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Review Article

Interaction of neurotransmitters and neurochemicals with lymphocytes

Daniel Kerage[a,b], Erica K. Sloan[c,d,e], Stephen R. Mattarollo[a], Pamela A. McCombe[f,g,*]

[a] The University of Queensland Diamantina Institute, Brisbane, Australia
[b] Transplant Research Program, Boston Children's Hospital, Boston, MA, United States of America
[c] Drug Discovery Biology Theme, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC 3052, Australia
[d] Division of Surgery, Peter MacCallum Cancer Centre, Melbourne, VIC 3000, Australia
[e] Cousins Center for Neuroimmunology, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, USA
[f] The University of Queensland Centre for Clinical Research, Royal Brisbane and Women's Hospital, Brisbane, Australia
[g] Royal Brisbane and Women's Hospital, Herston, Brisbane, Australia

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ABSTRACT

Neurotransmitters and neurochemicals can act on lymphocytes by binding to receptors expressed by lymphocytes. This review describes lymphocyte expression of receptors for a selection of neurotransmitters and neurochemicals, the anatomical locations where lymphocytes can interact with neurotransmitters, and the effects of the neurotransmitters on lymphocyte function. Implications for health and disease are also discussed.

1. Introduction

Cells of the nervous system communicate with each other by means of chemical messengers, termed neurotransmitters, that move across synapses to activate receptors on postsynaptic cells (Wilkinson and Brown, 2015). The brain also produces molecules (called neurochemicals) that act on receptors but do not fulfil the criteria for neurotransmitters. Since immune cells express receptors that can be stimulated by these neurotransmitters and neurochemicals, the nervous system can influence the function of lymphocytes.

Communication between the immune system and the nervous system is two-way: lymphocytes also produce signaling molecules including cytokines that can affect the nervous system (Chavan et al., 2017). Bidirectional communication between these systems allows fine-tuning of the homeostatic response to a changing environment (Sloan and Walker, 2019). However, this review focuses on the interaction of neurotransmitters and neurochemicals with lymphocytes. We also review how modulation of lymphocytes by neurotransmitters and neurochemicals may be leveraged for disease treatment, and explore how drugs that influence neurotransmitters could affect human health.

2. Neurotransmitters and neurochemicals

A neurotransmitter must meet four criteria (Orrego, 1979). Firstly, it must be synthesized in neurons. Secondly, it will be present in the presynaptic terminal and released in amounts sufficient to exert a defined action on the postsynaptic neuron or target cells in effector organs. Thirdly, exogenous administration should mimic the action of the endogenously produced neurotransmitter. Fourthly, intrinsic mechanisms exist for its removal from its site of action. Neurotransmitters can be (a) biogenic amines including serotonin, dopamine, epinephrine (adrenaline), and norepinephrine (noradrenaline), (b) neuropeptides including substance P, and (c) amino acids including glutamate and γ-aminobutyric acid (GABA) (Kavalali, 2015; Orrego, 1979; Rangel-Gomez and Meeter, 2016; Wilkinson and Brown, 2015). Here, we review a selection of neurotransmitters that modulate immune function (see Table 1). We also review endocannabinoids and endorphins because these systems are frequently subject to pharmacological manipulation with possible physiological consequences for immune regulation, and adenosine which is important at the intersection of metabolism with the immune systems.

3. Where do lymphocytes come into contact with neurotransmitters and neurochemicals?

As defined above, a neurotransmitter must be produced by neurons. Lymphocytes can be exposed to neurotransmitters in the blood or tissue. T-cells entering the central nervous system (CNS) encounter neurotransmitters at the site of release from neurons. Neurotransmitters are also found in blood. For example, acetylcholine can be detected in

* Corresponding author at: The University of Queensland Centre for Clinical Research, Royal Brisbane and Women's Hospital, Brisbane, Australia.
E-mail address: pamela.mccombe@uq.edu.au (P.A. McCombe).

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Table 1
Neurotransmitter and neurochemical receptors on immune cells and strategies for therapeutic intervention.

Name	Receptors identified on lymphocytes	Immune cell targets	Possible modifying drugs	References
Epinephrine & norepinephrine	Adrenergic	Macrophage, monocyte, dendritic cells, natural killer cells, T lymphocytes, B lymphocytes	Beta blockers, adrenergic drugs	(Wu et al., 2018)
Dopamine	D2, D3, D4 and D5	Macrophage, natural killer, T lymphocytes, B lymphocytes	Anti-psychotics and Parkinsons disease drugs	(Talhada et al., 2018)
Acetylcholine	Muscarinic and nicotinic	Macrophage, dendritic cells, T lymphocytes, B lymphocytes	Cholinesterase inhibitors	(Fujii et al., 2017a)
Glutamate	mGluR1, mGluR5, AMPA, NMDA	Dendritic cells, T lymphocytes	AMPA agonists (for epilepsy), NMDA receptor antagonists (for psychosis)	(Fallarino et al., 2010)
GABA	$GABA_A$ (plus others)	Monocyte, macrophage, neutrophil, T lymphocytes, B lymphocytes	GABA agonists (for spasticity, anxiety, anesthesia)	(Jin et al., 2013)
Serotonin	5HT1, 5HT1A, 5-HT1B, 5-HT2A, 5-HT3, 5-HT3A and 5-HT7.	Macrophage, dendritic cells, eosinophils, platelets, T lymphocytes, B lymphocytes	Anti-depressants, migraine medications	(Herr et al., 2017)
Substance P	NK1	Macrophages, T lymphocytes, B lymphocytes	NK1 agonists (used as anti-emetic)	(Mashaghi et al., 2016)
CGRP	CGRP receptor	Antigen presenting cells, mast cells, T & B lymphocytes,	Anti-CGRP monoclonal antibodies	(Assas et al., 2014, Holzmann, 2013, Mikami et al., 2011)
Endocannabinoids	CB2	Macrophages, mast cells, activated T lymphocytes, B lymphocytes	Medical and recreational cannabis	(Chiurchiu, 2016)
Endorphins	μ, δ, κ	Monocytes, dendritic cells, natural killer cells, T lymphocytes, B lymphocytes	Medical use, narcotic abuse	(Bidlack, 2000)
Adenosine	A2A	Macrophage, dendritic cells, neutrophils, mast cells, T lymphocytes	Adenosine receptor antagonists (in development)	(Hasko et al., 2008)

blood (Watanabe et al., 1986), as can catecholamines (Yamaguchi and Kopin, 1979) and CGRP (Tfelt-Hansen and Le, 2009). Levels of substance P are increased in the blood after stroke (Lorente et al., 2016) and endocannabinoid levels in plasma are increased with exercise (Thompson et al., 2016). As well as being produced by neurons, neurotransmitters and neurochemicals are produced by other cells, including lymphocytes (Chen et al., 2015; Cosentino et al., 2007; Mossner and Lesch, 1998; Orrego, 1979; Wilkinson and Brown, 2015), resulting in both autocrine and paracrine action on immune cells (Rangel-Gomez and Meeter, 2016).

Primary (thymus, bone marrow) and secondary (lymph nodes, gut and spleen) lymphoid organs are innervated by nerves. These nerves release neurotransmitters that interact with lymphocytes (Bellinger et al., 1993; Bellinger et al., 2008; Calvo, 1968; Felten and Felten, 1988; Felten et al., 1993; Fink and Weihe, 1988; Nance and Sanders, 2007) {Nance, 2007 #8843}. Such innervation contributes to the development of immune cells (Bellinger et al., 2008). The dopaminergic reward system of the brain also influences immunity (Ben-Shaanan et al., 2016) as do nociceptive pathways that play a role in the integration of the immune and neural responses to injury (Pinho-Ribeiro et al., 2017). The locations where the nervous system affects the immune system are now discussed.

(A) INNERVATION OF THE BONE MARROW: The sympathetic nervous system (SNS) provides the major nerve supply to the bone marrow (Calvo, 1968; Felten et al., 1985; Weihe et al., 1991) and regulates the production and release of lymphocytes (Ueda et al., 2005, Webber et al., 1970,Katayama et al., 2006).

(B) INNERVATION OF THE THYMUS: The thymus is innervated by the SNS (Nance et al., 1987; Tollefson and Bulloch, 1990). SNS nerve fibers enter through the perivascular network, and branch into the deep cortical region, upper cortical and subcapsular regions, septa, corticomedullary junction and medulla (al-Shawaf et al., 1991; Mignini et al., 2003). Noradrenergic innervation of the thymus has been demonstrated through tyrosine hydroxylase (TH) staining (Vizi and Elenkov, 2002), with high density of nerve fibers near the cortico-medullary junction and less in the subcapsule and cortex area (al-Shawaf et al., 1991; Cavallotti et al., 1999). Activation of β-adrenergic receptors by norepinephrine released from SNS nerves has inhibitory effects on the maturation, proliferation and differentiation of thymocytes (Leposavic et al., 2011; Madden and Felten, 2001).

(C) INNERVATION OF THE SPLEEN: The prevertebral sympathetic ganglia that are associated with the celiac-superior mesenteric plexus innervate the spleen. This neural network extends to the white and red pulp, and marginal zone with nerve endings in close proximity to splenic T cells, B cells and dendritic cells (DCs) (Ackerman et al., 1987; Bellinger et al., 1987; Felten et al., 1987; Felten et al., 1985). Studies so far have found only sympathetic innervation of the spleen (Felten et al., 1987; Felten and Olschowka, 1987; Nance and Sanders, 2007; Straub, 2004).

(D) INNERVATION OF THE LYMPH NODES: SNS fibers enter the hilus of lymph nodes along with blood vessels, run along the vascular and lymphatic networks in the medulla, paracortex and cortical regions (Felten et al., 1984; Fink and Weihe, 1988), and branch into the T cell zones in the parenchyma of the medulla and paracortex (Novotny and Kliche, 1986). The SNS does not innervate the B cell-rich germinal centers (Felten et al., 1984; Sloan et al., 2007). SNS neural networks in lymphoid organs are in close contact with immune cells and regulate the immune response (Sloan et al., 2007; Sloan et al., 2006).

(E) NOCICEPTIVE PATHWAYS: Nociceptive pathways include the peripheral nerves that respond to noxious stimuli (Dubin and Patapoutian, 2010) and the central nervous system pathways that are activated by these peripheral nerves. Nociceptive nerves release specific neurotransmitters that can influence the immune system (Pinho-Ribeiro et al., 2017; Ren and Dubner, 2010).

(F) CNS PATHWAYS: There is growing understanding that the brain regulates neural signaling to immune cells in peripheral organs. The

ventral tegmental area (VTA) is the brain reward system involved in pleasure and incentive salience, as well as response to stress (Dutcher and Creswell, 2018; Kasanova et al., 2017). The VTA is connected by the mesolimbic pathway to the nucleus accumbens, the amygdala and the prefrontal cortex (Richard et al., 2013). This system drives behaviors such as eating and reproduction. In disease, the brain reward system is linked to addiction, gambling and obesity. The brain reward system stimulates innate and adaptive immunity through modulation of the sympathetic nervous system (SNS) (Ben-Shaanan et al., 2016; Ben-Shaanan et al., 2018).

4. Interaction of neurotransmitters and neurochemicals with lymphocytes

4.1. Epinephrine and norepinephrine

Epinephine is a hormone and neurotransmitter that is produced by the adrenal medulla and neurons (Wood, 2006). The splanchnic sympathetic nerve controls the release of epinephrine from the adrenal medulla (de Diego et al., 2008; Esler et al., 1988; Esler et al., 1990). Norepinephrine is produced in brainstem nuclei, by sympathetic nerves within organs and by the adrenal gland. The main source of norepinephrine is nerve terminals of the post-ganglionic SNS (Eriksson et al., 1996; Furlan et al., 2016). Peripheral blood mononuclear cells (PBMC) also synthesize catecholamines, including epinephrine, norepinephrine and dopamine, and their metabolites (Bellinger et al., 2008; Elenkov et al., 2000; Scheiermann et al., 2012). Activation of the tyrosine hydroxylase pathway stimulates the synthesis of dopamine, which leads to production of norephinephrine and epinephrine. Adrenocorticotropic hormone (ACTH) stimulates the adrenal cortex leading to increased production of cortisol, which enhances epinephrine biosynthesis (Sneader, 2001; Wood, 2006). The main physiologic triggers of epinephrine and norepinephrine release are perturbations of physiological homeostasis, such as physical threat, noise exposure, psychological stress or change in temperature. Circadian rhythm also has an impact on immune function through the SNS (Scheiermann et al., 2013). Epinephrine and norepinephrine have physiologically important effects on metabolic activity, blood flow to muscles and cardiac output. Norepinephrine regulates the circadian rhythm, dreaming and learning (Wood, 2006).

Epinephrine and norepinephrine induce their activity by binding to α- and β-adrenergic receptors (Burn et al., 1950). Adrenergic receptors are expressed on immune cells including T cells and B cells, macrophages and NK cells, β_2-adrenergic receptor the dominant sub-type on most immune cells (Bergquist et al., 1994; Cosentino et al., 2007).

By binding to adrenergic receptors, epinephrine and norepinephrine regulate immune activity (Sneader, 2001, Wood, 2006). Signaling through β_2-adrenergic receptors on lymphocytes regulates cellular trafficking from lymphoid organs (Bellinger et al., 2008; Elenkov et al., 2000; Nakai et al., 2014). Lymphocyte trafficking from lymph nodes is dependent on sphingosine-1-phosphate receptor-1, and occurs when retention signals mediated by the chemokine receptor CCR7 are overcome (Nakai et al., 2014; Pham et al., 2008). Activation of lymphocyte β_2-adrenergic receptors promotes CCR7-dependent retention signals, thereby inhibiting lymphocyte egress from lymph nodes and preventing lymphocyte migration to inflamed tissues. The SNS directly innervates lymphoid tissues and the release of norepinephrine from nerve terminals controls recruitment of myeloid cells into tissues by modulating the expression of adhesion and chemo-attractant molecules by vascular endothelial cells (Scheiermann et al., 2012). Adrenergic signaling in immune cells modulates inflammation by regulating cytokine production. Initial upregulation of pro-inflammatory cytokines including IL1β and TNFα (Porterfield et al., 2012; Scanzano and Cosentino, 2015) is modulated by upregulation of IL10, which dampens pro-inflammatory signaling (Agac et al., 2018).

Activation of the SNS has been linked to diseases, in part due to inhibition of T_H1-mediated inflammation and impaired CD8 T cell-mediated adaptive immunity, and a shift to enhanced T_H2 responses (Elenkov et al., 2000; Marino and Cosentino, 2013). In multiple sclerosis, β_2 adrenergic receptors are increased in peripheral mononuclear cells (Arnason et al., 1988; Zoukos et al., 1992) and in experimental autoimmune encephalitis, increasing norepinephrine leads to reduced severity (Simonini et al., 2010). In rheumatoid arthritis there is a decrease in density and affinity of β_2-adrenergic receptors on peripheral mononuclear cells such as CD8 T cells and B cells (Baerwald et al., 1997; Wahle et al., 2001). This is seen particularly on cells in synovial fluid, which means that these lymphocytes are less responsive to the suppressive activities of catecholamines (Baerwald et al., 1997) leading to increased tissue damage (Wahle et al., 2006). However, in chronically inflamed joints, it has been suggested that the end result is zones of inflammation that are cut off from regulation by the SNS, so that inflammation is ongoing (Pongratz and Straub, 2014).

In cancer, SNS signaling impairs anti-cancer immune responses and increases tumor cell invasion to accelerate cancer progression and metastasis (Bucsek et al., 2017; Nissen et al., 2018; Scheiermann et al., 2013; Sloan et al., 2010). These studies suggest that immune responses could be controlled through pharmacological interventions that stop catecholamine signaling through β-adrenergic receptors.

4.2. Dopamine

Dopamine is produced in the brain (Klein et al., 2019; Wang et al., 2009) and by sympathetic nerves that innervate secondary lymphoid organs. Dopamine has also been identified in different immune cell populations including $CD4^+CD25^+$ regulatory T cells, granulocytes, T and B cells (Cosentino et al., 2007; Levite, 2008). Dopamine acts on G-protein-coupled receptors (D1–D5) to regulate biological effects including control of movement, emotion, cognition, cardiovascular and endocrine functions (Levite, 2008; Missale et al., 1998). Dopamine receptors are expressed by human and mouse lymphocytes (Alberio et al., 2012; Levite, 2016; Mignini et al., 2013; Pacheco et al., 2009). Binding of dopamine leads to reduced cAMP levels in stimulated lymphocytes (Santambrogio et al., 1993).

Dopamine has effects on lymphocyte proliferation and differentiation (Bergquist et al., 1994; Pacheco et al., 2014). These effects are dependent on the dopamine receptors expressed (e.g. D2-5), T cell subtype, T cell activation status and dopamine concentration (Levite, 2008; Levite et al., 2001; Santambrogio et al., 1993). D3 is preferentially expressed on naïve CD8 T cells (Watanabe et al., 2006). Highly selective agonists targeting dopamine D2 and D3 receptors on T cells enhance T cell adhesion to fibronectin by sensitizing $\alpha_4\beta_1$ and $\alpha_5\beta_1$ integrins (Levite, 2008, 2016; Levite et al., 2001). Such T cell adhesion is important for trafficking and extravasation of T cells following tissue injury or infection (Levite et al., 2001). By working synergistically with CXCL12, CCL19 and CCL21, dopamine enhances chemotactic migration of naïve CD8 T cells to the lymph nodes; this can be reversed by a D3 antagonist (Watanabe et al., 2006). Dopamine stimulates T cell activation resulting in TNFα and IL-10 cytokine production from naïve T cells (Besser et al., 2005). By activating T cell D1 receptors, dopamine activates T cells by dampening Treg function (Cosentino et al., 2007). Collectively, these results indicate that dopamine can regulate immune responses.

Dysregulation of the dopamine signalling and abnormal dopamine receptor expression in lymphocytes has been reported in various disease conditions including Alzheimer's disease (Barbanti et al., 2000a), migraine (Barbanti et al., 2000b), schizophrenia (Ilani et al., 2001), multiple sclerosis (Giorelli et al., 2005), and Parkinson's disease (Barbanti et al., 1999). As a result, there are ongoing efforts to develop antagonists and ligands to target dopamine receptors for treatment of neurological disorders (Levite, 2008; Orrego, 1979; Rangel-Gomez and Meeter, 2016; Wilkinson and Brown, 2015). In immunological disorders, there also appears to be role for dopamine. For example,

dopamine enhanced the expansion of Th_{17} cells in blood from patients with multiple sclerosis (Ferreira et al., 2014) and dysregulation of dopamine has been implicated in the development of autoimmune disorders and proposed as a target for therapy (Levite et al., 2017; Vidal and Pacheco, 2019).

4.3. Acetylcholine

Acetylcholine is a neurotransmitter synthesized in neurons from choline and acetyl-coenzyme A by the enzyme choline acetyltransferase (Baig et al., 2018). In the synaptic cleft, acetylcholine is degraded by acetylcholinesterase to choline and acetate. Acetylcholine signals from neuron to neuron or from neuron to glandular and muscle cells (Baig et al., 2018). Immune cells can interact with cholinergic nerves associated with lymph vessels, or from acetylcholine synthesized by immune cells themselves (D'Andrea et al., 2013).

Choline acetyltransferase has been identified in different immune cells including CD4 and CD8 T cells (Hagforsen et al., 2000; Kawashima et al., 2012; Wessler and Kirkpatrick, 2008) and is responsible for acetylcholine synthesis in T cells and mononuclear leukocytes (Kawashima and Fujii, 2004; Kawashima et al., 2012). Acetylcholine is stored in vesicles, and externalized by exocytosis via acetylcholine vesicular transporters. It is also likely that acetylcholine is synthesized on demand and is directly released without storage (Kawashima et al., 2012). The majority of blood acetylcholine resides within the mononuclear leukocyte fraction, mainly in lymphocytes (Kawashima and Fujii, 2000; Kawashima et al., 2012).

Acetylcholine signals through muscarinic and nicotinic receptors. There are five types of muscarinic receptors (M1-M5) (Abrams and Andersson, 2007). All five muscarinic receptors are found in the CNS, and M1-M4 are additionally expressed in different tissues (Platt and Riedel, 2011). M1 receptors are also found in secretory glands such as salivary, mucosal or sweat glands, M2 in cardiac tissues, and M3 in smooth muscle and secretory glands (Carlson and Kraus, 2018; Cremaschi et al., 2004). Muscarinic receptors are involved in regulation of heart rate, smooth muscle contraction and neural signaling. Nicotinic receptors are ligand-gated ion channels found on muscle and also at certain autonomic ganglia (Skok, 2002; Wang et al., 2002b). The binding of acetylcholine to neuronal nicotinic receptors results in a conformational change and formation of an ion pore that allows the movement of cations, specifically the influx of Ca^{2+} ions that stimulate the release of neurotransmitters (Baig et al., 2018; Cremaschi et al., 2004; Platt and Riedel, 2011).

Muscarinic and nicotinic acetylcholine receptors are expressed on immune cell populations including T and B cells, DCs, and macrophages (Kawashima and Fujii, 2000, 2003; Kawashima et al., 2012). Activation of mouse CD4 T cells increased expression of some nicotinic receptor subtypes (α4 and α7 subunit) suggesting that the expression pattern of nicotinic receptors varies with activation status (Qian et al., 2011). Stimulation of T cells with phorbol 12-myristate 13-acetate (PMA) or phytohemagglutinin (PHA) results in upregulation of choline acetyltransferase and muscarinic M5 receptor genes.

Cholinergic signaling has effects on lymphocyte function. Mice lacking muscarinic M1 receptor showed a defect in early CD8 T cell differentiation into cytolytic T cells when stimulated in vitro (Sinha et al., 2001; Zimring et al., 2005). Nicotine dose-dependently downregulates gene expression of all nicotinic receptors (Kawashima and Fujii, 2004). These findings suggest that nicotine, and therefore smoking, negatively regulate immune function by suppressing the expression of nicotinic receptors in lymphocytes. Furthermore, in vitro stimulation of muscarinic and nicotinic receptors causes functional and biochemical changes in immune cells. It is therefore likely that acetylcholine released from parasympathetic cholinergic nerve terminals acts on muscarinic and nicotinic receptors on immune cells causing immunosuppressive effects (Fujii et al., 2017b).

Cholinergic pathways in the brain play a role in learning and memory. During the course of the normal aging process, concentrations of acetylcholine tend to decrease and in Alzheimer's disease, acetylcholine levels can drop significantly (Muir, 1997). Cholinesterase inhibitors are used to treat the symptoms of Alzheimer's disease (Hampel et al., 2019). In the peripheral nervous system, cholinergic transmission is abnormal in myasthenia gravis which arises when the body produces antibodies against nicotinic cholinergic receptors (Drachman et al., 1980). Drugs that inhibit acetylcholinesterase have been shown to be effective in myasthenia gravis (Maggi and Mantegazza, 2011) but little is known about the effects of these therapies on immune function. Given the effects of acetylcholine on immune function, there have been suggestions that targeting the cholinergic system could be a useful approach in treating inflammation (Hoover, 2017) and multiple sclerosis (Di Bari et al., 2017).

4.4. Glutamate

Glutamate is a non-essential amino acid that is synthesized from α-ketoglutarate. Glutamate enters the CNS *via* a high affinity energy-dependent active transport system (Meldrum, 2000). There are five glutamate transporters in the mammalian CNS. Two of these are found in glia (glial glutamate and aspartate transporter (GLAST) and glial glutamate transporter (GLT)), and three are in neurons (excitatory amino-acid carrier 1 (EAAC1), excitatory amino acid transporters-4 and 5 (Meldrum, 2000). Glutamate can also be synthesized from the glutamate-glutamine cycle through the catalytic action of glutaminase. This can occur in presynaptic neurons or non-neuronal glial cells of the central and peripheral nervous system. There are also reports of production of glutamate by lymphocytes (Garg et al., 2008).

Glutamate acts *via* metabotropic or ionotropic glutamate receptors. Metabotropic glutamate receptor-7 (mGluR7) and mGluR8 are located within the presynaptic grid, mGluR2 and mGluR3 on the pre-terminal axon, and mGluR1/mGluR5 on the perisynaptic glia and astrocytes (Lujan et al., 1996; Meldrum, 2000; Shigemoto et al., 1996). Alternatively, glutamate engages three postsynaptic ionotropic receptors, named after their agonists: N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionicacid (AMPA) and kainate. The effects of glutamate activity on the kainate receptor at the presynaptic neuron is inhibitory as it decreases glutamatergic transmission in the hippocampus (Meldrum, 2000; Nedergaard et al., 2002). Glutamate transporters, and receptors including metabotropic receptors mGluR1 and mGluR5, ionotropic receptors AMPA and kainate, are also expressed on immune cells including lymphocytes (Boldyrev et al., 2012; Ganor and Levite, 2014; Lujan et al., 1996; Meldrum, 2000; Vladychenskaya et al., 2011; Xue and Field, 2011). NMDA receptors are also found on lymphocytes and upregulated after lymphocyte activation (Orihara et al., 2018).

Glutamate has effects on lymphocyte function. Glutamate enhances chemotactic migration of normal naive T cells towards CXCL12 (Ganor et al., 2003), stimulates AMPA receptors on T cells leading to activation, and triggers integrin-dependent adhesion of T cells to laminin and fibronectin (Ganor et al., 2003). NMDA receptor agonists increase T_H2 cell activity (Orihara et al., 2018). Glutamate promotes T cell proliferation in response to myelin oligodendrocyte glycoprotein and myelin basic protein, which are antigens implicated in multiple sclerosis (Koehler et al., 2002). Glutamate activates group I metabotropic receptors mGluR1 and mGluR5 promoting intracellular Ca^{2+} mobilization and expression of early inducible genes in T cells (Miglio et al., 2005). Glutamate augments potassium channel Kv1.3 gating potentiating T cell responsiveness to immune stimuli (Levite, 2008). Some of the *ex vivo* studies indicate that glutamate may be immunosuppressive especially at pathophysiological concentrations, since incubation of peripheral human lymphocytes with high concentrations of glutamate decreased the capacity of lymphocytes to respond to stimuli (Lombardi et al., 2001). While these high concentrations might not be achieved in the blood, they could be reached locally in

compartments such as intestinal epithelium and joint synovial fluid, indicating physiological relevance (Ganor and Levite, 2014; Xue and Field, 2011).

High amounts of glutamate are found in the brain of individuals with multiple sclerosis, and this is believed to cause neurotoxicity (Levite, 2008; Meldrum, 2000). In EAE, the animal model of multiple sclerosis, blocking glutamate carboxypeptidase II reduced inflammation (Ha et al., 2016). Glutamate toxicity has also been associated with the ischemic cascade that is associated with spinal cord injury, stroke, traumatic brain injury and other complications of the CNS such as Parkinson's or Alzheimer's disease and amyotrophic lateral sclerosis (Meldrum, 2000). AMPA receptor antagonists are being developed as anti-epileptic medications (Tyrlikova et al., 2018). Glutamate agonists are being developed for use in psychosis (Stone, 2011). It has been proposed that modification of glutamate receptors could be a strategy to control inflammation in autoimmunity (Gammon et al., 2017).

4.5. Gamma-aminobutyric acid (GABA)

GABA is synthesized by decarboxylation of glutamate by the enzyme glutamic acid decarboxylase (GAD). This process includes two GAD isoforms (GAD65 and GAD67) which differ in gene distribution, but also exhibit diverse functions (Erlander et al., 1991; Walls et al., 2011). GABA is widely distributed in the brain, and acts as an inhibitory neurotransmitter (Bloom and Iversen, 1971; Blum and Mann, 2002). In addition to production by the nervous system, T cells and macrophages secrete GABA (Wu et al., 2017).

GABA acts on the $GABA_A$, $GABA_B$ and $GABA_C$ receptors (Dionisio et al., 2011), which have subunits; for instance, there are 19 $GABA_A$ receptor subunits (Alam et al., 2006; Mendu et al., 2012). In the synaptic cleft, GABA signaling is terminated by reuptake through high-affinity GABA transporters (GAT) in the presynaptic membranes. These transporters include GAT-1, GAT-2, GAT-3 and betaine-GABA transporter (BGT-1). After uptake, GABA is metabolized further by transaminases which terminate GABA signaling (Dionisio et al., 2011; Redecker, 1999). GAT-1 and GAT-3 are expressed in the CNS, while GAT-2 and BGT-1 are found in tissues such as liver, kidney and intestine (9). Thus, GABAergic system mainly includes GAD, GABA-T, GATs, $GABA_A$ and $GABA_B$ receptors (Dionisio et al., 2011; Redecker, 1999; Wu et al., 2017). GABA receptors have been identified on lymphocytes; buts their role in regulating functional phenotypes remain scarcely investigated (Alam et al., 2006; Dionisio et al., 2011; Wu et al., 2017). The type and level of expression of these receptors varies widely and may depend on the physiological status of the model under investigation. The GABA receptor subtypes expressed and the levels of expression vary widely on immune cells, and may depend on the disease context under investigation (Barragan et al., 2015; Bhat et al., 2010; Mendu et al., 2011; Mendu et al., 2012).

GABA transporters that play a role in secretion of GABA have been identified in monocytes/macrophages and CD4 T cells (Bhat et al., 2010). GABA transporter GAT-1 is expressed on activated T cells, and inhibits the proliferation of CD4 T cells (Redecker, 1999). Exposure of lymphocytes to GABA reduces T cell proliferation (Bjurstom et al., 2008). GABA signaling regulates the function of antigen presenting cells (APC) inhibiting T cell activation and generation of pro-inflammatory cytokines (Barragan et al., 2015; Bhat et al., 2010). While GABA receptors are expressed in immune cells, their role in regulating functional phenotypes such as migration, proliferation and cytokine production remain scarcely investigated (Alam et al., 2006, Dionisio et al., 2011, Wu et al., 2017).

GABA is involved in the pathogenesis of various disease conditions (Bhat et al., 2010; Prud'homme et al., 2015). GABA is thought to contribute to the pathophysiology of anxiety (Andlin-Sobocki et al., 2005; Wittchen et al., 2005). Increased sensitization of glutamatergic signaling elicits hyper-excitation of neurons and development of epileptogenic seizures (Notenboom et al., 2006). Moreover, dysregulation in glutamatergic and GABAergic signaling have been linked with neurodegenerative changes associated with cerebral stroke (Lyden et al., 2000). GABA also has a role in immune diseases. GABA is severely decreased in multiple sclerosis patients (Demakova et al., 2003), and increasing the concentration of GABA in the CNS has been shown to improve the outcome of experimental autoimmune encephalomyelitis, a mouse model of multiple sclerosis (Bhat et al., 2010). GABA treatment decreases inflammation associated with rheumatoid arthritis (Tian et al., 2011) and delays the onset of type 1 diabetes (Tian et al., 2004). GABA agonists are in clinical use in the treatment of spasticity (Mondrup and Pedersen, 1984). Drugs that act on GABA receptors are being developed for anxiety (Chen et al., 2018) and in anesthesia (Brohan and Goudra, 2017).

4.6. Serotonin

Serotonin, also known as 5-hydroxytryptamine (5-HT), is a hormone and a neurotransmitter. 5-HT is derived from tryptophan by the actions of tryptophan hydroxylase (Walther and Bader, 2003), with tryptophan converted to 5-hydroxytryptophan which is further decarboxylated to 5-HT (Ahern, 2011). 5-HT is packaged into vesicles by vesicular monoamine transporter in neuroendocrine cells (Weihe et al., 1994). 5-HT can be secreted into the bloodstream where it is taken up by circulating platelets and stored at high concentrations (Walther et al., 2003). Platelets release 5-HT upon activation, dramatically increasing plasma 5-HT concentrations (McNicol and Israels, 1999). 5-HT exhibits autocrine and paracrine effects in the gut, brain and other organs (Saudou and Hen, 1994; Shajib and Khan, 2015; Tork, 1990). In the brain, serotonin is produced by the raphe nuclei and has effects of mood and cognition (Leiser et al., 2015; Olivier, 2015). In addition, serotonin can be produced by lymphocytes (Young et al., 1993).

Approximately 18 genes encode at least 15 5-HT receptors. These receptors have been categorized into 7 subfamilies (5-HT1-7). Except for 5-HT3, which is a ligand-gated channel, these receptors are G-protein coupled (Baloira et al., 2012; Giannaccini et al., 2011). Serotonin receptors are expressed in immune cells and have immunoregulatory effects on monocytes, lymphocytes, mast cells and platelets (Ahern, 2011). 5-HT receptors expressed in lymphocytes include 5HT1, 5HT1A, 5-HT1B, 5-HT2A, 5-HT3, 5-HT3A and 5-HT7. Activation of 5-HT2 receptors on T-cells by mast cell-derived 5-HT, results in delayed-type hypersensitivity (Mossner and Lesch, 1998; Rivera-Baltanas et al., 2014; Shajib and Khan, 2015). Similarly, platelet-secreted 5-HT initiates T cell-dependent contact sensitivity via immunoglobulin E (IgE) (Matsuda et al., 1997). 5-HT potentiates T cell proliferation and activity including cytokine production (IL-16, IL-2), intracellular Na^+ influx, phosphorylation of ERK1/2 in naive T cells and increased CD4/CD8 ratio (Mossner and Lesch, 1998). Stimulation of 5-HT1A receptors increases survival and S-phase transition of T cells (Abdouh et al., 2004). Naive T cells mainly express 5-HT7 which enhances T cell activation upon stimulation by 5-HT (Leon-Ponte et al., 2007). On other hand, 5-HT2A is mostly expressed on activated T cells and suppresses CD4 T cell activation (Nau Jr et al., 2015).

Alteration in 5-HT physiology is associated with anxiety and depressive disorders (Freitas-Ferrari et al., 2010). Individuals with obsessive-compulsive disorder have reduced 5-HT transporter (5-HTT) levels and 5-HT2A with decreased binding capabilities (Hesse et al., 2005; Perani et al., 2008). 5-HT receptors are altered in patients with depression (Rivera-Baltanas et al., 2014). 5-HT2A is highly expressed in peripheral lymphocytes and the CNS (Inoue et al., 2011; Pandey et al., 1990). Lower levels of 5-HT2A receptor binding has been shown in autistic male patients (Murphy et al., 2006), and decreased levels of 5-HT transporter in the medial frontal cortex of children with autism (Makkonen et al., 2008). In schizophrenia, the serotonergic pathway interacts with the dopaminergic pathway to exacerbate the outcome (Kapur and Remington, 1996), but as yet no significant changes have been observed in 5-HT receptors or 5-HTT expression among

schizophrenic subjects (Frankle et al., 2005). 5-HT has been associated with inflammatory conditions of the gut like inflammatory bowel disease (Manocha and Khan, 2012). Many common medications act on the serotonergic system (for example, selective serotonin reuptake inhibitors), and it is thought that these cause immune suppression, although larger systematic studies are required to confirm this (Eyre et al., 2016). Fluoxetine, a selective serotonin reuptake inhibitor, can suppress experimental autoimmune encephalomyelitis (Bhat et al., 2017).

4.7. Substance P

Substance P is a peptide primarily produced by sensory neurons, and found in the brainstem and dorsal horns of the spinal cord, but also more widely in the brain (Chang and Leeman, 1970; Johnson et al., 2016). It is encoded by the TAC1 gene and is a member of the tachykinin peptide hormone family (Severini et al., 2002). TAC1 also encodes other three neuropeptides — neurokinin A, neuropeptide K, and neuropeptide γ (Severini et al., 2002) that will not be described in this review. Substance P is the most extensively studied mediator of nociceptive stimuli, neuroimmunoregulation and neurogenic inflammation (Carraway and Leeman, 1979; Krause et al., 1992; Severini et al., 2002). There are some reports of production of substance P by lymphocytes (Lambrecht et al., 1999; Zhang et al., 2017).

Substance P binds to cell surface receptors of the neurokinin (NK) family. These G protein–coupled receptors include NK1, NK2 and NK3 (Hafidi et al., 2002; Harrison et al., 2004). Of these, NK1 has high affinity for substance P, and is the best characterised (Bright et al., 2017; Monastyrskaya et al., 2005). NK1 is expressed in neurons (Todd et al., 2000), endothelial cells (Greeno et al., 1993), smooth muscle cells (Maghni et al., 2003), fibroblasts (Liu et al., 2006) and epithelial cells (Bockmann, 2002). Activation of NK1 leads to stimulation of phospholipase C and adenylate cyclase that generate second messengers including diacylglycerol (DAG), inositol trisphosphate (IP3), and cyclic AMP. These second messengers are responsible for intracellular signaling that regulates gene expression. NK1 is expressed by immune cells including NK cells (Feistritzer et al., 2003), eosinophils, mast cells (van der Kleij et al., 2003), T and B cells (Payan et al., 1983), macrophages (Germonpre et al., 1999), dendritic cells (Marriott and Bost, 2001), microglia and astrocytes (Chauhan et al., 2008).

Activation of NK1 receptor on lymphocytes regulates T cell proliferation, differentiation and production of cytokines (Chang and Leeman, 1970; Kang et al., 2004; Krause et al., 1992; Lai et al., 1998; Levite, 2008; Liu et al., 2006; Mantyh, 1991; Payan et al., 1983). Substance P also regulates the proliferation of bone marrow mononuclear cells (Kang et al., 2004; Mantyh, 1991; Payan et al., 1983). Substance P enhances T cell adhesion to lymphocyte function-associated antigen 1 (LFA-1) and ICAM-1 on endothelial cells enhancing T cell chemotaxis. Further, substance P induces migration of innate immune cells including neutrophils by stimulating synthesis of cytokines including macrophage inflammatory proteins (MIP-1β or CCL4), CCL5, monocyte chemoattractant protein-1 (MCP-1 or CCL2), and CXCL2, as well as expression of cytokine receptors (Kang et al., 2004; Mashaghi et al., 2016).

In disease states, substance P can regulate the immune response by skewing the inflammatory response toward T_H17, T_H1 or T_H2 depending on the context (Cunin et al., 2011; Levite, 1998). Substance P is thought to contribute to the maintenance of inflammation during the chronic phase of multiple sclerosis by promoting extensive infiltration of the CNS by macrophages, dendritic cells, T cells and other immune cells (Hickey, 1999; Whitney et al., 2009). Trauma and infections of the CNS are associated with elevated pro-inflammatory cytokines (Ziebell and Morganti-Kossmann, 2010), and immunomodulatory neuropeptides including substance P (Ho et al., 1997). The non-peptide tachykinin antagonist, CP-96,345, has been shown to downregulate T_H1-type cytokines and improve the outcome of multiple sclerosis (Hafidi et al., 2002; Harrison et al., 2004; Monastyrskaya et al., 2005). Substance P increases pain under pathological conditions by recruiting glial cells to the site of injury (Grace et al., 2014). For instance, pain after bone fracture has been linked to increased expression of glial activation markers, which is alleviated by antagonizing NK1 (Li et al., 2015). In Parkinson's disease, substance P increases microglial and astrocyte activation and though mechanisms that are suppressed by NK1 antagonists (Barker, 1986). Substance P can enhance blood–brain barrier permeability by disrupting endothelial cell-cell tight junctions, resulting in oedema particularly during traumatic brain or spinal cord injury and stroke (Lewis et al., 2013). This has led to interest in targeting substance P receptors as therapy (Grace et al., 2014; Lewis et al., 2013; Li et al., 2015), and the development of an NK1 agonist as a treatment for nausea after chemotherapy (Aapro et al., 2015).

4.8. Calcitonin gene-related peptide (CGRP)

Calcitonin gene related peptide (CGRP) belongs to the calcitonin family and exists in two isoforms in humans (α-CGRP and β-CGRP) (Russell et al., 2014). α-CGRP is formed from tissue-specific alternative splicing of the primary mRNA transcript of the calcitonin gene (Amara et al., 1982), while β-CGRP is encoded by a pseudogene (Rezaeian et al., 2009). β-CGRP is the least studied in humans. α-CGRP is mainly released from the central and peripheral nervous systems, while β-CGRP is produced by the immune system, pituitary gland and gut. Afferent nerve fibers that produce CGRP are abundant in non-inflamed lymphoid organs including bone marrow, thymus and lymph nodes, but are poorly distributed in the spleen, lung and the gut (Weihe et al., 1991). CGRP-containing nerve fibers are present in the paracortex of lymph nodes, and appear to establish direct contacts with macrophages, mast cells and DCs in the skin (Hosoi et al., 1993; Stead et al., 1987; Weihe et al., 1991). There have been reports of production of CGRP by lymphocytes (Wang et al., 2002a; Xing et al., 2000). T cells treated with mitogens (Wang et al., 2002a) or B cells stimulated with nerve growth factor (NGF) show increased CGRP production. Indeed neutralization of NGF inhibits the synthesis of CGRP from macrophages and B cells indicating the role of NGF in CGRP synthesis (Bracci-Laudiero et al., 2002). CGRP binds to calcitonin-receptor like receptors (CLR) (Russell et al., 2014). Both local and systemic CGRP levels increase during inflammation (e.g. neurogenic inflammation) and are responsible for transmission of pain, for example in migraine. There are CGRP receptors on lymphocytes (McGillis et al., 1991). Binding of CGRP to receptors on lymphocytes leads to increased CAMP levels (Wang et al., 1992).

Treatment of cells and experimental animals with CGRP inhibits the effector function of different immune cells (Assas et al., 2014; Benemei et al., 2009). CGRP decreases the expression of MHC class II, CD86 (a costimulatory receptor) and a panel of cytokines including CCL4, TNFα and IL-1β by APC (Asahina et al., 1995; Harzenetter et al., 2007; Tokoyoda et al., 2004). Consistent with these studies, *in vivo* administration of CGRP attenuates cutaneous inflammation induced by inflammatory agents (Clementi et al., 1994; Kitazawa and Streilein, 2000).

CRGP could impact the adaptive immune response by promoting chemotaxis of T cells and APC to sites of inflammation. CGRP enhances T cell adhesion to fibronectin (Levite et al., 1998). CGRP induces migration of immature dendritic cells, CD4 and CD8 T cells, but not B cells or mature dendritic cells (Dunzendorfer et al., 2001; Talme et al., 2008). CGRP is also an inhibitor of APC thereby impacting T cell activity (Asahina et al., 1995; Fox et al., 1997). T_H1 cells stimulated with APC pre-treated with CGRP have impaired capacity to secrete CXCL9, CXCL10 and IFN-γ, but the same APC enhance the ability of T_H2 cells to produce CCL17, CCL22 and IL-4 (Ding et al., 2008). CGRP also selectively reduces IFN-γ secretion by CD4 T cells but promotes IL-4 production (Tokoyoda et al., 2004). However, when CD4 T cells are stimulated with anti-CD3, CGRP impairs IL-4 release, but enhances IL-4

production when CD4 T cells are stimulated with anti-CD28.

CGRP stimulates the release of IL-13 from lymphocytes derived from patients with allergic dermatitis (Antunez et al., 2009). CGRP inhibits the production of pro-inflammatory cytokines IL-1β, TNFα, IL-12p40 and CCL4 from peripheral mononuclear cells including monocytes and dendritic cells (Harzenetter et al., 2007; Torii et al., 1997). Moreover, endothelial cells exposed to increasing concentrations of CGRP exhibit decreased expression of chemokines CXCL1, CCL2 and CXCL8, and reduced ability to chemoattract leukocytes (Huang et al., 2011). Indeed, CGRP treatment protects mice with endotoxemia (Gomes et al., 2005) and liver injury (Kroeger et al., 2009).

In non-obese diabetic (NOD) mice expressing a human CGRP transgene in pancreatic beta cells, local production of CGRP strongly attenuated infiltration of immune cells into islets, and decreased the incidence of insulin-dependent diabetes mellitus (Khachatryan et al., 1997). Moreover, in a rat model of inflammatory bowel disease and experimental colitis, neutralization of CGRP accentuated disease (Reinshagen et al., 1998; Reinshagen et al., 2000). In experimental autoimmune encephalomyelitis, CGRP reduces inflammation (Rossetti et al., 2018). Taken together, these studies indicate that CGRP plays a role as an anti-inflammatory mediator responsible for preventing tissue damage during inflammation or injury. Monoclonal antibodies directed against CGRP are now available for the treatment of migraine (Tso and Goadsby, 2017). The effects of these therapies on lymphocyte function are presently unknown.

4.9. Endocannabinoids

Endocannabinoids are bioactive lipids found widely in the brain (Lu and Mackie, 2016). The first identified endocannabinoid was anandamide (Devane et al., 1992). Activated T and B lymphocytes also produce endocannabinoids (Patti et al., 2016; Sido et al., 2016). Endocannabinoids have physiological effects on the immune system, metabolism and locomotion (Haugh et al., 2016; Thompson et al., 2016). Cannabinoids act on CB1 and CB2 receptors (Cabral et al., 2015; Haugh et al., 2016), which are the targets of cannabis that is used recreationally or medically. Cannabinoid receptors are expressed in the ventral tegmental area and play a role in drug-seeking behavior (Chen et al., 2017). CB2 cannabinoid receptors are expressed in cells of the immune system (Haugh et al., 2016; Malfitano et al., 2014).

Cannabinoids suppress autoreactive lymphocytes (Dittel, 2008) and T cell function (Cencioni et al., 2010). Cannabinoids induce functional Treg cells in vitro (Dhital et al., 2017). In a mouse model of inflammatory bowel disease, a CB2 agonist enhanced differentiation of Treg cells and suppressed disease (Gentili et al., 2018). Recreational users of cannabis have been shown to have suppression of T cell activity (Pacifici et al., 2003). There is current interest in the medical use of cannabinoids (Fraguas-Sanchez and Torres-Suarez, 2018; Olah et al., 2017), including for immunosuppression in autoimmune disease (Katchan et al., 2016). In particular there have been suggestions for the use of cannabinoids in rheumatic disease (Katz-Talmor et al., 2018) and type 1 diabetes (Lehmann et al., 2016). In multiple sclerosis, cannabinoids are approved for the treatment of spasticity, but do not affect disease activity (Zajicek et al., 2005). However cannabinoids affect numerous pathways and further investigation has been recommended (Baker et al., 2007)

4.10. Endorphins

Endorphins are peptides that act as endogenous opioids. There are four families of endorphins; the best known are beta-endorphins and the enkephalins (Corder et al., 2018). Beta-endorphin is produced by the pituitary gland, whereas enkephalins are produced more widely in the brain (Henry et al., 2017). Endorphins play a role in the response to pain and modulate the response to stress (Ironside et al., 2018). Endorphins are produced after exercise and social laughter (Manninen et al., 2017). Lymphocytes also produce opioids that contribute to analgesia at sites of inflammation (Hua, 2016). Endorphins act on opioid receptors (mu, delta, kappa and nociceptin) of which the mu receptor (the morphine receptor) is best known (Corder et al., 2018; Pasternak, 2018; Valentino and Volkow, 2018). There are opioid receptors on lymphocytes and the effect of opioids on lymphocytes is immune suppressive (Brack et al., 2011, Cechova et al. 2018).

There are suggestions that production of β-endorphins could regulate autoimmunity (Morch and Pedersen, 1995). This has been used as a rationale for the use of low dose naltrexone by practitioners of alternative medicine (Li et al., 2018). There have also been suggestions that endorphins can play a role in prevention of carcinogenesis (Zhang et al., 2015). Opioids are widely used in the treatment of pain, sometimes on a chronic basis, and in the community. The overall effect of chronic opioid use on the immune system is thought to be immune suppressive (Roy et al., 2011) although the details are complex (Liang et al., 2016).

4.11. Adenosine

Adenosine is a purine nucleoside, formed from the breakdown of adenosine triphosphate (ATP) (Ernst et al., 2010). ATP is hydrolyzed to adenosine diphosphate (ADP), which is further dephosphorylated to adenosine monophosphate (AMP). Cellular ADP and AMP can be rephosphorylated in the mitochondria in a process that requires molecular oxygen (North, 2016). However, in hypoxic environments some AMP is dephosphorylated to adenosine by cell membrane-associated nucleotidases. Adenosine is stored and exocytosed by different cells including neurons, microglia and astrocytes. It is not released as a typical neurotransmitter, but rather as a by-product of metabolic activity, through nucleoside transporters (Yao et al., 2011).

Adenosine binds to four G-protein coupled adenosine receptors A1, A2A, A2B and A3. A2A is the major receptor subtype on lymphocytes (Cekic and Linden, 2014; Di Virgilio and Adinolfi, 2017). By binding to adenosine type 2A receptors in coronary vascular smooth muscle cells, adenosine induces smooth muscle relaxation. Moreover, adenosine is a neuromodulator that promotes sleep and suppresses wake-up cycles (Costa and Biaggioni, 1998; Di Virgilio and Adinolfi, 2017). In the extracellular space, adenosine engages purine P1 and P2 receptors on neuronal and non-neuronal cells like endothelial cells, oligodendrocytes and microglia cells promoting various cellular functions (Fields, 2011; Fields and Burnstock, 2006; George et al., 2015).

Activation of A2A on T cells and iNKT cells prevents production of pro-inflammatory cytokines (Lappas et al., 2005; Ohta et al., 2009). Adenosine signaling via A2B on the high endothelial venules (HEV) restricts lymphocyte migration across HEV, but also activation of A2B on APC negatively regulate T cell activation. Engagement of A2A suppresses the expression of intercellular adhesion molecule 1 (ICAM-1) on lymphocytes, IFNγ production and chemotactic factors severely attenuating lymphocyte extravasation into inflamed tissues. By ligating A2A, adenosine regulates T cell receptor (TCR) activation via the adenylate cyclase/cyclic AMP axis and protein kinase A activities. Protein kinase A can control TCR signaling by phosphorylating downstream molecules including the cyclic AMP response element binding protein (CREB), C-terminal Src kinases and nuclear factor of activated T cells (NF-AT). Protein kinase A may also promote or diminish T cell survival depending on the strength and duration of TCR signal (Linden and Cekic, 2012).

In Alzheimer's disease, there is loss of the A1 adenosine receptor in the hippocampus (Stone et al., 2009). Cerebral ischemia is a condition with a decrease in blood supply to the brain, that can be attenuated by "ischaemic pre-conditioning". Adenosine plays a neuroprotective role during the initial phases of ischemic pre-conditioning, (Gidday, 2006). A2A is highly expressed in striatopallidal neurons, and adenosine signaling can regulate neurotransmission in the basal ganglia (Schwarzschild et al., 2006). Antagonizing A2A slows the progression of

Parkinson's disease (Antonelli et al., 2006; Schwarzschild et al., 2006; Stasi et al., 2015), demonstrating the potential for drug discovery by targeting the adenosine pathway. Adenosine is produced in high concentrations in tumours, where it can suppress the immune response; there are currently clinical trials of adenosine antagonists in cancer immunotherapy (Gaudreau et al., 2016; Leone and Emens, 2018). There are also reports of the use of adenosine receptor antagonist for treatment of psychosis (Asaoka et al., 2019).

5. Discussion

This review has summarized evidence that lymphocytes express receptors for neurotransmitters and neurochemicals, and that stimulation by neurotransmitters and neurochemicals affects lymphocyte function (Table 1). Neurotransmitter receptor expression on lymphocytes permits signals from the brain to influence the immune system, via the peripheral nervous system. In addition to effects on lymphocytes, other immune cells have receptors for neurotransmitters and neurochemicals, indicating that neural signaling regulates multiple aspects of the immune response. We have outlined how lymphocytes interact with circulating neurotransmitters and neurochemicals, as well as neurotransmitters released from nerve fibers within lymphoid organs (Felten and Felten, 1988; Sloan et al., 2007). This allows regulation of immunity in response to a changing external environment, including circadian responses to light changes and regulation of homeostasis in response to acute injury and both psychological and physiological stress (Nissen et al., 2018; Scheiermann et al., 2013; Sloan et al., 2010).

The findings described here provide a physiological framework for understanding how factors including stress and pain impact disease, and imply that neural-immune communication may be targeted to enhance immunity. It also provides a theoretical basis for the possible effects of behavioral interventions such as meditation, which modify neurotransmitter levels and affect the immune system, although randomized trials suggest that more work in this field is required (Black and Slavich, 2016). The role of neurotransmitter signaling to the immune system is currently being explored in cancer, where multiple clinical studies are evaluating the effect of β-blockers – which stop norepinephrine signaling to β-adrenergic receptors – on long-term cancer outcomes including metastasis and recurrence (Hiller et al., 2018). As immunotherapy is increasingly included in cancer treatment regimes, neural regulation of immunity may be harnessed to enhance immunotherapy treatment response.

The ability of neurotransmitters and neurochemicals to influence lymphocytes has other implications. Neurotransmitter function is regulated by drugs that are used as treatment for diverse diseases (see Table 1). These drugs are often used over extended periods, raising the possibility of long-term effects on immune function. Future studies are warranted to explore the significance of treatment-induced neural modulation of immunity. It is also plausible that neurotransmitter signalling could be targeted to modulate immune function. In addition to ongoing trials in cancer that are described above, this approach could be useful in autoimmune diseases where new therapies are required, and in the perioperative period were surgery-induced immune response may slow recovery (Hiller et al., 2018; Marik and Flemmer, 2012). In this study, we have highlighted the extensive role for neurotransmitters in lymphocyte biology and show the importance of neurotransmitters in regulation of immunity, as well as the potential for leveraging neurotransmitter activity for therapy.

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