon receptor
ASMT	acetylserotonin O-methyltransferase
BBB	blood brain barrier
BDNF	brain-derived neurotrophic factor
CCR7	C-C chemokine receptor type 7
CNS	central nervous system
CREB	cAMP response element binding protein
DAMPs	danger-associated molecular patterns
DCs	dendritic cells
EC	enterochromaffin cells

ENS	enteric nervous system
GI	gastro-intestinal tract
GPCR	G-protein coupled receptor
HIOM	hydroxyindole-O-methyl transferase
IAA	indole-3-acetic acid
IAld	indole-3-aldeyde
IDO	indoleamine 2, 3-dioxygenase
INMT	indolethylamine-N-methyltransferase
iNOS	nitric oxide synthase
ITIMs	immune-based inhibitory tyrosine motifs
KAT	kynurenine aminotransferase
KP	kynurenine pathway
KynA	kynurenic acid
LAT1	large amino acid transporter
MAO	monoamine oxidases
MDD	major depressive disorder
MT	melatonin receptor
NAM	negative allosteric modulator
NAS	N-acetylserotonin
NF-κB	nuclear factor κ-light-chain-enhancer of activated B cells
PAM	positive allosteric modulator
PAMPs	Pathogen-associated molecular patterns
PKA	protein kinase A
PLC	phospholipase C
QA	quinolinic acid
ROS	reactive oxygen species
RZR/ROR	retinoid Z receptors and retinoid orphan receptors
SERT	serotonin reuptake transporter
SP	serotonin pathway
SSRIs	selective serotonin reuptake inhibitors
TDO	tryptophan 2, 3-dioxygenase
TPH	tryptophan hydroxylase
TrkB	tyrosine kinase B
Trp	Tryptophan
VMAT	vesicular monoamine transporter

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References

[1] R. Dantzer, Neuroimmune Interactions: From the Brain to the Immune System and Vice Versa, Physiol Rev. 98 (2018) 477-504. https://doi.org/10.1152/physrev.00039.2016.

[2] R. Hardeland, R.J. Reiter, B. Poeggeler, D.X. Tan, The significance of the metabolism of the neurohormone melatonin: antioxidative protection and formation of bioactive substances, Neurosci Biobehav Rev. 17 (1993) 347-357. https://doi.org/10.1016/s0149-7634(05)80016-8.

[3] S.O. Silva, V.F. Ximenes, L.H. Catalani, A. Campa, Myeloperoxidase-catalyzed oxidation of melatonin by activated neutrophils, Biochem Biophys Res Commun. 279 (2000) 657-662. https://doi.org/10.1006/bbrc.2000.3993.

[4] D.X. Tan, L.C. Manchester, R.J. Reiter, B.F. Plummer, J. Limson, S.T. Weintraub, W. Qi, Melatonin directly scavenges hydrogen peroxide: a potentially new metabolic pathway of melatonin biotransformation, Free Radic Biol Med. 29 (2000) 1177-1185. https://doi.org/10.1016/s0891-5849(00)00435-4.

[5] G. Mondanelli, C. Volpi, The double life of serotonin metabolites: in the mood for joining neuronal and immune systems, Curr Opin Immunol. 70 (2020) 1-6. https://doi.org/10.1016/j.coi.2020.11.008.

[6] M. Berger, J.A. Gray, B.L. Roth, The expanded biology of serotonin, Annu Rev Med. 60 (2009) 355-366. https://doi.org/10.1146/annurev.med.60.042307.110802.

[7] L.F. Mohammad-Zadeh, L. Moses, S.M. Gwaltney-Brant, Serotonin: a review, J Vet Pharmacol Ther. 31 (2008) 187-199. https://doi.org/10.1111/j.1365-2885.2008.00944.x.

[8] D.J. Walther, M. Bader, A unique central tryptophan hydroxylase isoform, Biochem Pharmacol. 66 (2003) 1673-1680. https://doi.org/10.1016/s0006-2952(03)00556-2.

[9] C. Jonnakuty, C. Gragnoli, What do we know about serotonin?, J Cell Physiol. 217 (2008) 301-306. https://doi.org/10.1002/jcp.21533.

[10] J. Vriend, R.J. Reiter, Melatonin feedback on clock genes: a theory involving the proteasome, J Pineal Res. 58 (2015) 1-11. https://doi.org/10.1111/jpi.12189.

[11] D.C. Klein, S.L. Coon, P.H. Roseboom, J.L. Weller, M. Bernard, J.A. Gastel, M. Zatz, P.M. Iuvone, I.R. Rodriguez, V. Bégay, J. Falcón, G.M. Cahill, V.M. Cassone, R. Baler, The melatonin rhythm-generating enzyme: molecular regulation of serotonin N-acetyltransferase in the pineal gland, Recent Prog Horm Res. 52 (1997) 307-357; discussion 357-358.

[12] C. Scheiermann, Y. Kunisaki, P.S. Frenette, Circadian control of the immune system, Nat Rev Immunol. 13 (2013) 190-198. https://doi.org/10.1038/nri3386.

[13] A. Carrillo-Vico, P.J. Lardone, N. Alvarez-Sánchez, A. Rodríguez-Rodríguez, J.M. Guerrero, Melatonin: buffering the immune system, Int J Mol Sci. 14 (2013) 8638-8683. https://doi.org/10.3390/ijms14048638.

[14] R.J. Nelson, D.L. Drazen, Melatonin mediates seasonal changes in immune function, Ann N Y Acad Sci. 917 (2000) 404-415. https://doi.org/10.1111/j.1749-6632.2000.tb05405.x.

[15] R.P. Markus, Z.S. Ferreira, P.A.C.M. Fernandes, E. Cecon, The

immune-pineal axis: a shuttle between endocrine and paracrine melatonin sources, Neuroimmunomodulation. 14 (2007) 126-133. https://doi.org/10.1159/000110635.

[16] R.P. Markus, E. Cecon, M.A. Pires-Lapa, Immune-pineal axis: nuclear factor κB (NF-kB) mediates the shift in the melatonin source from pinealocytes to immune competent cells, Int J Mol Sci. 14 (2013) 10979-10997. https://doi.org/10.3390/ijms140610979.

[17] M. Marçola, S. da Silveira Cruz-Machado, P.A.C.M. Fernandes, A.W.A. Monteiro, R.P. Markus, E.K. Tamura, Endothelial cell adhesiveness is a function of environmental lighting and melatonin level, J Pineal Res. 54 (2013) 162-169. https://doi.org/10.1111/j.1600-079X.2012.01025.x.

[18] J.L. Mauriz, P.S. Collado, C. Veneroso, R.J. Reiter, J. González-Gallego, A review of the molecular aspects of melatonin's anti-inflammatory actions: recent insights and new perspectives, J Pineal Res. 54 (2013) 1-14. https://doi.org/10.1111/j.1600-079X.2012.01014.x.

[19] Z.S. Ferreira, P.A.C.M. Fernandes, D. Duma, J. Assreuy, M.C.W. Avellar, R.P. Markus, Corticosterone modulates noradrenaline-induced melatonin synthesis through inhibition of nuclear factor kappa B, J Pineal Res. 38 (2005) 182-188. https://doi.org/10.1111/j.1600-079X.2004.00191.x.

[20] N. Herr, C. Bode, D. Duerschmied, The Effects of Serotonin in Immune Cells, Front Cardiovasc Med. 4 (2017) 48. https://doi.org/10.3389/fcvm.2017.00048.

[21] M. Wan, L. Ding, D. Wang, J. Han, P. Gao, Serotonin: A Potent Immune Cell Modulator in Autoimmune Diseases, Front Immunol. 11 (2020) 186. https://doi.org/10.3389/fimmu.2020.00186.

[22] V. Gobin, K. Van Steendam, D. Denys, D. Deforce, Selective serotonin reuptake inhibitors as a novel class of immunosuppressants, Int Immunopharmacol. 20 (2014) 148-156. https://doi.org/10.1016/j.intimp.2014.02.030.

[23] M. Filip, M. Bader, Overview on 5-HT receptors and their role in physiology and pathology of the central nervous system, Pharmacol Rep. 61 (2009) 761-777. https://doi.org/10.1016/s1734-1140(09)70132-x.

[24] N.L. Baganz, R.D. Blakely, A dialogue between the immune system and brain, spoken in the language of serotonin, ACS Chem Neurosci. 4 (2013) 48-63. https://doi.org/10.1021/cn300186b.

[25] M. Idzko, E. Panther, C. Stratz, T. Müller, H. Bayer, G. Zissel, T. Dürk, S. Sorichter, F. Di Virgilio, M. Geissler, B. Fiebich, Y. Herouy, P. Elsner, J. Norgauer, D. Ferrari, The serotoninergic receptors of human dendritic cells: identification and coupling to cytokine release, J Immunol. 172 (2004) 6011-6019. https://doi.org/10.4049/jimmunol.172.10.6011.

[26] K. Holst, D. Guseva, S. Schindler, M. Sixt, A. Braun, H. Chopra, O. Pabst, E. Ponimaskin, The serotonin receptor 5-HT$_7$R regulates the morphology and migratory properties of dendritic cells, J Cell Sci. 128 (2015) 2866-2880. https://doi.org/10.1242/jcs.167999.

[27] M. de las Casas-Engel, A. Domínguez-Soto, E. Sierra-Filardi, R. Bragado, C. Nieto, A. Puig-Kroger, R. Samaniego, M. Loza, M.T. Corcuera, F. Gómez-Aguado, M. Bustos, P. Sánchez-Mateos, A.L. Corbí, Serotonin skews human macrophage polarization through HTR2B and HTR7, J Immunol. 190 (2013) 2301-2310. https://doi.org/10.4049/jimmunol.1201133.

[28] N.M. Kushnir-Sukhov, J.M. Brown, Y. Wu, A. Kirshenbaum, D.D. Metcalfe, Human mast cells are capable of serotonin synthesis and release, J Allergy Clin Immunol. 119 (2007) 498-499. https://doi.org/10.1016/j.jaci.2006.09.003.

[29] A. Szabo, P. Gogolak, G. Koncz, Z. Foldvari, K. Pazmandi, N. Miltner, S. Poliska, A. Bacsi, S. Djurovic, E. Rajnavolgyi, Immunomodulatory capacity of the serotonin receptor 5-HT2B in a subset of human dendritic cells, Sci Rep. 8 (2018) 1765. https://doi.org/10.1038/s41598-018-20173-y.

[30] J. Yin, R.H. Albert, A.P. Tretiakova, B.A. Jameson, 5-HT(1B) receptors play a prominent role in the proliferation of T-lymphocytes, J Neuroimmunol. 181 (2006) 68-81. https://doi.org/10.1016/j.jneuroim.2006.08.004.

[31] M. León-Ponte, G.P. Ahern, P.J. O'Connell, Serotonin provides an accessory signal to enhance T-cell activation by signaling through the 5-HT7 receptor, Blood. 109 (2007) 3139-3146. https://doi.org/10.1182/blood-2006-10-052787.

[32] F. Fazzino, C. Montes, M. Urbina, I. Carreira, L. Lima, Serotonin transporter is differentially localized in subpopulations of lymphocytes of major depression patients. Effect of fluoxetine on proliferation, J Neuroimmunol. 196 (2008) 173-180. https://doi.org/10.1016/j.jneuroim.2008.03.012.

[33] Y. Chen, M. Leon-Ponte, S.C. Pingle, P.J. O'Connell, G.P. Ahern, T lymphocytes possess the machinery for 5-HT synthesis, storage, degradation and release, Acta Physiol (Oxf). 213 (2015) 860-867. https://doi.org/10.1111/apha.12470.

[34] D.J. Walther, J.-U. Peter, S. Winter, M. Höltje, N. Paulmann, M. Grohmann, J. Vowinckel, V. Alamo-Bethencourt, C.S. Wilhelm, G. Ahnert-Hilger, M. Bader, Serotonylation of small GTPases is a signal transduction pathway that triggers platelet alpha-granule release, Cell. 115 (2003) 851-862. https://doi.org/10.1016/s0092-8674(03)01014-6.

[35] M.D. Gershon, Review article: roles played by 5-hydroxytryptamine in the physiology of the bowel, Aliment Pharmacol Ther. 13 Suppl 2 (1999) 15-30.

[36] E. Miller, A. Morel, L. Saso, J. Saluk, Melatonin Redox Activity. Its Potential Clinical Application in Neurodegenerative Disorders, Curr Top Med Chem. (2014).

[37] L.H. Opie, S. Lecour, Melatonin has multiorgan effects, Eur Heart J Cardiovasc Pharmacother. 2 (2016) 258-265. https://doi.org/10.1093/ehjcvp/pvv037.

[38] R.J. Reiter, D.X. Tan, L.C. Manchester, M. Pilar Terron, L.J. Flores, S. Koppisepi, Medical implications of melatonin: receptor-mediated and receptor-independent actions, Adv Med Sci. 52 (2007) 11-28.

[39] A. Carrillo-Vico, A. García-Pergañeda, L. Naji, J.R. Calvo, M.P. Romero, J.M. Guerrero, Expression of membrane and nuclear melatonin receptor mRNA and protein in the mouse immune system, Cell Mol Life Sci. 60 (2003) 2272-2278. https://doi.org/10.1007/s00018-003-3207-4.

[40] S. García-Mauriño, D. Pozo, J.R. Calvo, J.M. Guerrero, Correlation between nuclear melatonin receptor expression and enhanced cytokine production in human lymphocytic and monocytic cell lines, J Pineal Res. 29 (2000) 129-137. https://doi.org/10.1034/j.1600-079x.2000.290301.x.

[41] J.A. García, H. Volt, C. Venegas, C. Doerrier, G. Escames, L.C. López, D. Acuña-Castroviejo, Disruption of the NF-κB/NLRP3 connection by

melatonin requires retinoid-related orphan receptor-α and blocks the septic response in mice, FASEB J. 29 (2015) 3863-3875. https://doi.org/10.1096/fj.15-273656.

[42] J.R. Calvo, C. González-Yanes, M.D. Maldonado, The role of melatonin in the cells of the innate immunity: a review, J Pineal Res. 55 (2013) 103-120. https://doi.org/10.1111/jpi.12075.

[43] W.-G. Deng, S.-T. Tang, H.-P. Tseng, K.K. Wu, Melatonin suppresses macrophage cyclooxygenase-2 and inducible nitric oxide synthase expression by inhibiting p52 acetylation and binding, Blood. 108 (2006) 518-524. https://doi.org/10.1182/blood-2005-09-3691.

[44] D.L. Drazen, D. Bilu, S.D. Bilbo, R.J. Nelson, Melatonin enhancement of splenocyte proliferation is attenuated by luzindole, a melatonin receptor antagonist, Am J Physiol Regul Integr Comp Physiol. 280 (2001) R1476–R1482. https://doi.org/10.1152/ajpregu.2001.280.5.R1476.

[45] P.J. Lardone, J.M. Guerrero, J.M. Fernández-Santos, A. Rubio, I. Martín-Lacave, A. Carrillo-Vico, Melatonin synthesized by T lymphocytes as a ligand of the retinoic acid-related orphan receptor, J Pineal Res. 51 (2011) 454-462. https://doi.org/10.1111/j.1600-079X.2011.00909.x.

[46] P.J. Lardone, A. Carrillo-Vico, P. Molinero, A. Rubio, J.M. Guerrero, A novel interplay between membrane and nuclear melatonin receptors in human lymphocytes: significance in IL-2 production, Cell Mol Life Sci. 66 (2009) 516-525. https://doi.org/10.1007/s00018-008-8601-5.

[47] X. Yu, D. Rollins, K.A. Ruhn, J.J. Stubblefield, C.B. Green, M. Kashiwada, P.B. Rothman, J.S. Takahashi, L.V. Hooper, TH17 cell differentiation is regulated by the circadian clock, Science. 342 (2013) 727-730. https://doi.org/10.1126/science.1243884.

[48] N. Álvarez-Sánchez, I. Cruz-Chamorro, A. López-González, J.C. Utrilla, J.M. Fernández-Santos, A. Martínez-López, P.J. Lardone, J.M. Guerrero, A. Carrillo-Vico, Melatonin controls experimental autoimmune encephalomyelitis by altering the T effector/regulatory balance, Brain Behav Immun. 50 (2015) 101-114. https://doi.org/10.1016/j.bbi.2015.06.021.

[49] M.F. Farez, I.D. Mascanfroni, S.P. Méndez-Huergo, A. Yeste, G. Murugaiyan, L.P. Garo, M.E. Balbuena Aguirre, B. Patel, M.C. Ysrraelit, C. Zhu, V.K. Kuchroo, G.A. Rabinovich, F.J. Quintana, J. Correale, Melatonin Contributes to the Seasonality of Multiple Sclerosis Relapses, Cell. 162 (2015) 1338-1352. https://doi.org/10.1016/j.cell.2015.08.025.

[50] P. Medrano-Campillo, H. Sarmiento-Soto, N. Álvarez-Sánchez, A.I. Álvarez-Ríos, J.M. Guerrero, I. Rodríguez-Prieto, M.J. Castillo-Palma, P.J. Lardone, A. Carrillo-Vico, Evaluation of the immunomodulatory effect of melatonin on the T-cell response in peripheral blood from systemic lupus erythematosus patients, J Pineal Res. 58 (2015) 219-226. https://doi.org/10.1111/jpi.12208.

[51] G. Tosini, K. Ye, P.M. Iuvone, N-acetylserotonin: neuroprotection, neurogenesis, and the sleepy brain, Neuroscientist. 18 (2012) 645-653. https://doi.org/10.1177/1073858412446634.

[52] S. Bachurin, G. Oxenkrug, N. Lermontova, A. Afanasiev, B. Beznosko, G. Vankin, E. Shevtzova, T. Mukhina, T. Serkova, N-acetylserotonin, melatonin and their derivatives improve cognition and protect against beta-amyloid-induced neurotoxicity, Ann N Y Acad Sci. 890 (1999) 155-166. https://doi.org/10.1111/j.1749-6632.1999.tb07990.x.

[53] J. Wen, P.S. Ariyannur, R. Ribeiro, M. Tanaka, J.R. Moffett, B.F. Kirmani, A.M.A. Namboodiri, Y. Zhang, Efficacy of N-Acetylserotonin and Melatonin in the EAE Model of Multiple Sclerosis, J Neuroimmune Pharmacol. 11 (2016) 763-773. https://doi.org/10.1007/s11481-016-9702-9.

[54] J.-M. Yoo, B.D. Lee, D.-E. Sok, J.Y. Ma, M.R. Kim, Neuroprotective action of N-acetyl serotonin in oxidative stress-induced apoptosis through the activation of both TrkB/CREB/BDNF pathway and Akt/Nrf2/Antioxidant enzyme in neuronal cells, Redox Biol. 11 (2017) 592-599. https://doi.org/10.1016/j.redox.2016.12.034.

[55] G. Mondanelli, A. Coletti, F.A. Greco, M.T. Pallotta, C. Orabona, A. Iacono, M.L. Belladonna, E. Albini, E. Panfili, F. Fallarino, M. Gargaro, G. Manni, D. Matino, A. Carvalho, C. Cunha, P. Maciel, M. Di Filippo, L. Gaetani, R. Bianchi, C. Vacca, I.M. Iamandii, E. Proietti, F. Boscia, L. Annunziato, M. Peppelenbosch, P. Puccetti, P. Calabresi, A. Macchiarulo, L. Santambrogio, C. Volpi, U. Grohmann, Positive allosteric modulation of indoleamine 2,3-dioxygenase 1 restrains neuroinflammation, Proc. Natl. Acad. Sci. U.S.A. 117 (2020) 3848-3857. https://doi.org/10.1073/pnas.1918215117.

[56] J.A. Boutin, E. Marcheteau, P. Hennig, N. Moulharat, S. Berger, P. Delagrange, J.-P. Bouchet, G. Ferry, MT3/QR2 melatonin binding site does not use melatonin as a substrate or a co-substrate, J Pineal Res. 45 (2008) 524-531. https://doi.org/10.1111/j.1600-079X.2008.00631.x.

[57] A. Galano, D.X. Tan, R.J. Reiter, On the free radical scavenging activities of melatonin's metabolites, AFMK and AMK, J Pineal Res. 54 (2013) 245-257. https://doi.org/10.1111/jpi.12010.

[58] S. de O. Silva, V.F. Ximenes, J.A. Livramento, L.H. Catalani, A. Campa, High concentrations of the melatonin metabolite, N1-acetyl-N2-formyl-5-methoxykynuramine, in cerebrospinal fluid of patients with meningitis: a possible immunomodulatory mechanism, J Pineal Res. 39 (2005) 302-306. https://doi.org/10.1111/j.1600-079X.2005.00247.x.

[59] Z. Janjetovic, Z.P. Nahmias, S. Hanna, S.G. Jarrett, T.-K. Kim, R.J. Reiter, A.T. Slominski, Melatonin and its metabolites ameliorate ultraviolet B-induced damage in human epidermal keratinocytes, J Pineal Res. 57 (2014) 90-102. https://doi.org/10.1111/jpi.12146.

[60] J. Jaworek, J. Szklarczyk, J. Bonior, M. Kot, M. Goralska, P. Pierzchalski, R.J. Reiter, U. Czech, R. Tomaszewska, Melatonin metabolite, N(1)-acetyl-N(1)-formyl-5-methoxykynuramine (AFMK), attenuates acute pancreatitis in the rat: in vivo and in vitro studies, J Physiol Pharmacol. 67 (2016) 411-421.

[61] J.C. Mayo, R.M. Sainz, D.-X. Tan, R. Hardeland, J. Leon, C. Rodriguez, R.J. Reiter, Anti-inflammatory actions of melatonin and its metabolites, N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) and N1-acetyl-5-methoxykynuramine (AMK), in macrophages, J Neuroimmunol. 165 (2005) 139-149. https://doi.org/10.1016/j.jneuroim.2005.05.002.

[62] S.O. Silva, M.R. Rodrigues, V.F. Ximenes, A.E.B. Bueno-da-Silva, G.P. Amarante-Mendes, A. Campa, Neutrophils as a specific target for melatonin and kynuramines: effects on cytokine release, J Neuroimmunol. 156 (2004) 146-152. https://doi.org/10.1016/j.jneuroim.2004.07.015.

[63] M. Rao, M.D. Gershon, The bowel and beyond: the enteric nervous system in neurological disorders, Nat Rev Gastroenterol Hepatol. 13 (2016)

517-528. https://doi.org/10.1038/nrgastro.2016.107.

[64] S.M. Collins, M. Surette, P. Bercik, The interplay between the intestinal microbiota and the brain, Nat Rev Microbiol. 10 (2012) 735-742. https://doi.org/10.1038/nrmicro2876.

[65] S. Grenham, G. Clarke, J.F. Cryan, T.G. Dinan, Brain-gut-microbe communication in health and disease, Front Physiol. 2 (2011) 94. https://doi.org/10.3389/fphys.2011.00094.

[66] G. Clarke, S. Grenham, P. Scully, P. Fitzgerald, R.D. Moloney, F. Shanahan, T.G. Dinan, J.F. Cryan, The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner, Mol Psychiatry. 18 (2013) 666-673. https://doi.org/10.1038/mp.2012.77.

[67] R. Diaz Heijtz, S. Wang, F. Anuar, Y. Qian, B. Björkholm, A. Samuelsson, M.L. Hibberd, H. Forssberg, S. Pettersson, Normal gut microbiota modulates brain development and behavior, Proc Natl Acad Sci U S A. 108 (2011) 3047-3052. https://doi.org/10.1073/pnas.1010529108.

[68] J.-H. Lee, J. Lee, Indole as an intercellular signal in microbial communities, FEMS Microbiol Rev. 34 (2010) 426-444. https://doi.org/10.1111/j.1574-6976.2009.00204.x.

[69] S. Raboni, S. Bettati, A. Mozzarelli, Tryptophan synthase: a mine for enzymologists, Cell Mol Life Sci. 66 (2009) 2391-2403. https://doi.org/10.1007/s00018-009-0028-0.

[70] S. Migliarini, G. Pacini, B. Pelosi, G. Lunardi, M. Pasqualetti, Lack of brain serotonin affects postnatal development and serotonergic neuronal circuitry formation, Mol Psychiatry. 18 (2013) 1106-1118. https://doi.org/10.1038/mp.2012.128.

[71] L.C. Murrin, J.D. Sanders, D.B. Bylund, Comparison of the maturation of the adrenergic and serotonergic neurotransmitter systems in the brain: implications for differential drug effects on juveniles and adults, Biochem Pharmacol. 73 (2007) 1225-1236. https://doi.org/10.1016/j.bcp.2007.01.028.

[72] M.-T. Liu, Y.-H. Kuan, J. Wang, R. Hen, M.D. Gershon, 5-HT4 receptor-mediated neuroprotection and neurogenesis in the enteric nervous system of adult mice, J Neurosci. 29 (2009) 9683-9699. https://doi.org/10.1523/JNEUROSCI.1145-09.2009.

[73] E. Fiorica-Howells, L. Maroteaux, M.D. Gershon, Serotonin and the 5-HT(2B) receptor in the development of enteric neurons, J Neurosci. 20 (2000) 294-305.

[74] G. Oxenkrug, Serotonin-kynurenine hypothesis of depression: historical overview and recent developments, Curr Drug Targets. 14 (2013) 514-521. https://doi.org/10.2174/1389450111314050002.

[75] W. Wu, J.A. Nicolazzo, L. Wen, R. Chung, R. Stankovic, S.S. Bao, C.K. Lim, B.J. Brew, K.M. Cullen, G.J. Guillemin, Expression of tryptophan 2,3-dioxygenase and production of kynurenine pathway metabolites in triple transgenic mice and human Alzheimer's disease brain, PLoS One. 8 (2013) e59749. https://doi.org/10.1371/journal.pone.0059749.

[76] P. Perez-Pardo, Y. Grobben, N. Willemsen-Seegers, M. Hartog, M. Tutone, M. Muller, Y. Adolfs, R.J. Pasterkamp, D. Vu-Pham, A.M. van Doornmalen, F. van Cauter, J. de Wit, J.G. Sterrenburg, J.C.M. Uitdehaag, J. de Man, R.C. Buijsman, G.J.R. Zaman, A.D. Kraneveld, Pharmacological validation of TDO as a target for Parkinson's disease, FEBS J. (2021). https://doi.org/10.1111/febs.15721.

[77] A.A. Fatokun, N.H. Hunt, H.J. Ball, Indoleamine 2,3-dioxygenase 2 (IDO2) and the kynurenine pathway: characteristics and potential roles in health and disease, Amino Acids. 45 (2013) 1319-1329. https://doi.org/10.1007/s00726-013-1602-1.

[78] A. Fiore, P.J. Murray, Tryptophan and indole metabolism in immune regulation, Curr Opin Immunol. 70 (2021) 7-14. https://doi.org/10.1016/j.coi.2020.12.001.

[79] L.M.F. Merlo, L. Mandik-Nayak, IDO2: A Pathogenic Mediator of Inflammatory Autoimmunity, Clin Med Insights Pathol. 9 (2016) 21-28. https://doi.org/10.4137/CPath.S39930.

[80] I. Cervenka, L.Z. Agudelo, J.L. Ruas, Kynurenines: Tryptophan's metabolites in exercise, inflammation, and mental health, Science. 357 (2017). https://doi.org/10.1126/science.aaf9794.

[81] J. Savitz, The kynurenine pathway: a finger in every pie, Mol Psychiatry. 25 (2020) 131-147. https://doi.org/10.1038/s41380-019-0414-4.

[82] E. Wirthgen, A. Hoeflich, A. Rebl, J. Günther, Kynurenic Acid: The Janus-Faced Role of an Immunomodulatory Tryptophan Metabolite and Its Link to Pathological Conditions, Front Immunol. 8 (2017) 1957. https://doi.org/10.3389/fimmu.2017.01957.

[83] M. Platten, E.A.A. Nollen, U.F. Röhrig, F. Fallarino, C.A. Opitz, Tryptophan metabolism as a common therapeutic target in cancer, neurodegeneration and beyond, Nat Rev Drug Discov. 18 (2019) 379-401. https://doi.org/10.1038/s41573-019-0016-5.

[84] T.V. Lanz, S.K. Williams, A. Stojic, S. Iwantscheff, J.K. Sonner, C. Grabitz, S. Becker, L.-I. Böhler, S.R. Mohapatra, F. Sahm, G. Küblbeck, T. Nakamura, H. Funakoshi, C.A. Opitz, W. Wick, R. Diem, M. Platten, Tryptophan-2,3-Dioxygenase (TDO) deficiency is associated with subclinical neuroprotection in a mouse model of multiple sclerosis, Sci Rep. 7 (2017) 41271. https://doi.org/10.1038/srep41271.

[85] G. Mondanelli, R. Bianchi, M.T. Pallotta, C. Orabona, E. Albini, A. Iacono, M.L. Belladonna, C. Vacca, F. Fallarino, A. Macchiarulo, S. Ugel, V. Bronte, F. Gevi, L. Zolla, A. Verhaar, M. Peppelenbosch, E.M.C. Mazza, S. Bicciato, Y. Laouar, L. Santambrogio, P. Puccetti, C. Volpi, U. Grohmann, A Relay Pathway between Arginine and Tryptophan Metabolism Confers Immunosuppressive Properties on Dendritic Cells, Immunity. 46 (2017) 233-244. https://doi.org/10.1016/j.immuni.2017.01.005.

[86] S.T. Wilkinson, G. Sanacora, A new generation of antidepressants: an update on the pharmaceutical pipeline for novel and rapid-acting therapeutics in mood disorders based on glutamate/GABA neurotransmitter systems, Drug Discov Today. 24 (2019) 606-615. https://doi.org/10.1016/j.drudis.2018.11.007.

[87] A.K. Walker, E.E. Wing, W.A. Banks, R. Dantzer, Leucine competes with kynurenine for blood-to-brain transport and prevents lipopolysaccharide-induced depression-like behavior in mice, Mol Psychiatry. 24 (2019) 1523-1532. https://doi.org/10.1038/s41380-018-0076-7.

[88] S. Guloksuz, B. Arts, S. Walter, M. Drukker, L. Rodriguez, A.-M. Myint, M.J. Schwarz, R. Ponds, J. van Os, G. Kenis, B.P.F. Rutten, The impact of electroconvulsive therapy on the tryptophan-kynurenine metabolic pathway, Brain Behav Immun. 48 (2015) 48-52. https://doi.org/10.1016/j.bbi.2015.02.029.

[89] R. Moaddel, M. Shardell, M. Khadeer, J. Lovett, B. Kadriu, S. Ravichandran, P.J. Morris, P. Yuan, C.J. Thomas, T.D. Gould, L. Ferrucci, C.A. Zarate, Plasma metabolomic profiling of a ketamine and placebo crossover trial of major depressive disorder and healthy control subjects, Psychopharmacology (Berl). 235 (2018) 3017-3030. https://doi.org/10.1007/s00213-018-4992-7.

[90] L. Lanser, P. Kink, E.M. Egger, W. Willenbacher, D. Fuchs, G. Weiss, K. Kurz, Inflammation-Induced Tryptophan Breakdown is Related With Anemia, Fatigue, and Depression in Cancer, Front Immunol. 11 (2020) 249. https://doi.org/10.3389/fimmu.2020.00249.

[91] B.J. Van den Eynde, N. van Baren, J.-F. Baurain, Is There a Clinical Future for IDO1 Inhibitors After the Failure of Epacadostat in Melanoma?, Annual Review of Cancer Biology. 4 (2020) 241-256. https://doi.org/10.1146/annurev-cancerbio-030419-033635.

[92] L. Sforzini, M.A. Nettis, V. Mondelli, C.M. Pariante, Inflammation in cancer and depression: a starring role for the kynurenine pathway, Psychopharmacology (Berl). 236 (2019) 2997-3011. https://doi.org/10.1007/s00213-019-05200-8.

[93] A. Lewis-Ballester, S. Karkashon, D. Batabyal, T.L. Poulos, S.-R. Yeh, Inhibition Mechanisms of Human Indoleamine 2,3 Dioxygenase 1, J Am Chem Soc. 140 (2018) 8518-8525. https://doi.org/10.1021/jacs.8b03691.

[94] Y. Li, N. Hu, D. Yang, G. Oxenkrug, Q. Yang, Regulating the balance between the kynurenine and serotonin pathways of tryptophan metabolism, FEBS J. 284 (2017) 948-966. https://doi.org/10.1111/febs.14026.

[95] H.A. Walsh, S. Daya, Inhibition of hepatic tryptophan-2,3-dioxygenase: superior potency of melatonin over serotonin, J Pineal Res. 23 (1997) 20-23. https://doi.org/10.1111/j.1600-079x.1997.tb00330.x.

[96] M. Modoux, N. Rolhion, S. Mani, H. Sokol, Tryptophan Metabolism as a Pharmacological Target, Trends Pharmacol Sci. 42 (2021) 60-73. https://doi.org/10.1016/j.tips.2020.11.006.

[97] E.S. Wohleb, T. Franklin, M. Iwata, R.S. Duman, Integrating neuroimmune systems in the neurobiology of depression, Nat Rev Neurosci. 17 (2016) 497-511. https://doi.org/10.1038/nrn.2016.69.

[98] F.M. das G. Corsi-Zuelli, F. Brognara, G.F. da S. Quirino, C.H. Hiroki, R.S. Fais, C.M. Del-Ben, L. Ulloa, H.C. Salgado, A. Kanashiro, C.M. Loureiro, Neuroimmune Interactions in Schizophrenia: Focus on Vagus Nerve Stimulation and Activation of the Alpha-7 Nicotinic Acetylcholine Receptor, Front Immunol. 8 (2017) 618. https://doi.org/10.3389/fimmu.2017.00618.

[99] I. Bjelobaba, D. Savic, I. Lavrnja, Multiple Sclerosis and Neuroinflammation: The Overview of Current and Prospective Therapies, Curr Pharm Des. 23 (2017) 693-730. https://doi.org/10.2174/1381612822666161214153108.

[100] M.T. Heneka, M.J. Carson, J. El Khoury, G.E. Landreth, F. Brosseron, D.L. Feinstein, A.H. Jacobs, T. Wyss-Coray, J. Vitorica, R.M. Ransohoff, K. Herrup, S.A. Frautschy, B. Finsen, G.C. Brown, A. Verkhratsky, K. Yamanaka, J. Koistinaho, E. Latz, A. Halle, G.C. Petzold, T. Town, D. Morgan, M.L. Shinohara, V.H. Perry, C. Holmes, N.G. Bazan, D.J. Brooks, S. Hunot, B. Joseph, N. Deigendesch, O. Garaschuk, E. Boddeke, C.A. Dinarello, J.C. Breitner, G.M. Cole, D.T. Golenbock, M.P. Kummer, Neuroinflammation in

Alzheimer's disease, Lancet Neurol. 14 (2015) 388-405. https://doi.org/10.1016/S1474-4422(15)70016-5.

[101] Q. Wang, Y. Liu, J. Zhou, Neuroinflammation in Parkinson's disease and its potential as therapeutic target, Transl Neurodegener. 4 (2015) 19. https://doi.org/10.1186/s40035-015-0042-0.