Critical Neurotransmitters in the Neuroimmune Network

Thomas Wesley Hodo¹,²,³†, Maria Teresa Prudente de Aquino¹†, Akiko Shimamoto¹† and Anil Shanker¹,²,³,⁴,⁵,⁶*†

¹ Department of Biochemistry, Cancer Biology, Neuroscience and Pharmacology, Meharry Medical College School of Medicine, Nashville, TN, United States, ² Department of Microbiology and Immunology, Meharry Medical College School of Medicine, Nashville, TN, United States, ³ School of Graduate Studies and Research, Meharry Medical College, Nashville, TN, United States, ⁴ Host-Tumor Interactions Research Program, Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, United States, ⁵ Vanderbilt Center for Immunobiology, Vanderbilt University Medical Center, Nashville, TN, United States, ⁶ Vanderbilt Institute for Infection, Immunology and Inflammation, Vanderbilt University Medical Center, Nashville, TN, United States

Immune cells rely on cell-cell communication to specify and fine-tune their responses. They express an extensive network of cell communication modes, including a vast repertoire of cell surface and transmembrane receptors and ligands, membrane vesicles, junctions, ligand and voltage-gated ion channels, and transporters. During a crosstalk between the nervous system and the immune system these modes of cellular communication and the downstream signal transduction events are influenced by neurotransmitters present in the local tissue environments in an autocrine or paracrine fashion. Neurotransmitters thus influence innate and adaptive immune responses. In addition, immune cells send signals to the brain through cytokines, and are present in the brain to influence neural responses. Altered communication between the nervous and immune systems is emerging as a common feature in neurodegenerative and immunopathological diseases. Here, we present the mechanistic frameworks of immunostimulatory and immunosuppressive effects critical neurotransmitters — dopamine (3,4-dihydroxyphenethylamine), serotonin (5-hydroxytryptamine), substance P (trifluoroacetate salt powder), and L-glutamate — exert on lymphocytes and non-lymphoid immune cells. Furthermore, we discuss the possible roles neurotransmitter-driven neuroimmune networks play in the pathogenesis of neurodegenerative disorders, autoimmune diseases, cancer, and outline potential clinical implications of balancing neuroimmune crosstalk by therapeutic modulation.

Keywords: T cell neuroimmunology, dopamine, glutamate, serotonin, substance P, cancer, neurodegenerative disorders, immunotherapy

INTRODUCTION

The nervous and immune systems present the body with two main interfaces to perceive, integrate, and respond to environmental insults or internal injuries. Both systems adapt to ever-changing conditions to mount their responses. While propounding his network theory of the immune system, Niels Jerne had highlighted functional similarities in the recognition mechanisms and memory formation capabilities of the nervous and immune systems (1).
Epithelial cells and immune cells stand at the frontline defense against the tissue insults arising from trauma, injury, or infection. Recent advances in neuroscience have added neurons to the frontline arsenal with an intricate bidirectional communication between the nervous and immune systems. Altered communication between the two systems is emerging as a common feature in neurodegenerative and immunopathological diseases.

Experiments conducted by Medawar et al. in the late 1940s introduced the notion that the brain parenchyma is an immunoprivileged site on the basis of the observations that skin allografts implanted into the brain parenchyma elicited a delayed graft rejection (2). This was attributed to a lack of lymphatics and antigen presentation in the brain. Lately, it has been found that the blood-brain barrier is more permissive than the blood-brain barrier to immune cells. This allows immune cells to circulate within the meninges to carry out surveillance in the central nervous system (CNS) under homeostatic conditions and capture antigens draining from the brain parenchyma or cerebral spinal fluid via glymphatics into the cervical lymph nodes (LN) (3–5). Recently, using single-cell high-dimensional cytometry all subsets of immune cells were shown to be present in the brain (6–8). Inflammatory pathways triggered by cytokines produced by immune cells in the CNS in conjunction with CNS-infiltrating lymphocytes and “inflammaging” lie at the heart of neurodegenerative diseases (9, 10). There is also evidence of the modulation of anti-bacterial (11) and anti-tumor (12) immune responses by the brain’s reward system. It is now known that highly invasive bacterial pathogens, such as Streptococcus pyogenes promote their survival by hijacking pain and neuronal regulation of the immune response (13). Thus, balancing neuroimmune crosstalk in diseased individuals may offer a novel strategy for therapeutic development to treat various pathologies.

Anatomical proximity and molecular mechanisms of communication, including receptors and signaling messengers, shared by the nervous and immune systems facilitate their crosstalk. Millions of years of evolutionary pressure has shaped the co-evolution of mammalian neuroimmune networks to maintain cellular and physiological homeostasis in the context of changes happening in the body's external and internal (blood pressure, pH, or temperature) environments. Despite an exciting progress over the last decades in understanding the partnership of neuroscience and immunology, precise mechanisms of neuroimmune crosstalk remain enigmatic (14, 15). Here, we review the known mechanistic frameworks of neuroimmune networks with respect to critical neurotransmitters.

**NEUROIMMUNE CROSSTALK DURING IMMUNE ONTOGENY, CELLULAR PROGRAMMING AND FUNCTION**

Neuroimmune crosstalk can be traced to the early steps of immune system ontogenesis. Hematopoietic stem cell (HSC) niche-forming mesenchymal stem cells (MSC) in perinatal bone marrow arise from the neural crest. These niche-forming MSCs share a common origin with peripheral sympathetic neurons and Schwann cells, an ontogenic relationship that underscores the sympathetic regulation of adult HSC activity (16). Schwann cells ensheathe bone marrow nerves and control HSC quiescence through activation of latent transforming growth factor β (TGFβ) (17) or HSC mobilization through neuron-derived catecholamines or norepinephrine (18, 19). CNS-resident immune cells include microglia, perivascular, meningeal and choroid plexus macrophages as well as astrocytes. Microglia arise from the embryonic yolk sac erythromyeloid precursors (EMP), which are also thought to give rise to macrophages in other tissues of the body (20). EMPs penetrate the CNS early during development (21).

Neuroimmune interactions guide cellular programming in tissues. This is evident, for example, in the framework of enteric nervous system and intestinal macrophages. In the gut, lamina propria macrophages (LpM) exhibit an inflammatory while muscularis macrophages (MM) anti-inflammatory tissue-protective phenotypes. Upon luminal bacterial infection, MMs enhance tissue-protective programs (e.g., increased expression of Arg1 and Chi3I genes), accumulate near sympathetic nerve fibers and present high levels of β2 adrenergic receptors (β2AR) for norepinephrine signaling (22). Such a cellular network between enteric neurons and macrophages affords intra-tissue adaptation to protect from distal threats.

Vasoconstriction-stimulatory adrenergic nerve innervation of the peripheral secondary lymphoid organs, such as spleen, observed in mammals signifies a functional layer of CNS influence on immune system (23, 24). Indeed, catecholamines produced by the adrenal medulla and the postganglionic fibers of the sympathetic nervous system (SNS) affect immune cell activation, proliferation, and apoptosis. It is postulated that neuroimmune functional crosstalk evolved, for instance, to eliminate parasites that cannot be taken care of by cell-mediated immunity (25). The sensation of itch as a parasite invades the skin leads to a reflex action of scratching; worms in the gut initiate peristalsis; and parasites in the lung lead to cough and enhanced mucus production. In these situations, T helper-2 (T_{H2})-stimuli activate sensory neurons in tissues, and parasites are eliminated by a joint neuroimmune defense: a release of histamine, T_{H2} response in the abundance of interleukin-4 (IL-4) secretion (which sensitize nociceptors), and production of mucus (due to neuroimmune effort) and IgE antibodies.

Immune cells also provide signals that impact the nervous system. Besides sending signals to the brain through cytokines, peripheral immune cells are present in the brain to influence neural responses. For example, IFNγ-producing T cells are predominant in the subventricular zone of aged brains, where they suppress proliferation of neural stem cells (26). In a stroke, regulatory T (T_{reg}) cells accumulate in the brain to accelerate neurological recovery (27). Moreover, during hypothermia macrophages become an alternative source of catecholamines such as noradrenaline to sustain thermogenesis (28, 29) through activation of the sympathetic nervous system pathway in warm-blooded (homeotherm) animals. Macrophages in adipose tissues of mice exposed to cold temperatures upon activation through IL-4/IL-13-dependent mechanisms produce...
noradrenaline, which stimulates β3 adrenergic receptors and activates thermogenic genes (29). Therefore, neurotransmitters through their defined signals can play a variety of roles in maintaining the body homeostasis.

**CNS LINKS TO INNATE INFLAMMATORY RESPONSES AND ADAPTIVE IMMUNE CELLS**

CNS-resident immune cells including microglial, perivascular, meningeal, and choroid plexus macrophages as well as astrocytes participate in an innate inflammatory response upon engagement of their Toll-like receptors (TLR) with highly conserved motifs of danger-associated molecular patterns (DAMP) or pathogen-associated molecular patterns (PAMP) on stressed or infected tissue. This response can damage neurons and other brain cells through chronic production of pro-inflammatory cytokines and other mediators. A well-established feedback circuit exists between inflammatory cytokines and the hypothalamic-pituitary-adrenal (HPA) axis, a major brain-associated regulatory mechanism underlying stress responses (30–32). The HPA axis also plays a critical role in controlling the physiology and function of thymus, the T cell production center and a sensor of immunological homeostasis in the body (33–35). The studies conducted by Selye in 1936 showed that various physiologic or pathologic stress stimuli led to adrenal enlargement and involution of thymus (36). Subsequent studies in mice and humans confirmed that the activation of HPA axis caused thymic involution (37–39). Studies have also shown in murine models that progressive ascitic growth of lymphomas producing an immunosuppressive inflammatory environment causes thymic atrophy (40, 41), which could be reversed with the administration of thymic hormones (42, 43). These observations point to a role of HPA-thymus axis in the control of immunological homeostasis.

The CNS is hardwired to monitor the presence of cytokines and molecular products of inflammation. IL-1β is a key pro-inflammatory cytokine in the inflammasome pathway that is secreted in response to any stress, including oxidative stress, and stimulates the HPA axis (44–47). In turn, adrenal cortex synthesizes glucocorticoids (GC) that can cause thymic involution, neutrophil mobilization, myeloid, and granulocyte differentiation and eosinophilia (48–52) or polarize immune cells from inflammatory to tissue-protective non-inflamed phenotypes (44, 45). GC upon binding with GC receptors (GR) on macrophages can switch their inflammatory cytokine secretions, such as TNFα, IFNγ, and IL-1β, to tissue-protective types such as TGFβ and IL-10. This promotes tissue repair by enhancing phagocytosis of cells undergoing apoptosis while preventing their necrosis (53, 54) (Figure 1, left). In addition, a cytokine storm of IL-1β causes hyperalgesia, a common characteristic of any sickness (55).

Another prominent link is between the vagus nerve and the immune system. The vagus nerve originates from the nucleus ambiguous and dorsal motor nucleus of the brainstem. In humans, it comprises 80,000–100,000 fibers as a major conduit for transmitting sensory information from most visceral organs to the brain (56). Vagus nerve forms a synapse at the celiac ganglion with the adrenergic splenic nerve, which comes in contact with lymphocytes expressing β2AR (57, 58). Norepinephrine (NE) released from the adrenergic splenic nerve terminals activates β2AR that facilitates the synthesis of acetylcholine (ACh) from lymphocytes (44, 59). The ACh thus released activates the cognate α7 nicotinic ACh receptors (α7nAChR) on neighboring monocytes and macrophages (44, 60, 61). Signal transduction following ACh-induced activation of α7nAChR increases intracellular Ca2+, decreases nuclear translocation of the nuclear factor κ-light-chain-enhancer of activated B cells (NFκB), stabilizes mitochondrial membranes, and inhibits inflammasome activity to reduce the production of inflammatory cytokines, such as TNFα, IL-1, IL-6, and IL-18 (62–65). Thus, activation of the vagus nerve attenuates the systemic inflammatory response by macrophages through the release of ACh (Figure 1). The cholinergic signaling is also known to suppress accumulation of neutrophils (66). This neuronal reflex circuit is called cholinergic anti-inflammatory pathway (58, 67). Neural signals through the afferent vagus nerve can attenuate the exacerbated “non-resolving inflammation” by acting on dendritic cells (DC) and lymphocytes (54, 60). It was recently shown that nerve impulses recorded from the vagus nerve of mice exposed to IL-1β and TNF exhibited distinct shape, amplitude, and firing rates, suggesting that the information present in afferent sensory signals within the vagus nerve can discriminate between specific cytokines (68). It is suggested that IL-1β receptors are present on vagal paragangial glomus cells that act as secretory sensory neurons and release neurotransmitters in response to hypoxemia (low pO2), hypercapnia (high pCO2), or acidosis (low pH) (69, 70). Thus, the CNS and the immune system exchange information to act collectively in health and disease.

An extensive crosstalk between innate immune pathways and neuronal circuits has a bearing on human diseases (71). Likewise, adaptive T cells and cytokines associated with adaptive responses, such as IL-4, IFN-γ, and IL-17, have been implicated in neuroimmune crosstalk. IL-4 derived from CD4+ T cells present in the meninges has been shown to prevent the pro-inflammatory differentiation of resident meningeal myeloid cells in mice and induce the expression of brain-derived neurotrophic factor in astrocytes (72). IFNγ from meningeal T cells supports neuronal circuits that are associated with social behavior (73), whereas IFNγ from choroid plexus T cells has been associated with memory function and hippocampal neurogenesis (74–76). In addition, brain development during embryogenesis is influenced by cytokines derived from maternal adaptive immune cells. Maternal TH17 cells have been shown to induce structural alterations in the cortex and autism-like behavioral abnormalities (77).

**IMMUNOMODULATORY NEUROTRANSMITTERS**

Neuroimmune interaction depends on cell-to-cell contacts and on soluble communication molecules that include cytokines, chemokines, neuropeptides, neurotrophins, and
neurotransmitters. Various leukocytes at different activation states synthesize neurotransmitters and express their receptors to participate in neuroimmunomodulatory circuitry (78–81). Similarly, neurons express pattern-recognition receptors (PRR), including TLRs and cytokine receptors, to influence immune pathways (82). This provides a common molecular platform for neuroimmune network for handling responses against obnoxious threats, including those triggered by PAMP (83–86). Macrophages, DC, T cells, and other immune cells express ionotropic, metabotropic, and G-protein-coupled receptors for various neurotransmitters (87–89). Besides ACh and NE, a variety of neurotransmitters, such as dopamine, serotonin, substance P, γ-aminobutyric acid (GABA), and glutamate modulate immune responses. While glutamate is the main excitatory neurotransmitter, GABA is the chief inhibitory neurotransmitter in the mature mammalian CNS. Outside the brain, GABA is produced by pancreatic β-cells as well as T cells and macrophages that express all components of GABAergic system, including its receptors, transporters, and metabolic enzymes. GABA acts as a negative regulator of macrophage and microglial production of inflammatory cytokines and T cell activation by blocking calcium signaling and NFκB activity (90). It is implicated in several autoimmune diseases, such as experimental autoimmune encephalomyelitis (EAE), multiple sclerosis (MS), inflammatory bowel disease (IBD), type-1 diabetes, arthritis, and dermatitis.

A review of the entire range of neurotransmitters involved in neuroimmune interaction is beyond the scope of this article. Prior reviews have covered the cholinergic (acetylcholine), catecholaminergic (norepinephrine and epinephrine), and vagal nerve regulation of immunity (65, 91). Detailed reviews are also available on the role of enteric nervous system in the regulation of immune responses in the gastrointestinal (GI) tract (92, 93), as well as on the HPA axis, a stress-responsive combinatorial axis of CNS and endocrine systems, with major immunoregulatory mechanism for fine-tuning the innate and adaptive immunity.
GABAergic neuroimmune interactions have also been reviewed extensively (90, 98–100).

In the present article, we have reviewed the available knowledge on four critical neurotransmitters, namely, dopamine, serotonin, substance P, and glutamate that are known to be broadly present outside the nervous system. We discuss their effects on immune responses and potential clinical implications of their modulation. Activation of the neurotransmitter receptors on immune cells can result in the stimulation or suppression of myeloid and lymphoid cells through a variety of effects. In our discussion, any activation of neurotransmitter receptors leading to an enhanced immune response is categorized as an immunostimulatory effect irrespective of the disease. This includes the situation where the decreased suppressive activity of an immune cell, such as Treg, results in an overall augmented immune effector function. By contrast, an activation of these receptors leading to a reduced immune cell development, differentiation, numbers, function, increased immune cell death, dysfunction, or tolerance is categorized as an immunosuppressive effect.

**Dopamine**

Dopamine or 3,4-dihydroxyphenethylamine (DA) belongs to the catecholamine and phenethyamine families. It is found in plants with the highest concentrations observed in bananas (101), and in most multicellular animals, including cnidarians (102). This dates the emergence of DA as a neurotransmitter to the earliest appearance of the nervous system, over 500 million years ago in the Cambrian Period (103). It is synthesized from L-tyrosine by tyrosine hydroxylase in the ventral tegmental area and the substantial nigra pars compacta neurons of the CNS that innervates primary and secondary lymphoid organs (104–106). In the brain, DA functions as a major player in the motivational component of reward behavior and regulates arousal and mood besides controlling motor movement. Across a wide range of vertebrates, DA spike triggers behavior-switching and response selection that confers motivational salience for an organism’s growth and survival (102, 107).

Outside the CNS, DA functions as an exocrine or paracrine messenger (108). In the immune system, it affects leukocytes in the LN, spleen, bone marrow, and circulation (109). Immune cells such as activated T H1, T H2 and mature DC express tyrosine hydroxylase that synthesize DA, and store it in vesicles expressing vesicular monoamine transporter subtype 1/2 (VMAT1/2) (110–112). Moreover, all five subtypes of DA receptors (DR), namely, D1-D5, are expressed in immune cells. DRs are metabotropic G-protein-coupled receptors (GPCR), meaning that they exert effects via a second messenger system. DRs form a heteromeric G-protein-coupled receptors (GPCR), meaning that they exert effects via a second messenger system. DRs form a heteromeric family (124). DA mediated signaling acts synergistically with IL-4 by upregulating IL-2Rx-STAT5 pathway and reducing inhibitory histone trimethylation at T H2 gene loci of GATA-3 (124). This mechanism became marginal after sympathetic nerves turned adrenergic in the adult lung. Thus, the communication between dopaminergic nerves and T H2 cells underlies the susceptibility of post-natal lung to hypersensitivity reactions by coordinating release of IL-4 and histamine (which sensitize nociceptors), production of mucus and IgE antibodies (airway irritancy) and cough behavior.

D1 activation on DCs expressed extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinase (JNK) and NFκB activity that facilitated cytokine production and promoted T H2 and T H17 differentiation in humans and mouse models (112, 118, 132). D1 activation also stimulated DC tyrosine hydroxylase activity for the synthesis of DA during antigen presentation to T cells, consequently activating D1 on primed T H1 cells. The increased DA binding with D1 on primed T H1 cells increased their intracellular levels of cAMP, inducing T H2 polarization (112). Conversely, D1/2 antagonist berberine reduces the secretion of LPS-induced cytokines such as INF-γ, TNF-α, IL-6, and IL-1β from murine macrophages and DCs (133).

On the other hand, D1 activation on Treg cells downregulate their migratory, adhesive, and suppressive abilities, which in turn result in an augmented effector function (121). In addition, human follicular T H (T F H) cells can synthesize and release DA that upon binding with D1 on B cells increases their expression of inducible T cell costimulatory ligand (ICOSL) and CD40L and improves their survival (122). This DA-mediated mechanism
may offer an important advantage for the control of infections by facilitating T<sub>FH</sub>-B cell synapses (122).

D<sub>3</sub> activation triggers chemotactic migration in human and murine naïve CD8<sup>+</sup>T cells (105). It facilitates CD8<sup>+</sup>T cell β<sub>1</sub> integrin binding to fibronectin and intercellular adhesion molecule (ICAM) of the endothelium allowing extravasation of T cells to their target sites (105, 119, 120). Indeed, a D<sub>3</sub> antagonist U-99194-A inhibited the homing of naïve CD8<sup>+</sup>T cells to the inguinal LN in mice (105). Thus, a collaborative DA-mediated network of DC, T<sub>FH</sub>, and B cells along with decreased T<sub>reg</sub> suppressive activity could be helpful in priming and sustaining CD8<sup>+</sup>T cell cytolytic responses against parasitic infections and in immunosuppressive conditions.

**Immunosuppressive Effects**

DA signaling through D<sub>4</sub> is known to suppress lymphocyte function by attenuating secretion of IL-2 and IFNγ in human T cells through upregulation of master transcription factor Krüppel-like factor (KLF-2) and inhibition of ERK1/2 kinases (126–128). DA inhibits the expression of lymphocyte-specific protein tyrosine kinases, Lck, and Fyn, which are critical for TCR signal transduction (127). Under *in vitro* conditions of elevated physiological concentrations of DA, CD8<sup>+</sup> T cells were found to be more susceptible to D<sub>1</sub> family receptor-mediated inhibition of proliferation and downregulation of cytolytic activity relative to CD4<sup>+</sup> T cells (129). Activation of D<sub>4</sub> facilitated quiescence of activated T cells through the expression of KLF-2 (128). Moreover, DA released from T cells can result in enhanced production of intracellular reactive oxygen species leading to oxidative stress and apoptosis in human peripheral blood lymphocytes in an autocrine mechanism to downregulate their own proliferation and differentiation (126, 131). D<sub>5</sub> activation by DA on NK cells suppressed their proliferation and IFNγ production without affecting apoptosis or cell death (130). In a mouse model of septic polymicrobial peritonitis, the stimulation of sciatic nerve inhibited the production of TNF, monocyte chemotactic protein-1, IL-6, and INFγ (130). In a mouse model of septic polymicrobial peritonitis, the stimulation of sciatic nerve inhibited the production of TNF, monocyte chemotactic protein-1, IL-6, and INFγ (130). In DCs, D<sub>2</sub> activation inhibited adenylyl cyclase activity and reduced intracellular levels of cAMP, which in turn impaired T cell proliferation and cytokine production (132). Overall, it appears that by selectively triggering specific DR on immune cells DA may provide for an immunological behavior-switching and context-dependent immunostimulatory or immunoinhibitory response selection for an organism’s survival.

**Clinical Implications**

Several autoimmune diseases have been linked to DA modulation. In an experimental model of colitis, administration of berberine diminished inflammation in the colon by reducing the levels of IFN-γ and IL-17 secretions from...
colonic macrophages (135). In IBD, dopaminergic system is responsible for altered T cell signaling leading to augmented effector function and decreased suppressive role of T<sub>reg</sub> via D<sub>5</sub> (123). Patients with MS downregulate D<sub>5</sub> on T cells with inability to reduce proliferation or IFN-γ secretion when DA is administered, suggesting a dysregulated DA function in MS pathology (136). In relapsing MS patients, suppressive function of T<sub>reg</sub> was restored by diminishing the effects of DA on T cells after IFN-β treatment (123). Also, administration of a D<sub>1</sub> antagonist SCH-23390 downregulated IL-6–dependent T<sub>H17</sub> response (137).

The impaired immune responses by DA is also linked to a number of brain disorders, such as schizophrenia (138), Alzheimer’s disease (AD) (139, 140) and Parkinson’s disease (PD) (141). Besides microglia, the brain-specific macrophages, CNS-infiltrating lymphocytes play a significant role in these brain disorders. Schizophrenia patients express more D<sub>5</sub> (142) whereas patients with AD express lower D<sub>2</sub> on T cells compared to healthy controls (143). The progression of PD is dependent on CD4<sup>+</sup>T, not CD8<sup>+</sup>T, cell infiltration into the substantia nigra as well as loss of dopaminergic neurons of the nigrostriatal pathway (123, 144, 145). One study demonstrated that L-DOPA or a D<sub>2</sub> agonist bromocriptine administration to PD patients attenuated the increased expression of D<sub>1</sub> and D<sub>2</sub> on peripheral blood lymphocytes (146). It is also postulated that PD may originate from an autoimmune mechanism involving IgG antibodies that bind to DA neurons inducing their death (147, 148). In a PD-inducing neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model, dopaminergic cell death was almost exclusively caused by the substantia nigra-infiltrating CD4<sup>+</sup>T cells by a FasL-mediated cytolytic pathway, but not by IFN-γ-dependent mechanisms, in an environment replete with activated microglia and pro-inflammatory cytokines (144, 149, 150).

Thus, DA modulation may offer treatment alternatives to mitigate neuropathologies and autoimmune diseases. Based on
few studies discussed above, DA agonists may help in brain disorders such as PD whereas specific DR antagonists could help alleviate MS, schizophrenia, AD, colitis, and IBD.

Serotonin
Serotonin or 5-hydroxytryptamine (5-HT) is found in all bilateral animals including worms and insects (151), as well as in fungi and plants with the highest values present in nuts of walnut and hickory (152). In the brain, it is synthesized in serotonergic neurons in the Raphe nuclei located in the brainstem, and mediates various behavioral processes (153–155). However, neuronal 5-HT consists merely 10% of the 5-HT produced in the body. Majority of 5-HT is synthesized by enterochromaffin cells of the GI tract (156, 157), where it mainly regulates intestinal movements besides controlling bone mass and endothelial nitric oxide synthase activity (158). A GI parasite Entamoeba histolytica becomes more virulent in the presence of high levels of 5-HT in the gut, and secretes additional 5-HT to thrive by a phenomenon known as quorum sensing (159) (similar to quorum sensing in the regeneration of distressed hair follicles on skin in the presence of CCL2 and TNFα). The concentration of 5-HT and the strength of its signaling mediate brain’s perception of resource availability. In less complex animals, such as invertebrates, resources simply mean food availability (160, 161). In more complex arthropods and vertebrates, resources also can mean social dominance (162, 163). 5-HT spikes may elevate or lower an organism’s mood and behavior in response to the perceived abundance or scarcity of resources for its social growth and survival.

5-HT synthesis from enterochromaffin cells receiving short-chain fatty acids from the gut microbiota is transported in the bloodstream for uptake by innate and adaptive immune cells via membrane-expressing serotonin transporters (SERT) including platelets, which store it in granules (164, 165). Whenever platelets bind to the endothelial lesion in damaged tissue during blood clotting, 5-HT acts as a vasoconstrictor to stop bleeding, and as a fibrocyte mitotic factor to aid tissue-healing. In response to inflammation, mast cells, macrophages, and T cells can produce 5-HT on their own by upregulating the expression of tryptophan hydroxylase 1 and 2 enzymes required to synthesize 5-HT from 5-hydroxytryptophan (87, 166, 167).

Most immune cells express 5-HT receptors (5-HTR) on their membranes (168). There are 14 subtypes of 5-HTRs in vertebrate animals and all but 5-HT3 are GPCR. While 5-HT1 and 5-HT3 are coupled to Gαi/o proteins that inhibit adenylyl cyclase, 5-HT4, 5-HT6, and 5-HT7 are coupled to Gαs proteins that activate adenylyl cyclase for cAMP production. 5-HT2 is coupled to Gq/11 that activates phospholipase C-β, which facilitates the release of diacyl glycerol and formation of inositol 1,4,5-trisphosphate (IP3) (169, 170). Unlike all of these, 5-HT3 is a ligand-gated ion channel capable of transporting Na+ and K+ cations (168). Immune cells exhibit varied expression of these receptors. Microglia, the brain-resident macrophages, express 5-HT2B, 5-HT3A, and 5-HT7 receptors (171). 5-HT1A is expressed in mast cells (172) and macrophages (167); 5-HT1B is expressed in DC (169, 173); 5-HT1E in monocytes (174) and DC (169); 5-HT2A in eosinophils (175) and macrophages (176); and 5-HT4 and 5-HT7 in DC (169, 173). Among adaptive immune cells 5-HT1B, 5-HT2A, and 5-HT7 are expressed in T cells (177, 178), and 5-HT1 in both pre-B, mature and neoplastic B cells (179–181). Most of these 5-HT receptors impact activation or inhibition of immune responses (164). 5-HT can act both as a pro-inflammatory or anti-inflammatory tissue protective signaling molecule as observed in the intestinal mucosa via activation of 5-HT7 or 5-HT4 receptors, respectively (157). Various effects of 5-HT-triggered signaling on lymphoid and non-lymphoid cells are summarized in Table 2, and the immune network of 5-HT-mediated cell-to-cell communication is depicted in Figure 3.

Immunostimulatory Effects
Expression of 5-HT7 on naïve T cells is enhanced upon activation. In addition, activated T cells acquire the expression of 5-HT1B and 5-HT2A, and synthesize 5-HT in an autocrine manner. Moreover, 5-HT7 activation induces IL-2 secretion and T cell proliferation through rapid phosphorylation of ERK1/2 and IkBo (87, 164). 5-HT1B and 5-HT2A further promote the antigen-specific proliferation of human and murine TH1 and cytotoxic CD8+ T cells. Selective 5-HT1B antagonist SB-216641 and 5-HT2A inhibitor saropagrelate hydrochloride inhibited T cell production of IL2 and IFNy (177, 178). Also, exogenous 5-HT increased IL-10 production by TH2 cells ex vivo from MS patients (186). Thus, 5-HT may function as an intrinsic autocrine cofactor in T cell activation and function.

Tissue injury and inflammation stimulates the release of stored 5-HT from platelets and mast cells. During post-burn trauma, increased tissue 5-HT concentration supports wound healing as shown by an increased frequency of F4/80 macrophages in response to excisional punch biopsy on skin from mouse models (192). Moreover, under in vitro conditions murine peritoneal macrophages showed increased secretion of chemokine CCL2 and phagocytosis following 5-HT1A activation by its agonist (7)-8-hydroxy-2-(di-n-propyl-amino)-tetratin (190). Also, in mouse models of experimental colitis 5-HT2A blockade by ketanserin impaired macrophage migration and decreased the NFkB-mediated activity (182). 5-HT was found to stimulate different signaling pathways in human T cells depending on their stage of maturation. Using isotype-selective receptor agonists, it was revealed that 5-HT1B, 5-HT1E, and 5-HT2A stimulation induced intracellular Ca2+ mobilization via Gq/11 proteins in immature, but not mature, DC. Furthermore, functional studies indicated that activation of 5-HT1, 5-HT4, and 5-HT7 elevated cAMP in mature human DC and microglial M1/M2 cells, and enhanced their secretion of IL-1β, IL-6, IL-8, and IL-10 (169, 173, 189). 5-HT1A signaling played a role in the adhesion of bone marrow-derived mast cells as 5-HT1A-/- mice showed deficiency in their migration and adhesion (172). Also, 5-HT1B/1D receptor agonist sumatriptan increased the number of degranulated mast cells in the brain thalamus (187), and 5-HT2A activation increased endotoxin-induced mast cell activity in rats (188).

Immunosuppressive Effects
5-HT signaling has inhibitory effects especially on the pro-inflammatory activation of immune cells. It is well-accepted
that many SERT blockers including the serotonin selective reuptake inhibitors (SSRIs), which increase extracellular 5-HT concentration, have immunoinhibitory effects, such as reduced lymphocyte proliferation and decreased cytokine production by myeloid cells in both animals and humans (193–196). In a meta-analysis study of 827 patients suffering with major depressive disorder (MDD), the pooled effect estimate using bias-corrected standardized mean difference indicates that SSRI treatment decreases serum levels of pro-inflammatory cytokines, IL-6, TNFα, and IL-1β, and anti-inflammatory cytokine IL-10 (194, 197–199). In a murine LPS-induced septic shock model, fluoxetine markedly decreased circulating levels of TNFα (200). In a model of ovalbumin-sensitized allergic asthma, fluoxetine decreased monocyte-production of TNFα concomitant with decreased lung inflammation by reducing the number of macrophages, lymphocytes, neutrophils, and eosinophils (200). In this allergic asthma model, inhalation of 5-HT2A agonist (R)-2,5-dimethoxy-4-iodoamphetamine [(R)-DOI] prevents the development of mucus hyperproduction, airways inflammation, and pulmonary eosinophil recruitment. Further, agonistic activation of 5-HT2A inhibits the expression of a variety of TNFα-mediated inflammatory and immunomodulatory molecules, such as ICAM-1, VCAM-1, IL6, and NO synthase and NFκB activity in murine peripheral tissues including primary aortic smooth muscle cells, vasculature, and gut (183, 184). Other SSRIs such as venlafaxine and moclobemide reduced the antigen-specific humoral and delayed hypersensitivity Th1 cell-mediated immunity in mice with a reduction of the release of macrophage pro-inflammatory mediators and the expression of antigen-presentation markers (201). This suggests that SSRIs may owe some of their therapeutic effects to alleviation of the chronic inflammation. Also, exogenous 5-HT reduced ex vivo production of Th1 and Th17 cytokines from patients with MS, a demyelinating autoimmune disease mediated by Th1 and Th17 cells. Additionally, 5-HT reduced IFNγ and IL-17 secretion by CD8+ T cells, enhanced Treg function, and favored the expansion of FoxP3+CD39+ Treg and Treg17 cells, a novel Treg subset from MS patients (186).
Ionic permeability on voltage-gated $K^+$ channel is also regulated by 5-HT signaling as demonstrated in murine pre-B cells. Using specific receptor antagonists, it was found that $K^+$ conductance increased via the activation of 5-HT$_1$-like receptors, whereas it decreased via 5-HT$_3$ activation in pre-B cells. Moreover, 5-HT$_3$ agonist, 2-methyl-5-HT accelerated the inactivation of pre-B cells (181), suggesting that B cell activation may be deregulated by 5-HT$_3$, a ligand-gated cation channel (202). In mature DC, the activation of 5-HT$_4$ reduces the secretion of IL-12 and TNF-$\alpha$, and 5-HT$_4$ agonist tandospirone citrate inhibited their degranulation (169). One study also demonstrated that 5-HT or 5-HT$_3$ agonist reduced HIV-1 infection in primary culture of human macrophages by decreasing the expression of CCR5 and increasing the secretion of its ligand macrophage inflammatory protein-1$\alpha$ on macrophages (191).

**Clinical Implications**

TNF-$\alpha$-mediated inflammatory pathways have been strongly implicated in several diseases, including atherosclerosis, rheumatoid arthritis, psoriasis, type II diabetes, depression, schizophrenia, and AD. Activation of 5-HT$_2A$ represents a potential therapeutic avenue for the treatment of such disorders. Moreover, the inhibitory effects of 5-HT$_2A$ agonist (R)-DOI on TNF-$\alpha$-mediated inflammation last many hours after the administration of TNF-$\alpha$ (184). Thus, 5-HT-agonist-based therapies can prevent inflammation and may also treat inflammation-associated tissue stress or injury that has already occurred or is ongoing.

MDD is also heavily linked to systemic inflammatory responses through 5-HT (194, 195, 203–205). SSRIs alleviate depressive symptoms by decreasing the myeloid cell production of pro-inflammatory cytokines, resisting mast cell activation,

---

**FIGURE 3** | Immune network of serotonin-mediated cell-to-cell communication. In mast cells, 5-HT$_{1A}$ activation increases their migration and adhesion while 5-HT$_{1B}$ and 5-HT$_{2A}$ induces their degranulation and activity. 5-HT released from platelet ($P$) stores act upon myeloid and lymphoid cell subsets during inflammatory processes. As T cells differentiate, more 5-HT$_7$ are expressed together with 5-HT$_{1B}$ and 5-HT$_{2A}$, increasing intracellular Ca$^{2+}$. 5-HT$_7$ activation facilitates T cell proliferation through ERK1/2 phosphorylation and NF$\kappa$B activation. 5-HT$_{1B}$ and 5-HT$_{2A}$ activation promotes T cell production of IL-2 and IFN-$\gamma$ and antigen-specific proliferation in T$_H$ and CD8$^+$ T lymphocytes (CTL). 5-HT$_{2A}$ and 5-HT$_{2B}$ activation promotes IL-17 production from CD4$^+$ T cells. 5-HT$_{1A}$ activation has been implicated in decrease of CCR5, increase of CCL2 and MIP1$\alpha$ as well as phagocytosis by macrophages (M$\phi$) while 5-HT$_{2A}$ activation increases production of M2-type cytokines and migration. 5-HT signaling through 5-HT$_{1B}$, 5-HT$_{1E}$, 5-HT$_{2A}$, and 5-HT$_{2B}$ increases intracellular Ca$^{2+}$ in immature DCs. It also enhances DC maturation by upregulating cAMP levels through 5-HT$_4$ and 5-HT$_7$. Moreover, 5-HT$_1$, 5-HT$_4$, and 5-HT$_7$ activation on mature DCs promotes secretion of cytokines, such as IL-1$\beta$, IL-6, IL-8, and IL-10 whereas 5-HT$_{4}$ inhibits DC degranulation and production of IL-12 and TNF-$\alpha$. Upward solid red arrows depict upregulation of indicated molecules or effects whereas the downward solid arrows indicate the reverse. Thin red line arrows indicate cells that produce 5-HT.
and reducing chronic inflammation (193–196). MS patients with depression characterized with a high concentration of pro-inflammatory T<sub>H1</sub> and T<sub>H17</sub> cytokines are related to reduced synthesis and availability of 5-HT in the CNS (206). The <i>in vitro</i> treatment of PBMCs from MS patients with exogenous 5-HT reduced the production of T<sub>H1</sub> and T<sub>H17</sub> cytokines as well as increased the frequency of T<sub>reg</sub>, suggesting a critical role of 5-HT in downregulating an exacerbated inflammatory response in MS (186).

Dysregulation in 5-HT signaling affects multiple peripheral organs, such as the lung, heart, GI tract, genitourinary tract, and liver (158). The GI enterochromaffin cells synthesize 5-HT for release into the bloodstream linking it to several GI disorders, including irritable bowel syndrome (IBS) and constipation (157, 207, 208). SERT-expressing platelets containing 5-HT stores also affect gut inflammation that underlies GI disorders (209–211). A mouse model of colitis showed increased levels of 5-HT and IL-13 in the gut (212). Patients diagnosed with IBS or other bowel diseases show high levels of 5-HT and an increased frequency of T<sub>H17</sub> cells. In fact, both 5-HT<sub>R</sub> agonists and antagonists have been used to treat IBS that also helped with other related symptoms (213). 5-HT<sub>3</sub>, 5-HT<sub>4</sub>, and 5HT<sub>1B</sub> are the most important receptors for GI function. 5-HT<sub>4</sub> agonists (e.g., tegaserod) potentiate peristalsis initiated by 5-HT<sub>1</sub> stimulation and are thus helpful in chronic constipation and constipation-predominant form of IBS. 5-HT<sub>3</sub> antagonists (alosetron and cibenzutan) prevent the activation of 5-HT<sub>3</sub> on extrinsic afferent neurons and can decrease the visceral pain associated with IBS.

In addition, studies have shown that 5-HT may alleviate symptoms associated with asthma, such as severe bronchoconstriction, mucus buildup, and eosinophil-induced inflammation in response to allergens (169, 175). In rheumatoid arthritis (RA) analysis of patients and murine models show that 5-HT is responsible for balancing T<sub>H17</sub>/T<sub>reg</sub> populations (214). In a RA mouse model, the absence of 5-HT led to conversion of T<sub>reg</sub> into T<sub>H17</sub> cells, skewing the population to more pro-inflammatory type and worsening of tissue damage (185). In collagen-induced arthritis in Tph1<sup>−/−</sup> mice, which have markedly reduced peripheral serotonin levels, <i>ex vivo</i> serotonin and 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> agonists restored IL-17 secretion from splenocytes and T<sub>H17</sub> cell differentiation (185). Also, mast cell production of 5-HT worsened thrombocytopenia in dengue virus infections through platelet activation via 5-HT<sub>1</sub> (215).

Thus, 5-HT modulation can alleviate various TNFα-mediated inflammatory diseases, depressive disorders linked to systemic inflammation and GI disorders. Also, in solid tumor microenvironments, tryptophan-catabolizing enzyme indoleamine 2,3-dioxygenase is present at high concentrations (216, 217). This may impair the synthesis of 5-HT, a tryptophan metabolite, and decrease 5-HT autocrine signaling in T cells (87). Consequently, this may downregulate anti-tumor T cell immunity. Optimization of 5-HT signaling should thus be helpful in cancer.

**Substance P**

Substance P (trifluoroacetate salt powder; SP) is an undecapeptide of the tachykinin neuropeptide family. SP is released from the terminals of specific sensory nerves in brain regions of the CNS regulating emotion (hypothalamus, amygdala, and the periaqueductal gray) as well as in most peripheral regions (218, 219). In addition, it is secreted by immune cells such as macrophages, eosinophils, lymphocytes, and dendritic cells. SP exerts its biological activity through G-protein–coupled neurokinin receptors (NKRs), namely, neurokinin 1 receptor (NK1R), NK2R, and NK3R (220). SP has the highest affinity to its endogenous receptor NK1R that is primarily expressed in epithelial cells, fibroblasts and immune cells (218, 219, 221). The NKRs activate phospholipase C, protein kinase C and adenyl cyclase, and mobilize intracellular Ca<sup>2+</sup> (219). SP and NK1R are found in close association with serotonin and neurons containing norepinephrine (222). The NKR promoter contains regions that are sensitive to cAMP, AP-1, AP-4, CEBPB, and epidermal growth factor (223). Because these regions are related to cytokine-triggered signal transduction pathways, cytokines are likely to induce NK1R transcription factors (224). NK1R is distributed over cytoplasmic membranes of many cell types, including neurons, glia, endothelia of capillaries, lymphatics, fibroblasts, stem cells, and leukocytes. SP can thus influence or excite many cellular processes (219, 225).

SP acts as an immediate defense, repair and survival system in response to noxious stimuli (stressors) that may compromise biological integrity. Upon tissue damage, infection or other types of stress, SP is released from skin, musculoskeletal, respiratory, or GI tract cells and regulates permeability and contractility of the organs within those systems (218, 219, 226). SP signaling is known to associate with inflammatory processes, pain perception, modulation of behavior, stress responses, immune function, and vomiting reflex. Furthermore, common among biological processes, SP release and expression of NKRs may not subside in diseases marked by chronic inflammation, such as cancer.

The SP-NK1R system mediates interactions between neurons and immune cells, and modulates several aspects of the immune response, including leukocyte proliferation and activation, and cytokine expression (227). Reciprocally, cytokines may induce expression of SP and NK1R (228–230). Also, SP is involved in neurogenic inflammation, which is a local inflammatory response to certain types of infection or injury (231). Various effects of SP on immune cells are summarized in Table 3.

**Immunostimulatory Effects**

SP can help prolong an immune response critical for host survival. SP secretions are known to be increased during recruitment of innate immune cells to target sites causing an amplified immune inflammation by increasing cytokine production (234). SP levels are elevated in the immediate vicinity of lymphocytes (119). In a mouse model of EAE, NK1R antagonist reduced expression of the cellular adhesion molecules ICAM-1 and VCAM-1 on CNS endothelia and the secretion of pro-inflammatory T<sub>H1</sub> cytokines IFNγ and TNFα (219, 226). SP acts as a chemoattractant for lymphocytes and upregulates their integrins LFA-1 and VLA-4 to promote migration and extravasation into the target sites (226). SP induces IFNγ secretion in human T cells and promotes T<sub>H1</sub> response...
TABLE 3 | Summary of the effects of substance P on immune cell responses.

| Neurotransmitter | Receptors | Target immune cells | Implications in disease |
|------------------|-----------|---------------------|------------------------|
| Substance P      | NK1R      | Neutrophil           | Asthma                 |
|                  | NK2R      | Macrophage           | Dermatitis             |
|                  | NK3R      | T cell               | IBD                    |
|                  |           | B cell               | Rheumatoid Arthritis   |
|                  |           |                      | Psoriasis              |
|                  |           |                      | Diabetes               |
|                  |           |                      | Cancer                 |

Cellular adhesion and homing
Chemoattracts lymphocytes and upregulates their integrins LFA-1 and VLA-4 to promote migration and extravasation into the target sites (226). NK1R signaling increases the expression of the cellular adhesion molecules ICAM-1 and VCAM-1 on CNS endothelia (219, 226). Reduces CD8+ T cell migration (119).

Lymphocyte function
NK1R signaling increases the secretion of pro-inflammatory T helper 1 (Th1) cytokines IFN-γ and TNF-α (219, 226). Enhances T cell IL-2 secretion and proliferation (232). Favors Th17 differentiation and IFN-γ production (218). Truncated variant of NK1R with a lower affinity to SP prevents lymphocyte overactivation (219). NK1R downstream signaling in NK cells inhibit their degranulation and cytotoxicity by reducing intracellular calcium flux and pERK (233). Enhances B cell Ig secretion (219).

Myeloid cell function
Increases human monocyte secretion of IL-6, IL-23, and TNF-Like 1A (218). Promotes innate inflammation upon secretion following tissue damage, infection or stress (226).

Clinical Implications
In diseases associated with chronic inflammation, antagonism of the SP-NK1R system has been studied as a therapeutic intervention (219, 236). SP has a major impact on the pathology of fatal asthma. Asthma patients typically have increased SP-secreting non-adrenergic non-cholinergic (NANC) nerves and express higher levels of NK1R within the respiratory tract, which results in bronchoconstriction, mucus accumulation, vasodilation, and alveolus leakage (219, 237). SP promotes neutrophil chemotaxis to the lung by upregulating the expression of integrins for extravasation, chemokine receptors, degranulation, respiratory burst, IL-1β, and TNFα secretion (219, 238, 239). Another contributing factor is the inability of most asthma patients to produce sufficient amounts of neutral endopeptidase (NEP) to metabolize SP to an inactive compound (237). Thus, to attenuate immune cell recruitment and inflammation of the respiratory tract, NK1R antagonists such as CP96345 serve as potential therapeutic agents besides corticosteroid administration (226). Other contributors to SP-associated respiratory disease involve persistent infection by pathogens such as respiratory syncytial virus (RSV) and cigarette smoke. While virus infection results in constant inflammation attempting to trigger pathogen clearance, cigarette smoke...
induces NANC nerves to release SP and downregulate airway neutral endopeptidase activity (240, 241).

Similarly, in IBD SP-secreting NANC nerves in the enteric nervous system regulate GI contractility, permeability, and immune responsiveness. Unlike IBD, dermatitis involves inflammation due to physical stress such as scratches or lesions on the skin that result in SP release from NANC within the dermis and facilitate leukocyte recruitment to the target site causing swelling, itching, and redness. This effect is more pronounced in atopic dermatitis patients, for they generally have increased SP-secreting nerves and, thus, a higher concentration of SP in the skin (242, 243). In psoriasis patients also, SP is increased in psoriatic plaques and is responsible for IL-32 synthesis in keratinocytes, which in turn release pro-inflammatory cytokines and activate mast cells. The increased presence of inflammatory mediators and the concentration of SP may predict the severity of psoriasis (244). Likewise, arthritis exhibits a dense innervation of SP-secreting nerves in the joints with synoviocytes expressing abnormally high levels of NK1R. Accordingly, increased SP in the synovial fluid can lead to persistent inflammation of joints (219, 245, 246). In Type I and II diabetes models, treatment with SP reduced pancreatic β-cell destruction by decreasing activation of pancreatic islet cells, which are responsible for β-cell apoptosis (247). In cancer patients, treatment with NK1R antagonist, aprepitant, is used to prevent the nausea and vomiting that accompany chemotherapy (248).

**Glutamate**

L-glutamate, an anion of glutamic acid (2-aminobutyric acid; Glu), is one of the most abundant excitatory neurotransmitter present in every type of animal that has a nervous system, including the lower marine invertebrate ctenophores (249). It accounts for over 90% of the synaptic connections in vertebrates (250). It is synthesized from glutamine in the CNS by the enzyme glutaminase, and from α-ketoglutaric acid produced in the citric acid cycle. Because of its role in synaptic plasticity, Glu mediates cognitive processes of learning and memory formation in the CNS (251). In the peripheral nervous system (PNS), Glu regulates nociception as well as cardiovascular, respiratory, reproductive, and immune functions (104).

Glu is present in nearly all organs and tissues of the body as a non-essential amino acid. This made its function as a neurotransmitter difficult to be accepted until injections of Glu into the cerebral ventricles of dogs caused them to have seizures (252). It is released from synapses at high concentrations (10⁻⁵ M) or circulate in the blood plasma at lower concentrations (10⁻⁷-10⁻⁴ M) (253). Since excessive Glu can cause excitotoxicity that induces cell death, it is tightly regulated in the brain as well as in the periphery. It is actively transported out of the nervous system by a high affinity transport system, which maintains its concentration in brain fluids constant (254).

There are two receptor families for Glu: Metabotropic glutamate receptors (mGluRs) and ionotropic glutamate receptors (iGluRs). The metabotropic family includes GPCRs acting through second messenger systems to create slow sustained effects on their targets. There are eight mGluRs divided into three subgroups. Group I receptors (mGluR1 and mGluR5) are coupled to Gq that increases IP3 and diacyl glycerol by activating phospholipase C, and group II (mGluR2 and mGluR3) and III (mGluR4, mGluR6, mGluR7, and mGluR8) are coupled to Gi/Go that decreases CAMP levels by inhibiting adenyl cyclase (255). Both CNS and PNS use mGluRs (253).

The ionotropic receptors comprise three families that open membrane channels to allow ions to pass through when cells are activated. There are three types of iGluRs: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR), N-methyl-D-aspartate receptors (NMDAR), and kainate receptors (KARs). AMPARs are most abundant and ubiquitously expressed and are specialized for fast excitation. They increase membrane permeability for Na⁺ and K⁺ and can produce excitatory electrical pulses in the synapses in a fraction of a millisecond after being stimulated. AMPAR are comprised of homo- or heterotetramers of GluA1, GluA2, GluA3, and GluA4 subunits. Glu binds to two or more of the AMPAR subunits that allow the ion channel to open for Ca²⁺/Na⁺ influxes or K⁺ efflux, except they inhibit Ca²⁺ influx if GluA2 is involved (253). NMDARs are voltage-gated receptors that increase membrane permeability for Ca²⁺ when activated. They are predominantly expressed in the CNS for learning and memory. They exist as hetero-oligomers comprised of two GluN1 subunits and a combination of GluN2A, GluN2B, GluN2C, GluN2D, GluN3A, and GluN3B, which serve as regulatory subunits to form a tetramer or pentamer. Glu has higher affinity to AMPAR than to NMDAR (253). KARs are homo or heterotetramers comprised of GluK1, GluK2, GluK3, GluK4, and GluK5 subunits that, like AMPARs, also facilitate Na⁺ influx and K⁺ efflux. KARs are restricted to the brain and their functions are largely unknown.

The expression of GluRs and Glu transporters in lymphoid and myeloid cells, as well as the concentration of Glu in which immune cells are exposed to, can induce a pro or anti-inflammatory response (253, 256–259). While GluRs are expressed mostly on lymphoid cells, Glu transporters are prevalent in antigen presenting cells such as DC and macrophages. Various effects of Glu signaling in immune cells are summarized in Table 4 with Glu-mediated immune cell-to-cell communication depicted in Figure 4.

**Immunostimulatory Effects**

Activation of AMPAR induces β-integrin-mediated T cell adhesion to fibronectin and laminin. It also increases the CXCR4-mediated peripheral T cell chemotactic migration toward the chemokine CXCL12 (88). Stimulation of iGluRs during human T cell activation increases Ca²⁺ influx, IL-2 secretion and IL-2 receptor upregulation (265, 266). The iGluR-mediated Ca²⁺ influx requires negative membrane potential through a voltage-gated K⁺ channel Kᵥ1.3 that is activated by Glu (264). The activation of mGluRs also increases Ca²⁺ influx (266, 267). Group I mGluRs prevent the activation-induced cell death by decreasing FasL expression that is normally expressed on activated T cells (268, 269). Thus, while iGluRs appear to
TABLE 4 | Summary of the effects of glutamate on immune cell responses.

| Neurotransmitter | Receptors | Target immune cells | Implications in disease |
|------------------|-----------|---------------------|------------------------|
| Glutamate        | AMPAR     | Neutrophil           | Seizures               |
|                  | (GluA1-4) | Macrophage           | Epilepsy               |
|                  | NMDAR     | DC                  | Encephalomyelitis       |
|                  | (GluN1, GluN2A-D, GluN3A-B) | T cell | Multiple sclerosis |
|                  | KAR       | B cell              | Cancer                 |
|                  | (GluK1-5) |                     |                        |
|                  | mGluR1-8  |                     |                        |

Cellular adhesion and homing

AMPAR signaling induces β2-integrin-mediated T cell adhesion to fibronectin and laminin (88)
AMPAR signaling increases the CXCR4-mediated T cell chemotactic migration toward chemokine CXCL12 (88)
mGluR1 signaling induces neutrophil transmigration (260)

Lymphocyte function

Naive T cells constitutively express GluA3 and mGluR5 receptors (88, 261)
Activated T cells express mGluR1,5 and NMDAR GluN1 and/or GluN2B subunits (253)
NMDARs are upregulated on activated T cells to compensate for GluA3 downregulation due to autocrine/paracrine granzyme B-mediated proteolytic cleavage (262)
GluN1 is upregulated on CD4+ T cells, and leads to T_{H1} cell death and prevalence of T_{H2} responses (263)
iGluR mediates Ca^{2+} influx through a voltage-gated K+ channel K_{v}1.3 (264), and increases IL-2 secretion and IL-2 receptor in T cells (265, 266)
mGluR activation increases Ca^{2+} influx in T cells (266, 267)
mGluR1,5 signaling prevents the activation-induced cell death of activated T cells by decreasing FasL expression (268, 269)
mGluR1 signaling increases PI3K-Akt and ERK1/2 signaling, and promotes T cell activation, proliferation and secretion of Th1 cytokines IFN-γ, TNFα, IL-2, and IL-6 (261)
mGluR6 signaling inhibits T cell activation and proliferation through increased cAMP levels that suppress the activation of Ras/ERK, JNK, and NFκB but activates C-terminal Src kinase (273)
Glu production from glutamine hydrolysis produces epigenetic effects on chromatin accessibility and gene expression to promote Th17 but constrain T_{H1} and effector T cell differentiation (271)
Proteolytic breakdown of GluA3 into circulation facilitates the production of autoantibodies (262, 272)

Dendritic cell maturation and myeloid cell function

Mature DCs release Glu through their plasma membrane-expressed Xc-cystine-glutamate antiporter (273)
DCs express transmembrane excitatory amino acid transporters that regulate Glu extracellular concentrations (270, 274)
mGluR1 signaling upregulates myeloid cell production of inflammatory chemoattractants such as CXCL1, IL-6, and IL-8 (260)

Glu, Glutamate; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors; NMDAR, N-methyl-D-aspartate receptors; KAR, kainate receptors; iGluR, Ionotropic glutamate receptors; mGluR, Metabotropic glutamate receptors; PI3K, Phosphatidylinositol 3-kinase; Akt, Protein kinase B.

support early events of TCR signaling through Glu-activated K_{v}1.3 K+ channels, mGluR signaling sustains T cell activation and survival.

Naive T cells constitutively express GluA3 and mGluR5 (88, 261). In contrast, activated peripheral blood T cells express mGluR1,5 as well as GluN1 and/or GluN2B subunits (253). GluN1 is upregulated upon activation in human T cells to increase Ca^{2+} influx (275). NMDARs are upregulated on activated T cells most likely to compensate for GluA3 downregulation due to autocrine/paracrine granzyme B-mediated proteolytic cleavage (262). Furthermore, mature human DCs release significant amounts of Glu through their plasma membrane-expressed cystine-glutamate antiporter (xCT) (273). DCs also express transmembrane excitatory amino acid transporters (EAAT) that regulate extracellular concentrations of Glu to manage its excitotoxicity (270, 274). EAATs also function as antiporters on an electrochemical gradient of Na+, K+, and H+ concentrations, whereby one molecule of Glu is imported along with three Na+ and one H+ in exchange of one K+ export. In the presence of DC’s secreted Glu, while T cell activation is inhibited by an increased expression of mGluR5 (270), upregulation of mGluR1 in activated T cells counteracts its function (261). After productive Ag presentation by DC, mGluR1 signaling in T cells enhances their proliferation and secretion of T_{H1} pro-inflammatory cytokines. Depletion of Glu or mGluR1 blockade by antagonist CPCCOEt decreases human T cell proliferation and T_{H1} differentiation, and reduces IFN-γ, TNFα, IL-2, and IL-6 secretion (273). Moreover, activated T cells need to resist quiescence to develop and sustain effector functions. Glu plays a critical metabolic role to meet the energy demands of this activity. In addition, autocrine Glu impacts initial events during GluR-TCR interaction (MTP de Aquino, Hodo et al., manuscript in preparation). Activated T cells upregulate amino acid transporters (276) and enzymes that metabolize glutamine (277). Glu production upon glutamine hydrolysis by the enzyme glutaminase (278) produces epigenetic effects on chromatin accessibility and gene expression that promote T_{H17} but constrain T_{H1} and effector T cell differentiation (271). Accordingly, Glu can impact T cell function at multiple levels of activation and differentiation.
Immunosuppressive Effects

GluR signaling can contribute to immunosuppression. GluN1 is rapidly upregulated on CD4+ T cells, and leads to T_{H1} cell death and prevalence of T_{H2} responses in humans, interfering with the resolution chronic inflammatory diseases (263). DC-derived Glu stimulating the constitutively expressed mGluR5 on T cells blocks their activation. This is mediated through increased cAMP levels that suppress the activation of Ras/ERK, JNK, and NFkB but activates C-terminal Src kinase (270). Conversely, mGluR5 antagonism with 2-methyl-6-(phenylethynyl)pyridine enhances T cell proliferation, suggesting that mGluR5 may hinder T cell proliferation (273).

Thus, differential expression of GluRs on T cells could be another layer of regulation wherein upon non-cognate antigen presentation by DC mGluR5 signaling blocks T cell activation and mGluR1 signaling promotes T cell activation following the cognate antigen–TCR binding. During DC–T cell interaction, Glu and its receptors could be an effective system for regulating T cell-mediated responses. Depending on the T cell state (resting or activated), selective Glu agonists could decide T cell fate by inducing excitotoxic death via ionotropic NMDAR, by stimulating activation and proliferation via mGluR1 or inhibiting T cell activation via mGluR5 (89, 270, 279).

Clinical Implications

The immunomodulatory ability of Glu through GluRs expressed on lymphocytes is of clinical importance in autoimmune inflammatory diseases and cancer. Uncontrolled seizures and epileptic episodes are known to be caused by excessive Glu, activating ionotropic GluA3 and GluN1/GluN2 receptors. Also, the granzyme-B-mediated proteolytic breakdown of T cell GluA3 into circulation may facilitate the production of autoantibodies.
by recognizing those residues as foreign antigens and contribute to the pathogenesis of autoimmune epilepsy (262, 272). Similarly, GluA3-overexpressing autoreactive T cells could attack the myelin of nerves causing demyelinating diseases such as MS (280). In a mouse model of encephalomyelitis, GluR-expressing T cells were autoreactive to myelin basic protein (88).

GluR signaling can contribute to inflammatory environment wherein cancer cells thrive to sustain their growth and survival. In addition, GluR signaling can promote onecogenic signaling. T-leukemia and T-lymphoma cells overexpress mGluRs that promote intracellular Ca^{2+} and proliferative genes c-fos/c-jun (253). AMPA iGluRs increase the expression of matrix metalloprotein-9 (MMP-9) via MMP-inducer CD147 and promote tumor cell metastasis (281). Prostate cancer cells express prostate-specific membrane antigen (PSMA), a Glu carboxypeptidase II, also called folate hydrolase-1, which hydrolyzes Glu from vitamin B9 (folic acid) and other substrates. Glu thus released binds to GPCR mGluR1 to activate PI3K-Akt signaling that supports prostate cancer progression. The use of inhibitors against mGluR1 and PSMA in preclinical models regressed prostate cancer (282). Similarly, mGluR1 signaling in triple negative breast cancers promotes their progression, angiogenesis, and metastasis (260, 283). Also, mGluR1 and NMDAR antagonists increased dendritic branching and decreased the motility, migration and proliferation of human melanoma cells in xenograft models by inhibiting dynamin GTPase and blocking ERK1/2 pathway (284–286). Apparently, mGluR1 signaling has a direct effect on tumor cell growth and survival but it also increases inflammation within the tumor microenvironment by upregulating the production of inflammatory chemoattractants such as CXCL1, IL-6, and IL-8 and inducing neutrophil transmigration (260). Thus, blocking specific GluR signaling, which is exploited by tumors to survive and grow, and enhance tumor-promoting inflammation, could be a potential therapeutic approach to treat tumors and some autoimmune inflammatory diseases.

5-HT modulation can alleviate various TNFα-mediated inflammatory diseases, including depressive disorders linked to systemic inflammation, GI disorders, atherosclerosis, rheumatoid arthritis, psoriasis, type II diabetes, schizophrenia, and AD. Activation of 5-HT_{2A} represents a potential therapeutic avenue for the treatment of such disorders. Moreover, the inhibitory effects of 5-HT_{2A} agonists on TNFα-mediated inflammation last many hours after the administration of TNFα (184). Consequently, 5-HT-agonist-based therapies may also treat inflammation-associated tissue stress or damage. In addition, 5-HT may alleviate symptoms associated with asthma, such as severe bronchoconstriction, mucus buildup, and eosinophil-induced inflammation in response to allergens (169, 175). Also, optimization of 5-HT signaling should be helpful in cancer as in tumor microenvironments tryptophan-catabolizing enzyme indoleamine 2,3-dioxygenase is present at high concentrations (216, 217), which may impair the synthesis of 5-HT and decrease 5-HT autocrine signaling in T cells (87).

In diseases associated with chronic inflammation, antagonism of the SP-NK1R system is under investigation as a therapeutic intervention (219, 236). In cancer patients, treatment with NK1R antagonists is already used to prevent the nausea and vomiting that accompany chemotherapy (248).

The expression of GluRs and Glu transporters in lymphoid and myeloid cells, as well as the concentration of Glu in which immune cells are exposed to, can induce a pro or anti-inflammatory response (253, 256–259). GluR signaling can impact T cell activation and differentiation at multiple levels. While iGluRs appear to support early events of TCR signaling through Glu-activated K_{1.3} K+ channels, mGluR signaling sustains T cell activation and effector function. Also, differential expression of GluRs on T cells could be another layer of regulation wherein upon non-cognate antigen presentation by DC mGluR5 signaling blocks T cell activation and mGluR1 signaling promotes T cell activation following the cognate antigen–TCR binding. Selective Glu agonists could affect T cell fate by inducing excitotoxic death via ionotropic NMDAR, by stimulating activation and proliferation via mGluR1 or inhibiting T cell activation via mGluR3 (89, 270, 279). Moreover, Glu can contribute to inflammatory microenvironment wherein cancer cells thrive to sustain their growth and survival. Blocking specific GluR signaling that is exploited by tumors to enhance tumor-promoting inflammation could be a potential therapeutic approach.

The neuroimmune approaches could be harnessed to improve antitumor responses in metastatic cancers where we are far from achieving the goal of preventive or therapeutic modality assuring relapse-free survival (287). Tumor cells show chemotaxis toward neurotransmitters such as DA and other catecholamines (288). A neuro-neoplastic synapse has been observed following direct interactions of tumor cells with nerve cells (289). Tumors may also initiate their own innervation by the release of neurotrophic factors. Studies have revealed a prominent role of neurotransmitters in the tumor microenvironment contributing to the pathogenesis of cancers (290). Besides the acute “fight or flight” response triggered by catecholamines from sympathetic nerve terminals and adrenal glands, the sympathetic

---

**THERAPEUTIC POTENTIAL OF NEUROIMMUNE MODULATION**

An extensive crosstalk between immune cells and neurotransmitters has a bearing on human diseases. It is appears that immune effects mediated by DA are first pro-inflammatory T_{H1}-type, then switching to anti-inflammatory T_{H2}-type following activation (104, 125). A collaborative DA-mediated network of DC, T_{H} and B cells along with decreased T_{reg} suppressive activity could be helpful in sustaining CD8^{+}B cells for T cell effector responses in immunosuppressive pathologies. Therefore, by selectively triggering specific DR on immune cells DA may provide for an immunological behavior-switching and context-dependent immune stimulatory or inhibitory responses. This offers DA-mediated treatment alternatives to mitigate neuropathologies and autoimmune diseases. DA agonists may help in brain disorders such as PD whereas specific DR antagonists could help alleviate MS, schizophrenia, AD, colitis, and IBD.
Prospective neuroimmunotherapy scheme to optimize immune function in cancer and autoimmune pathologies. A crosstalk between immune cells and the central nervous system (CNS) has a bearing on human diseases. This offers treatment alternatives to mitigate cancer, neuropathologies and autoimmune diseases. The neurotransmitters present a high potential to act as therapeutic supplements to optimize the function of immune cells including eosinophils (Eo), neutrophils (N), macrophages (Mφ), innate lymphoid cells (ILC), dendritic cells (DC), or T cells. Some immune cells such as platelets (P) serve as stores of neurotransmitters. Select neurotransmitter agonists or antagonists could be developed and tested in combination with other therapeutic modalities to suppress or stimulate immune responses, respectively. Such an optimized neuroimmunotherapy could be helpful in debilitating chronic immunopathologies.

Activation of neurotransmitter receptors on lymphocytes by select neurotransmitters can modulate their migration and homing as well as differentiation, cytokine secretion, proliferation, survival, or effector function. As an example, adoptive T cell therapy for cancers can be improved by treating harvested tumor-infiltrating lymphocytes (TIL) with select neurotransmitter agonists or antagonists in vitro before transfer. Alternatively, neurotransmitter agonists or antagonists can be injected into the solid tumors to manipulate T cells or innate lymphoid cells (ILC) such as NK cells in situ. Optimization of such neuroimmunotherapy approaches could provide more effective holistic therapeutic benefits.

Dependent on the tissue-specific context, neurotransmitters are either immunostimulatory or immunosuppressive to peripheral immune responses. Various inflammatory pathologies including tumor microenvironment are integrated with the neural, immune, and endocrine systems. DA, 5-HT, SP, and Glu have pro-inflammatory effects on immune cells. On one hand, these pro-inflammatory effects may exacerbate disease severity, on the other, they may be channelized to reverse immunosuppression in chronic diseases. Moreover, neurotransmitter receptors have multiple subtypes that can be selectively triggered to elicit different types of immune responses. A neurotransmitter binding to a receptor on one subset of immune cells can promote an immunostimulatory response while promoting an inhibitory response in another immune subset depending on the repertoire of receptors and signaling targets involved in the downstream cascade of events. For example, in one nervous system can regulate gene expression in the tumor microenvironment (291). Although the SNS-mediated gene regulation or molecular mobility and defense programs have been correlated with tumor progression and metastasis (291, 292), they can be manipulated to cause tumor regression (293, 294). SNS ablation in an acute myelogenous leukemia model caused infiltration of leukemic cells into the bone marrow (294), suggesting separate mesenchymal niche activities for malignant and healthy hematopoietic stem cells in the bone marrow.

In head and neck cancer patients, adoptive transfer of peripheral blood T cells treated with Glu and DA promoted their CXCL12-guided migration to autologous tumors and elevated the expression of TCR downstream molecules (295). Another study showed that stimulation of the reward system through dopaminergic neurons in ventral tegmental area decreased tumor growth in mouse models by reducing myeloid-derived suppressor cells and increasing granzyme-B expression in tumor-infiltrating CD8+ T cells. A strong connection also exists between the mental state of the patient and cancer resolution by the immune system (12).

The neurotransmitters thus have a high potential to act as therapeutic supplements to boost or optimize immune cell responses. Neurotransmitters or their selective agonists or antagonists could be developed and tested in combination with other therapeutic modalities to suppress or stimulate immune responses, respectively (Figure 5). Such an optimized “neuroimmunotherapy” could be very helpful in debilitating chronic immunopathologies.
condition a neurotransmitter may activate migration, cytokine secretion, or integrin expression on naïve T cells while the same neurotransmitter may inhibit these functions when T cells have already been primed or stimulated. The concentration of neurotransmitters in circulation or in the immediate tissue vicinity may also determine the outcome of the elicited immune responses.

From an evolutionary perspective, the concerted activity of the nervous and immune systems is integral to tissue, organ and organismal health. The nervous system senses inflammatory immune responses. The vicinity may also determine the outcome of the elicited release of neurotransmitters in circulation or in the immediate tissue

...and organismic health. The nervous system senses inflammatory immune responses. The nervous system senses inflammatory immune responses. The vicinity may also determine the outcome of the elicited release of neurotransmitters in circulation or in the immediate tissue vicinity may also determine the outcome of the elicited immune responses.

...and organismic health. The nervous system senses inflammatory immune responses. The nervous system senses inflammatory immune responses. The vicinity may also determine the outcome of the elicited release of neurotransmitters in circulation or in the immediate tissue vicinity may also determine the outcome of the elicited immune responses.

...and organismic health. The nervous system senses inflammatory immune responses. The nervous system senses inflammatory immune responses. The vicinity may also determine the outcome of the elicited release of neurotransmitters in circulation or in the immediate tissue vicinity may also determine the outcome of the elicited immune responses.

...and organismic health. The nervous system senses inflammatory immune responses. The nervous system senses inflammatory immune responses. The vicinity may also determine the outcome of the elicited release of neurotransmitters in circulation or in the immediate tissue vicinity may also determine the outcome of the elicited immune responses.
20. Ginhoux F, Gualillo M. Tissue-resident macrophage ontogeny and homeostasis. *Immunity.* (2016) 44:439–49. doi: 10.1016/j.immuni.2016.02.024

21. Li Q, Barres BA. Microglia and macrophages in brain homeostasis and disease. *Nat Rev Immunol.* (2018) 18:225–42. doi: 10.1038/nri.2017.125

22. Gahany I, Muller PA, Feighery L, Oliveira TY, Costa-Pinto FA, Mucida D. Neuro-immune interactions drive tissue programming in intestinal macrophages. *Cell.* (2016) 166:378–91. doi: 10.1016/j.cell.2015.12.013

23. Zetterstrom BE. Effect of denervation on blood flow in the dog spleen during haemorrhagic shock. *Acta Chir Scand.* (1973) 119:111–6.

24. Greenway CV, Stark RD. Vascular responses of the spleen to rapid haemorrhagic shock in the anaesthetized cat. *J Physiol.* (1969) 204:169–79. doi: 10.1113/jphysiol.1969.sp008906

25. Foster SL, Seehus CR, Woof CJ, Talbot S. Sense and immunity: context-dependent neuro-immune interplay. *Front Immunol.* (2017) 8:1463. doi: 10.3389/fimmu.2017.01463

26. Dulken BW, Buckley MT, Navarro Negrodo P, Saligrama N, Cayrol R, Leeman DS, et al. Single-cell analysis reveals T cell infiltration in old neurogenic niches. *Nature.* (2019) 571:205–10. doi: 10.1038/s41586-019-1362-5

27. Ito M, Komai K, Mise-Omata S, Iizuka-Koga M, Noguchi Y, Kondo T, et al. Brain regulatory T cells suppress apoptosis and potentiate neurological recovery. *Nature.* (2019) 565:246–50. doi: 10.1038/s41586-018-0824-5

28. Barnès MA, Carson MJ, Nair MG. Non-traditional cytokines: how catecholamines and adipo-kinases influence macrophages in immunity, metabolism and the central nervous system. *Cytokine.* (2015) 72:210–9. doi: 10.1016/j.cyto.2015.01.008

29. Nguyen KD, Qiu Y, Cui X, Goh YP, Mwangi J, David T, et al. Alternately activated macrophages produce catecholamines to sustain adaptive thermogenesis. *Nature.* (2011) 480:104–8. doi: 10.1038/nature10653

30. Besedovsky H, del Rey A, Sorkin E, Dinarello CA. Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. *Science.* (1986) 233:652–4. doi: 10.1126/science.3014662

31. Turnbull AV, Rivier C. Regulation of the HPA axis by cytokines. *Brain Behav Immun.* (1995) 9:233–5. doi: 10.1006/brbi.1995.1026

32. Besedovsky HO A. del Rey: the cytokine-HPA axis feed-back circuit. *Brain Behav Immun.* (1995) 9:233–5. doi: 10.1006/brbi.1995.1026

33. Brooks BD, Lemos BD, Gerke VC, Zetterstrom BE. Effect of denervation on blood flow in the dog spleen during haemorrhagic shock. *Acta Chir Scand.* (1973) 119:111–6.

34. Dominguez-Gerpe L. Stress-induced alterations in the programmed natural killer cell cytotoxicity. *Brain Behav Immun.* (2019) 80:238–46. doi: 10.1016/j.bbi.2019.06.064

35. Savino W, Arzt E, Dardenne M. Immunoneuroendocrine connectivity: the paradigm of the thymus-hypothalamic/pituitary axis. *Neuroimmunomodulation.* (1999) 6:126–36. doi: 10.1159/000026372

36. Benes D, Lin L, McAlister WA, Inness KA, Sutherland TK, Lapi N, et al. Early activation of the hypothalamic-pituitary-adrenal-axis in very-low-birth-weight infants with small thymus at birth. *J Matern Fetal Neonatal Med.* (2008) 21:251–4. doi: 10.1080/14767050801927871

37. Blalock JE, Smith EM, Meyer WJ 3rd. The pituitary-adrenocortical axis and the immune system. *Clin Endocrinol Metab.* (1985) 14:1021–38. doi: 10.1016/S0009-836X(11)82103-6

38. Shanker. Is thymus redundant after adulthood? *Immunol Lett.* (2004) 91:79–86. doi: 10.1016/j.imlet.2003.12.012

39. Savino W, Arzt E, Dardenne M. Immunoneuroendocrine connectivity: the paradigm of the thymus-hypothalamic/pituitary axis. *Neuroimmunomodulation.* (1999) 6:126–36. doi: 10.1159/000026372

40. Berczi I. The stress concept and neuroimmunomodulation in modern biology. *Annu N Y Acad Sci.* (1989) 581:3–12. doi: 10.1111/j.1749-6632.1989.tb08969.x

41. de Felice C, Totti P, Musaro M, Peruzzi L, Paffetti P, Pasqui L, Magaldi R, et al. Early activation of the hypothalamic-pituitary-adrenal-axis in very-low-birth-weight infants with small thymus at birth. *J Matern Fetal Neonatal Med.* (2008) 21:251–4. doi: 10.1080/14767050801927871

42. Reardon C. Neuro-immune interactions in the cholinergic anti-inflammatory reflex. *Immunol Lett.* (2016) 178:92–8. doi: 10.1016/j.imlet.2016.08.006

43. Guoyt M, Simon T, Panzolini C, Ceppo F, Daoudlian D, Murris E, et al. Apical splenic nerve electrical stimulation discloses an anti-inflammatory pathway relying on adrenergic and nicotinic receptors in myeloid cells. *Brain Behav Immun.* (2019) 80:238–46. doi: 10.1016/j.bbi.2019.03.015

44. Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature.* (2000) 405:458–62. doi: 10.1038/35031700

45. Hodo et al. Therapeutic Prospects of Neuroimmune Modulation
63. Wang H, Yu M, Ochani M, Amella CA, Tanovic M, Susarla S, et al. Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. *Nature*. (2003) 421:384–8. doi: 10.1038/nature01339

64. Rosas-Ballina M, Olofsson PS, Ochani M, Valdes-Ferrer SI, Levine YA, Beardon C, et al. Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. *Science*. (2011) 334:98–101. doi: 10.1126/science.1209985

65. Chavan SS, Pavlov VA, Tracey KJ. Mechanisms and therapeutic relevance of neuro-immune communication. *Immunity*. (2017) 46:927–42. doi: 10.1016/j.immuni.2017.06.008

66. Huston JM, Rosas-Ballina M, Xue X, Dowling O, Ochani K, Ochani M, et al. Cholinergic neural signals to the spleen down-regulate leukocyte trafficking via CD11b. *J. Immunol*. (2009) 183:552–9. doi: 10.4049/jimmunol.0802684

67. Wu H, Li L, Su X. Vagus nerve through alpha7 nAChR modulates lung infection and inflammation: models, cells, and signals. *Biomed Res Int*. (2014) 2014:283525. doi: 10.1155/2014/283525

68. Zanos TP, Silverman HA, Levy T, Tsaava T, Battinelli E, Lorraine PW, et al. Regulation of learning and memory by meningeal immunity: a key role for IL-17A pathway in mice promotes autism-like phenotypes in *J. Neurosci*. (2017) 37:731–43. doi: 10.1152/jn.01100.2017

69. Goehler LE, Relton JK, Dripps D, Kiechle R, Tartaglia N, Maier SE, et al. Vagal paraganglia bind biotinylated interleukin-1 receptor antagonist: a possible mechanism for immune-to-brain communication. *Brain Res Bull*. (1997) 43:537–64. doi: 10.1016/S0361-9230(97)00020-8

70. Filiano AJ, Xu Y, Tutisson NJ, Marsh RL, Baker W, Smirnov I, et al. Unexpected role of interferon-gamma in regulating neuronal connectivity and social behaviour. *Nature*. (2016) 535:425–9. doi: 10.1038/nature18626

71. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Neurosci*. (2016) 16:22–34. doi: 10.1038/nri.2015.5

72. Derecki NC, Cardani AN, Yang CH, Quinnies KM, Crifhiel A, Lynch KR, et al. Regulation of learning and memory by meningeal immunity: a key role for IL-4. *J Exp Med*. (2010) 210:1067–80. doi: 10.1084/jem.20091419

73. Baruch K, Deczkowska A, David E, Castellano JM, Miller O, Kertesz A, et al. Aging. Aging-induced type I interferon response at the choroid plexus negatively affects brain function. *Science*. (2014) 346:89–93. doi: 10.1126/science.1252945

74. Kostanyan IA, Merkulova MI, Navolotskaya EV, Nurieva RI. Study of CNS-specific T cells shape brain immunity at the choroid plexus shifts toward destructive Th2 subtypes and neuronal nicotinic acetylcholine receptor subunits in human mononuclear leukocytes and leukemia cell lines. *Neurosci Lett*. (1999) 266:17–20. doi: 10.1016/S0304-3909(99)00259-1

75. Baruch K, Schwartz M. CNS-specific T cells shape brain function via the choroid plexus. *Brain Behav Immun*. (2013) 34:1–6. doi: 10.1016/j.bbi.2013.04.002

76. Baruch K, Ron-Harel N, Gal H, Deczkowska A, Shifrut E, Ndifon W, et al. CNS-specific immunity at the choroid plexus negatively affects brain function. *Brain Behav Immun*. (2013) 31:705–13. doi: 10.1016/j.bbi.2013.04.002

77. Choi GB, Yim YS, Wong H, Kim S, Kim H, Kim SV, et al. The maternal interleukin-17a pathway in mice promotes autoimmune-like phenotypes in offspring. *Science*. (2016) 351:933–9. doi: 10.1126/science.aad3014

78. Kostanyan IA, Merkulova MI, Navolotskaya EV, Nurieva RI. Study of CNS-specific T cells shape brain function via the choroid plexus. *Brain Behav Immun*. (2013) 34:1–6. doi: 10.1016/j.bbi.2013.04.002

79. Baruch K, Ron-Harel N, Gal H, Deczkowska A, Shifrut E, Ndifon W, et al. Diversity of mRNA expression for muscarinic acetylcholine receptor subtypes and neuronal nicotinic acetylcholine receptor subunits in human mononuclear leukocytes and leukemia cell lines. *Neurosci Lett*. (1999) 266:17–20. doi: 10.1016/S0304-3909(99)00259-1

80. Pettito JM, Huang Z, McCarthy DB. Molecular cloning of NPY-Y1 receptor cDNA from rat splenic lymphocytes: evidence of low levels of mRNA expression and [125I]NPY binding sites. *J. Neuroimmunol*. (1994) 49:81–6. doi: 10.1016/0165-5728(94)90234-8

81. Marino F, Cosentino M. Adrenergic modulation of immune cells: an update. *Amino Acids*. (2013) 45:53–71. doi: 10.1007/s00726-011-1186-6

82. Kiossis D, Pachnis V. Immune and nervous systems: more than just a superficial similarity? *Immunology*. (2009) 131:705–10. doi: 10.1016/j.immuni.2009.09.009

83. Park CK, Xu ZZ, Berta T, Han Q, Chen G, Liu XJ, et al. Extracellular microRNAs activate nociceptor neurons to elicit pain via TLR7 and TRPA1. *Neuron*. (2014) 82:47–54. doi: 10.1016/j.neuron.2014.02.011

84. Steinfeld BE, Silverman HA, Robbati S, Gunasekaran MK, Tsawa T, Battinelli E, et al. Cytokine-specific neurograms in the sensory vagus nerve. *Biomed Res Int*. (2016) 2016:174207. doi: 10.1155/2016/2016:174207

85. Watanabe Y, Nakayama T, Nakagubo D, Hieshima K, Jin Z, Katou F, et al. Dopamine selectively induces migration and homing of naive
115. Neve KA, Seamans JK, Trantham-Davidson H. Dopamine

116. Takahashi N, Nagai Y, Ueno S, Saeki Y, Yanagihara T. Human

117. Borroto-Escuela DO, Rodriguez D, Romero-Fernandez W, Kapla J, Jaithe M, et al. Dopamine by itself activates either D2, D3, or D1/D5 dopaminergic receptors in normal human T-cells and triggers an autocrine/paracrine inhibitory functional loop. *Blood*. (2007) 109:632–42. doi: 10.1182/blood-2006-01-028423

118. Nakano K, Higashi T, Takagi R, Hashimoto K, Tanaka Y, Matsumita S. Dopaminergic modulation of oxidative stress and apoptosis in human peripheral blood lymphocytes: evidence for a D1-like receptor-dependent protective effect. *Free Radic Biol Med*. (2004) 36:1233–40. doi: 10.1016/j.freeradbiomed.2004.02.065

119. McKenna F, McLaughlin PJ, Lewis BJ, Sibbring GC, Cummerson JA, Bowen-Jones D, et al. Dopamine receptor expression on human T- and B-lymphocytes, monocytes, neutrophils, eosinophils and NK cells: a flow cytometric study. *J Neuroimmunol*. (2002) 132:34–40. doi: 10.1016/S0165-5728(02)02880-1

120. Nakano K, Higashi T, Hashimoto K, Takagi R, Tanaka Y, Matsumita S. Antagonizing dopamine D1-like receptor inhibits TH1 cell differentiation: preventive and therapeutic effects on experimental autoimmune encephalomyelitis. *Biochem Biophys Res Commun*. (2008) 373:286–91. doi: 10.1016/j.bbrc.2008.06.012

121. Kipnis J, Cardon M, Avidan H, Lewitus GM, Mordechay S, et al. Dopamine, through the extracellular signal-regulated kinase pathway, downregulates CD4+CD25+ regulatory T-cell activity: implications for neurodegeneration. *J Neurosci*. (2004) 24:6133–43. doi: 10.1523/JNEUROSCI.0600-04.2004

122. Papa I, Saliba D, Ponzoni M, Bustamante S, Canete PF, Gonzalez-Figueroa P, et al. TFH-derived dopamine accelerates productive synapses in germinal centres. *Nature*. (2017) 547:318–23. doi: 10.1038/nature23013

123. Vidal PM, Pacheco R. Targeting the dopaminergic system in autoimmunity. *J Neuroimmunol Pharmacol*. (2020) 15:57–73. doi: 10.1007/s11481-019-09834-5

124. Wang W, Cohen JA, Wallapp A, Trieu KG, Barrios J, Shao F, et al. Age-related dopaminergic innervation augments T helper 2-type allergic inflammation in the postnatal lung. *Immunity*. (2019) 17:1102–18.e7. doi: 10.2139/jsimm.388987

125. Besser MJ, Ganyor Y, Levite M. Dopamine by itself activates either D2, D3, or D1/D5 dopaminergic receptors in normal human T-cells and triggers the selective secretion of either IL-10, TNFαpha or both. *J Neuroimmunol*. (2005) 169:161–71. doi: 10.1016/j.jneuroim.2005.07.013

126. Bergquist J, Tarkowski A, Ekmam R, Ewing A. Discovery of endogenous catecholamines in lymphocytes and evidence for catecholamine regulation of lymphocyte function via an autocrine loop. *Proc Natl Acad Sci USA*. (1994) 91:12912–6. doi: 10.1073/pnas.91.26.12912

127. Ghosh MC, Mondal AC, Basu S, Banerjee S, Majumder J, Bhattacharya D, et al. Dopamine inhibits cytokine release and expression of tyrosine kinases, Lck and Fyn in activated T cells. *Int Immunopharmacol*. (2003) 3:1019–26. doi: 10.1016/S1567-5769(03)01000-0

128. Sarkar C, Das S, Chakraborty D, Chowdhury UR, Basu D, Dasgupta PS, et al. Cutting Edge: stimulation of dopamine D4 receptors induce T cell quiescence by up-regulating Kruppel-like factor-2 expression through inhibition of ERK1/2 ERK2 phosphorylation. *J Immunol*. (2006) 177:7525–9. doi: 10.4049/jimmunol.177.17.7525

129. Kipnis J, Cardon M, Avidan H, Lewitus GM, Mordechay S, et al. Dopamine-induced modulation of oxidative stress and apoptosis in human peripheral blood lymphocytes: evidence for a D1-like receptor-dependent protective effect. *Free Radic Biol Med*. (2004) 36:1233–40. doi: 10.1016/j.freeradbiomed.2004.02.065

130. Pacheco R, Prado CE, Barrientos MJ, Bernales S. Role of dopamine in the regulation of the A2A adenosine and D2 dopamine receptor heteromer. *Eur J Immunol*. (2009) 39:216:31. doi: 10.1002/eji.200830313

131. Cosentino M, Pacheco R, Prado CE, Barrientos MJ, Bernales S. Role of dopamine in the model of the A2A adenosine and D2 dopamine receptor heteromer. *Front Immunol*. (2018) 9:829. doi: 10.3389/fimmu.2018.00829

132. Mikulak J, Bozzo L, Pontarini E, Tentorio P, Hudspeth K, et al. Dopamine inhibits the effector functions of activated NK cells via the upregulation of the D5 receptor. *J Immunol*. (2014) 193:2792–800. doi: 10.4049/jimmunol.1401114

133. Cosentino M, Rasini E, Colombo C, Marino F, Blandini F, Ferrari M, et al. Dopaminergic modulation of oxidative stress and apoptosis in human peripheral blood lymphocytes: evidence for a D1-like receptor dependent protective effect. *Free Radic Biol Med*. (2004) 36:1233–40. doi: 10.1016/j.freeradbiomed.2004.02.065

134. Torres-Rosas R, Yehia G, Pena G, Mishra P, del Rocio Thompson-Bonilla M, Moreno-Eutimio MA, et al. Dopamine mediates vagal modulation of the immune system by electroacupuncture. *Nat Med*. (2014) 20:291–5. doi: 10.1038/nm.3479

135. Yan F, Wang L, Shi Y, Cao H, Liu L, Washington MK, et al. Berberine promotes recovery of colitis and inhibits inflammatory responses in colonic macrophages and epithelial cells in DSS-treated mice. *Am J Physiol Gastrointest Liver Physiol*. (2012) 302:G504–14. doi: 11.1152/ajpgi.00312.2011

136. Giorelli M, Livrea P, Trojano M. Dopamine fails to regulate activation of peripheral blood lymphocytes from multiple sclerosis patients: effects of IFN-beta. *J Interferon Cytokine Res*. (2005) 25:395–406. doi: 10.1089/jir.2005.25.395

137. Nakano K, Yamaoka K, Hanami K, Saito K, Sasaguri Y, Yanagihara N, et al. Dopamine induces IL-6-dependent IL-17 production via D1-like receptor on CD4 naive T cells and D1-like receptor antagonist SCH-23390 inhibits cartilage destruction in a human rheumatoid arthritis/SCID mouse chimera model. *J Immunol*. (2011) 186:3745–52. doi: 10.4049/jimmunol.1002475

138. Muller N. Inflammation in Schizophrenia: pathogenetic aspects and therapeutic considerations. *Schizophrenia Bull*. (2018) 44:973–82. doi: 10.1093/schbul/shy024

139. Cao W, Zheng H. Correction to: peripheral immune system in aging and Alzheimer's disease. *Mol Neurodegener*. (2018) 13:58. doi: s13024-018-0290-4

140. Bengel FM. Imaging targets of the sympathetic nervous system: an update. *Brain Behav Immun*. (2010) 24:525–8. doi: 10.1016/j.bbi.2009.10.015

141. Hodo et al. Therapeutic Prospects of Neuroimmune Modulation August 2020 | Volume 11 | Article 1869

Frontiers in Immunology | www.frontiersin.org 21 1869
140. Cao W, Zheng H. Peripheral immune system in aging and Alzheimer's disease. *Mol Neurodegener.* (2018) 13:51. doi: 10.1186/s13204-018-0284-2

141. Phan S, Loike JD, Przedborski S. Neurodegeneration and inflammation in Parkinson's disease. *Parkinsonism Relat. Disord.* (2012) 18(Suppl.1):S207–9. doi: 10.1016/S1353-8020(11)70046-4

142. Boneberg EM, von Seydlitz E, Propper K, Watzl H, Rockstroh B, Illges H. D3 dopamine receptor mRNA is elevated in T cells of schizophrenic patients whereas D4 dopamine receptor mRNA is reduced in CD4+ T cells. *J Neuroimmunol.* (2006) 173:180–7. doi: 10.1016/j.jneuroim.2005.11.018

143. Barbanti P, Fabbrini G, Ricci A, Bruno G, Cerbo R, Bronzetti E, et al. Luigi Lenzi: reduced density of dopamine D2-like receptors on peripheral blood lymphocytes in Alzheimer's disease. *Mech Ageing Dev.* (2000) 120:65–75. doi: 10.1016/S0047-6374(00)00183-4

144. Bockhard V, Combadiere B, Prigent A, Laour Y, Perrin A, Beray-Berthat V, et al. Infiltration of CD4+ lymphocytes into the brain contributes to neurodegeneration in a mouse model of Parkinson disease. *J Clin Invest.* (2009) 119:182–92. doi: 10.1172/JCI36470

145. Gonzalez H, Contreras F, Prado C, Elgueta D, Franz D, Bernales S, et al. Dopamine receptor D3 expressed on CD4+ T cells favors neurodegeneration of dopaminergic neurons during Parkinson's disease. *J Immunol.* (2013) 190:5048–56. doi: 10.4049/jimmunol.1203121

146. Barbanti P, Fabbrini G, Ricci A, Cerbo R, Bronzetti E, Caronti B, et al. Increased expression of dopamine receptors on lymphocytes in Parkinson's disease. *Mov. Disorder.* (1999) 14:764–71. doi: 10.1002/1531-8257(19990915<75<6:AID-MDS100183>3.0.CO;2-W

147. Orr CE, Rowe DB, Mizuno Y, Mori H, Halliday GM. A possible role for humoral immunity in the pathogenesis of Parkinson's disease. *Brain.* (2005) 128:2665–74. doi: 10.1093/brain/awh625

148. Fiszer U. Does Parkinson's disease have an immunological basis? The evidence and its therapeutic implications. *BioDrugs.* (2011) 15:351–5. doi: 10.2165/00063030-200115060-00001

149. Ceselska A, Joniec I, Przybylowska A, Gromadzka G, Kurkowska-Jastrzebska I, Czlonkowska A, et al. Dynamics of expression of the mRNA for cytokines and inducible nitric synthase in a murine model of the Parkinson's disease. *Acta Neurobiol Exp.* (2003) 63:117–26.

150. Kurkowska-Jastrzebska I, Wronska A, Kohutnicka M, Czlonkowska A, Czlonkowska A. MHC class II positive microglia and lymphocytic infiltration are present in the substantia nigra and striatum in mouse model of Parkinson's disease. *Acta Neurobiol Exp.* (1999) 59:1–8.

151. Huser A, Rohwedder A, Apostolopoulos AA, Rohwedder A, Apostolopoulos AA, Feldman JM, Lee EM, Castleberry CA. Catecholamine and serotonin signalling - the gut and beyond. *Science.* (2018) 361:1126–8. doi: 10.1126/science.aaw1140

152. Feldman JM, Lee EM, Castleberry CA. Catecholamine and serotonin signalling - the gut and beyond. *Frontiers in Immunology.* www.frontiersin.org 22

153. Cools R, Roberts AC, Robbins TW. Serotoninergic regulation of emotional content and its therapeutic implications. *Trends Cogn Sci.* (2006) 10:293–6. doi: 10.1016/j.tibs.2006.01.004

154. Nakamura K, Sato T, Ohashi A, Hasegawa H. Role of a serotonin precursor in development of gut microvilli. *Am J Pathol.* (2012) 176:333–41. doi: 10.2353/ajpath.2008.070353

155. Millan MJ, Marin P, Bockaert J. Mannoury la cour: signaling at G-protein-coupled serotonin receptors: recent advances and future research directions. *Trends Pharmacol. Sci.* (2008) 29:454–64. doi: 10.1016/j.tips.2008.06.007

156. Idzko M, Panther E, Stratz C, Muller T, Bayer H, Zissel G, et al. The serotonergic receptors of human dendritic cells: identification and coupling to cytokine release. *J Immunol.* (2004) 172:6011–9. doi: 10.4049/jimmunol.172.10.6011

157. Nichols DE, Nichols CD. Serotonin receptors. *Chem Rev.* (2008) 108:1614–41. doi: 10.1021/cr078224o

158. Herr N, Bode C, Duerschmied D. The effects of serotonin in immune cells. *Front Cardiovasc Med.* (2017) 4:48. doi: 10.3389/fcvm.2017.00048

159. Kushnir-Sukhov NM, Gilfillan AM, Coleman JW, Brown JM, Bruening S, Thot M, et al. Metacrine: 5-hydroxytryptamine induces mast cell adhesion and migration. *J Immunol.* (2006) 177:6422–3. doi: 10.4049/jimmunol.177.9.6422

160. Muller D, Durk T, Blumenthal B, Grimm M, Cicko S, Panther E, et al. Idzko: 5-hydroxytryptamine modulates migration, cytokine and chemokine release and T-cell priming capacity of dendritic cells *in vitro* and in vivo. *PLoS ONE.* (2009) 4:e6453. doi: 10.1371/journal.pone.0006453

161. Durk T, Panther E, Muller T, Sorichter S, Ferrari D, Pizzirani C, et al. 5-Hydroxytryptamine modulates cytokine and chemokine production in LPS-primed human monocytes via stimulation of different 5-HT receptor subtypes. *Int Immunol.* (2005) 17:599–606. doi: 10.1093/intimm/dxh242

162. Boehme SA, Lio FM, Sikora L, Pandit TS, Lavrador K, Rao SP, et al. Cutting edge: serotonin is a chemotactic factor for eosinophils and functions additively with eotaxin. *J Immunol.* (2006) 177:6422–3. doi: 10.4049/jimmunol.177.9.6422

163. Mukulski Z, Zaslona Z, Cakarova L, Hartmann P, Wilhelm J, Tecott LH, et al. Serotonin activates murine alveolar macrophages through 5-HT2C receptors. *Am J Physiol Lung Cell Mol Physiol.* (2010) 299:L272–80. doi: 10.1152/ajplung.00032.2010

164. Yin J, Albert RH, Tretiakova AP, Jameson BA. 5-HT(1B) receptors play a prominent role in the proliferation of T-lymphocytes. *J Neuroimmunol.* (2006) 181:68–81. doi: 10.1016/j.jneuroim.2005.10.007

165. Inoue M, Okazaki T, Kitazono T, Mizushima M, Omata M, Ozaki S. The serotoninergic receptors of human dendritic cells: anatomy and behavioral function. *Am J Physiol Lung Cell Mol Physiol.* (2004) 287:L272–80. doi: 10.1152/ajplung.00032.2010

166. Bruening S, Toth M, et al. Metcalfe: 5-hydroxytryptamine modulates migration, cytokine and chemokine release and T-cell priming capacity of dendritic cells *in vitro* and in vivo. *PLoS ONE.* (2009) 4:e6453. doi: 10.1371/journal.pone.0006453

167. Yin J, Albert RH, Tretiakova AP, Jameson BA. 5-HT(1B) receptors play a prominent role in the proliferation of T-lymphocytes. *J Neuroimmunol.* (2006) 181:68–81. doi: 10.1016/j.jneuroim.2005.10.007

168. Boehme SA, Lio FM, Sikora L, Pandit TS, Lavrador K, Rao SP, et al. Cutting edge: serotonin is a chemotactic factor for eosinophils and functions additively with eotaxin. *J Immunol.* (2004) 173:3599–603. doi: 10.4049/jimmunol.173.6.3599

169. Monti E, Zaslona Z, Cakarova L, Hartmann P, Wilhelm J, Tecott LH, et al. Serotonin activates murine alveolar macrophages through 5-HT2C receptors. *Am J Physiol Lung Cell Mol Physiol.* (2010) 299:L272–80. doi: 10.1152/ajplung.00032.2010

170. Yin J, Albert RH, Tretiakova AP, Jameson BA. 5-HT(1B) receptors play a prominent role in the proliferation of T-lymphocytes. *J Neuroimmunol.* (2006) 181:68–81. doi: 10.1016/j.jneuroim.2005.10.007
179. Rinaldi A, Chiariavalli AM, Mian M, Zucca E, Tibiletti MG, Capella C, et al. Serotonin receptor 3A expression in normal and neoplastic B cells. Pathobiology. (2010) 77:129–35. doi: 10.1159/000292646

180. Mosnner R, Lesch KP. Role of serotonin in the immune system and in neuroimmune interactions. Brain Behav Immun. (1996) 12:249–71. doi: 10.1006/bbi.1998.0532

181. Chabbi-Achengli Y, Coman T, Collet C, Callebert J, Corcelli M, Lin NAu F Jr, Miller J, Saravia J, Ahlert T, Yu B, Happel KI, et al. Influence of cytokines. Exp Biol Med. (2016) 241:1540–50. doi: 10.1177/1535370216643769

182. Choquet D, Korn H. Dual effects of serotonin on a voltage-gated factor-alpha-induced inflammation with extraordinary potency. J Pharmacol Exp Ther. (2008) 327:316–23. doi: 10.1124/jpet.107.143461

183. Rinaldi A, Chiaravalli AM, Mian M, Zucca E, Tibiletti MG, Capella C, et al. Serotonin decreases HIV-1 replication in primary cultures of human macrophages through 5-HT(1A) receptors. Immunobiology. (2010) 215:186–97. doi: 10.1016/j.imbio.2010.07.001

184. Nazimek K, Bryniarski P, Bryk A, Myszk a H, et al. Altered serotonin transporter availability in patients with major depression. J Neuropsychopharmacol. (2008) 33:125–32. doi: 10.1038/jn.2008.80

185. Basterzi AD, Aydemir C, Kisa C, Aksaray S, Tuzer V, Yazici K, et al. IL-6 in human microglial MC-3 cells. Neuropharmacology. (2008) 55:1072–80. doi: 10.1016/j.neuropharm.2008.07.016

186. Nazimek K, Bryniarski P, Bryk A, Myszk a H, et al. Altered serotonin transporter availability in patients with major depression. J Neuropsychopharmacol. (2008) 33:125–32. doi: 10.1038/jn.2008.80

187. Maneglier B, Guillermijn GJ, Clayette P, Rogez-Kreuz C, Brew BJ, Dormont D, et al. Serotonin decreases HIV-1 replication in primary cultures of human macrophages through 5-HT(1A) receptors. Br J Pharmacol. (2008) 154:174–82. doi: 10.1038/bj.2008.80

188. Saad A, Shah A, Jeschke MG, Belo C, Qasim Hayat Murad S, et al. The role of serotonin during skin healing in post-thermal injury. Int J Mol Sci. (2018) 19:1034. doi: 10.3390/ijms19041034

189. Basterzi AD, Aydemir C, Kisa C, Aksaray S, Tuzer V, Yazici K, et al. IL-6 levels decrease with SSRI treatment in patients with major depression. Hum Psychopharmacol. (2005) 20:473–6. doi: 10.1002/hup.717

190. Lanquillon S, Krieg JC, Bening-Abu-Shach U, Vedder H. Cytokine production and treatment response in major depressive disorder. Neuropsychopharmacology. (2002) 20:270–9. doi: 10.1016/S0893-133X(00)00134-7

191. Roumestan C, Michel A, Bichon F, Portet K, Detoc M, Henriquez C, et al. Anti-inflammatory properties of desipramine and fluoxetine. Respir Res. (2007) 8:35. doi: 10.1186/1465-9211-8-35

192. Nazimek K, Kozlowski M, Bryniarski P, Strebol S, Bryk A, Myszk a H, et al. Repeatedly administered antidepressant drugs modulate humoral and cellular immune response in mice through action on macrophages. Exp Biol Med. (2016) 241:1540–50. doi: 10.1177/1535370216643769

193. Choquet D, Korn H. Modulation of voltage-dependent potassium channels in B lymphocytes. Biochem Pharmacol. (1988) 37:3797–802. doi: 10.1016/0006-2952(88)90058-5

194. Maes M. Major depression and activation of the inflammatory response system. Adv Exp Med Biol. (1999) 461:25–46. doi: 10.1016/S0065-2611(00)00848-8

195. Muiller N, Schwarz MJ. The immune-mediated alteration of serotonin and glutamate: towards an integrated view of depression. Mol Psychiatry. (2007) 12:988–1000. doi: 10.1038/sj.mp.4002006

196. Iqbal M, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. Biol Psychiatry. (2010) 67:446–57. doi: 10.1016/j.biopsych.2009.09.033

197. Hesse S, Moeller F, Petroff D, Lobies D, Lührdt J, Regenthal R, et al. Altered serotonin transporter availability in patients with multiple sclerosis. Eur J Neurol. (2014) 21:48–55. doi: 10.1111/ene.12336

198. Spiller R. Serotonin and GI clinical disorders. Neuropharmacology. (2008) 55:1072–80. doi: 10.1016/j.neuropharm.2008.07.016

199. Maneglier B, Guillermijn GJ, Clayette P, Rogez-Kreuz C, Brew BJ, Dormont D, et al. Serotonin decreases HIV-1 replication in primary cultures of human macrophages through 5-HT(1A) receptors. Br J Pharmacol. (2008) 154:174–82. doi: 10.1038/bj.2008.80

200. Saad A, Shah A, Jeschke MG, Belo C, Qasim Hayat Murad S, et al. The role of serotonin during skin healing in post-thermal injury. Int J Mol Sci. (2018) 19:1034. doi: 10.3390/ijms19041034

201. Kenis G, Maes M. Effects of antidepressants on the production of cytokines. Int J Neuropharmacol. (2002) 5:401–12. doi: 10.1017/S146114570023164

202. Wang L, Wang L, Liu L, Qiao D, Baldwin DS, Hou R. Effects of SSRIs on peripheral inflammatory markers in patients with major depressive disorder: a systematic review and meta-analysis. Brain Behav Immun. (2019) 79:24–38. doi: 10.1016/j.bbi.2019.02.021

203. Nazimek K, Strobel S, Bryniarski P, Kozlowski M, Filipczak-Bryniarska I, Bryniarski K. The role of macrophages in anti-inflammatory activity of antidepressant drugs. Immunology. (2017) 222:823–30. doi: 10.1111/imi.12801

204. Gobin V, Van Steendam K, Denys D, Deforce D. Selective serotonin reuptake inhibitors as a novel class of immunosuppressants. Int Immunopharmacol. (2014) 18:148–56. doi: 10.1016/j.intimp.2014.02.030

205. Sluzewski A, Rybakowski JK, Łaciak M, Mackiewicz A, Sobieska M, Wiktorewicz K. Interleukin-6 serum levels in depressed patients before and after treatment with fluoxetine. Ann N Y Acad Sci. (1995) 762:474–8. doi: 10.1111/j.1749-6632.1995.tb32372.x
BDNF/leptin axis causes cancer remission and inhibition. *Cell.* (2010) 142:52–64. doi: 10.1016/j.cell.2010.05.029

294. Hanoun M, Zhang D, Mizoguchi T, Pinho S, Pierce H, Kunisaki Y, et al. Acute myelogenous leukemia-induced sympathetic neuropathy promotes malignancy in an altered hematopoietic stem cell niche. *Cell Stem Cell.* (2014) 15:365–75. doi: 10.1016/j.stem.2014.06.020

295. Saussez S, Laumbacher B, Chantrain G, Rodriguez A, Gu S, Wank R, et al. Towards neuroimmunotherapy for cancer: the neurotransmitters glutamate, dopamine and GnRH-II augment substantially the ability of T cells of few head and neck cancer patients to perform spontaneous migration, chemotactic migration and migration towards the autologous tumor, and also elevate markedly the expression of CD3zeta and CD3epsilon TCR-associated chains. *J Neural Transm.* (2014) 121:1007–27. doi: 10.1007/s00702-014-1242-y

296. Sun J, Singh V, Kajino-Sakamoto R, Aballay A. Neuronal GPCR controls innate immunity by regulating noncanonical unfolded protein response genes. *Science.* (2011) 332:729–32. doi: 10.1126/science.1203411

297. Mendez-Ferrer S, Lucas D, Battista M, Frenette PS. Haematopoietic stem cell release is regulated by circadian oscillations. *Nature.* (2008) 452:442–7. doi: 10.1038/nature06685

298. Heidt T, Sager HB, Courties G, Dutta P, Iwamoto Y, Zaltsman A, et al. Chronic variable stress activates hematopoietic stem cells. *Nat Med.* (2014) 20:754–8. doi: 10.1038/nm.3589

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Copyright © 2020 Hodo, de Aquino, Shimamoto and Shanker. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.*