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Review Article

Non-traditional cytokines: How catecholamines and adipokines influence macrophages in immunity, metabolism and the central nervous system

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ABSTRACT

Catecholamines and adipokines function as hormones; catecholamines as neurotransmitters in the sympathetic nervous system, and adipokines as mediators of metabolic processes. It has become increasingly clear, however, that both also function as immunomodulators of innate and adaptive immune cells, including macrophages. Macrophages can respond to, as well as produce their own catecholamines. Dopamine, noradrenaline, and adrenaline are the most abundant catecholamines in the body, and can induce both pro-inflammatory and anti-inflammatory immune responses in macrophages, as well as non-immune processes such as thermogenesis. Though they are responsive to adipokines, particularly lipoproteins, leptin, and adiponectin, macrophages generally do not synthesize their own adipokines, with the exception being resistin-like molecules. Adipokines contribute to adverse metabolic and immune responses by stimulating lipid accumulation, foam cell formation and pro-inflammatory cytokine production in macrophages. Adipokines can also promote balance or resolution during metabolic and immune processes by promoting reverse lipid transport and expression of Th2 cytokines. This review will explore the mechanisms by which catecholamines and adipokines influence macrophage function in neural pathways, immunity and metabolism.

1. Introduction

Macrophages are essential components of the innate immune system. First identified by Metchnikoff for their potent phagocytic capabilities, which explains their name "big eater" in Greek, their function in engulfing and eliminating microbial pathogens is well-recognized. The importance of macrophages in other immune contexts, such as influencing adaptive immunity, mediating wound healing and downregulating inflammation is also appreciated. New studies, however, have revealed that the macrophage function extends beyond the immunological realm, affecting both the central nervous system and metabolism. First, macrophages respond to and can produce catecholamines, which are neurotransmitters that signal through the sympathetic nervous pathway. Second, macrophages make and respond to adipokines that influence the outcome of several metabolic diseases such as atherosclerosis. This suggests the requirement for multidisciplinary research spanning immunology, neuroscience and metabolism for the improved understanding of these critical cell-types. Here we review the main mediators of these neural–immune or metabolic–immune circuits, which are either synthesized by macrophages or influence their function, and discuss their function in neural pathways, immunity and metabolism.

2. Catecholamines

Catecholamines are hormones produced in both the adrenal medulla and the central nervous system. As neurotransmitters, catecholamines are an integral part of the sympathetic nervous pathway, also known as the "fight-or-flight response", which mediates essential physiologic responses including increased heart

Abbreviations: AAM, alternatively activated macrophage; Apo, apolipoprotein; CNS, central nervous system; FKN, fractalkine; HDL, high density lipoprotein; ICAM, intercellular adhesion molecule; IL, interleukin; LDL, low density lipoprotein; LPL, Lipoprotein lipase; lysoPC, lysophosphatidylcholine; MCP, monocyte chemoattractant protein; oxLDL, oxidized LDL; PPAR, peroxisome proliferator-activated receptor; RELM, resistin-like molecule; S1P, sphingosine-1-phosphate; TNF, tumor necrosis factor; TZD, thiazolidinedione; VCAM, vascular cell adhesion molecule.

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rate and blood pressure, mobilization of energy stores and control of core body temperature [1]. In addition to their hormonal and neurotransmitter roles, catecholamines also influence immune responses, and the importance of this neural-immune cross-talk via neurotransmitters and cytokines has been increasingly recognized [2]. For instance, stimulation of the vagus nerve can regulate inflammatory cytokine production, and conversely, macrophages and lymphocytes are able to synthesize catecholamines that influence the central nervous system (CNS) [3–5]. Additionally, immune cells express adrenergic receptors and are therefore responsive to catecholamines [6]. Catecholamine signaling in immune cells exerts a number of effects including cell activation, proliferation and apoptosis [7,8]. Furthermore, catecholamines can be locally produced by immune cells and act in both autocrine and paracrine ways [6]. Here, we focus on the macrophage-specific modulatory effects of catecholamines.

The most abundant catecholamines in the human body are dopamine, adrenaline and noradrenaline. Catecholamines are synthesized from the non-essential amino acid tyrosine by a series of enzymatic pathways [9]. First, tyrosine hydroxylase removes a hydroxyl group from tyrosine to produce the dopamine precursor L-DOPA. L-DOPA is decarboxylated to form dopamine, which is then catabolized to noradrenaline and adrenaline by hydroxylases. Dopamine binds dopamine receptors, while noradrenaline and adrenaline bind α and β-adrenergic receptors, all of which belong to a family of G protein-coupled receptors that signal through phospholipase C and cAMP/protein kinase A pathways [10,11]. In the immune system, myeloid cells express α and β-adrenergic receptors, while lymphocytes primarily express β-adrenergic receptors [1].

Functionally, catecholamine receptor signaling in macrophages has significant effects on the inflammatory response. Inhibition of the β-adrenergic receptor with the β-blocker propranolol, or depletion of adrenal catecholamines by adrenalectomy, led to increased LPS-induced tumor necrosis factor (TNF) α production in peritoneal macrophages [12]. Alveolar macrophages recovered from mice chronically treated with β-blockers produced more noradrenaline, interleukin (IL) 6 and TNFα following LPS treatment *ex vivo* [13]. Conversely, adrenaline, noradrenaline and dopamine treatment of RAW 264.7 macrophages inhibited LPS-induced production of nitric oxide [14]. Finally, treatment of RAW cells with dopamine or noradrenaline decreased proliferation and increased apoptosis [8]. Taken together, these studies suggest that macrophage responsiveness to catecholamines via the β-adrenergic receptor exerts an important immunoregulatory mechanism to reduce inflammation. Supportive of this, treatment of mice with β2-adrenergic agonists ameliorated LPS-induced endotoxemia and acute lung inflammation [15]. This was associated with alternatively activated macrophage (AAM) polarization, characterized by increased IL-4, IL-10 and Arginase-1 expression, and decreased expression of iNOS and IL-12 [16].

Recent data suggest that catecholamines can auto-regulate their levels and function by controlling expression of both tyrosine hydroxylase as well as catecholamine receptors [12]. For instance, adrenal catecholamines contribute to the paracrine regulation of macrophage synthesis of catecholamines and expression of the β-adrenergic receptor. Adrenalectomy resulted in decreased expression of β2-adrenergic receptor and increased expression of tyrosine hydroxylase by peritoneal macrophages presumably as a compensatory mechanism to increase catecholamine levels. Consistent with this, treatment with the β-blocker propranolol increased macrophage expression of tyrosine hydroxylase.

In contrast to the anti-inflammatory effect of β-adrenergic receptor signaling, stimulation of the α-adrenergic receptor of murine peritoneal macrophages in combination with LPS treatment led to increased TNFα and IL-1β expression compared with LPS alone [17]. Additionally, treatment of human monocytes with the α1-adrenergic receptor agonist phenylephrine hydrochloride promoted LPS-induced IL-1β [18]. Use of protein kinase C and MAP kinase inhibitors demonstrated that these signaling pathways were downstream of the α-adrenergic receptor-induced inflammatory response. Together, these observations suggest that the differential roles of catecholamines on macrophages may depend on the adrenergic receptor. Specifically in the context of LPS-induced inflammation, β-adrenergic receptors agonists inhibit inflammation, while α-adrenergic receptor signaling or β-adrenergic receptor blockers promote pro-inflammatory responses. The differential responses between α-adrenergic and β-adrenergic receptors is likely due to variance in G protein pairings with the receptors [11]. Briefly, α1 preferentially binds noradrenaline and signals via the PKC-activating Gq subunit, while α2 preferentially binds adrenaline and stimulates Gi, thereby decreasing cAMP. β1-adrenergic receptor equivalently binds noradrenaline and adrenaline, which leads to Gs subunit-mediated increases in cAMP. Though the β2 receptor also couples with the Gs subunit, its preferential binding partner is adrenaline. Influencing differential adrenergic receptor expression and G protein pairing on macrophages could therefore have therapeutic potential in dictating the inflammatory outcome of several disease conditions such as endotoxemia or acute respiratory disease.

In addition to regulation of inflammation by the sympathetic nervous system via catecholamine–adrenergic receptor signaling, macrophages are also influenced by the parasympathetic/cholinergic nervous system, through recognition of acetylcholine by nicotinic receptors. In this neural immune circuit, termed the inflammatory reflex, stimulation of the vagus nerve leads to the release of acetylcholine that acts on macrophages to downregulate expression of inflammatory cytokines such as TNFα. In a mouse model of sepsis, this pathway was critical in limiting inflammation, and was dependent on acetylcholine production by a small subset of memory T cells [19]. In more recent studies, Ulloa and colleagues utilized electroacupuncture at the sciatic nerve to protect mice from fatal sepsis induced by LPS treatment [4]. This protective mechanism was associated with decreased levels of TNFα, CCL2, IL-6, and IFN-γ in the serum, and dependent on vagal nerve stimulation and adrenal-derived catecholamines. Specifically, vagotomy or adrenalectomy abolished the production of catecholamines, and treatment with dopamine receptor agonists could rescue the adrenalectomized mice from fatal sepsis. Together, these studies demonstrate the importance of both dopaminergic and cholinergic nervous pathways in the regulation of the inflammatory immune response during sepsis.

In contrast to its role in preventing sepsis, macrophage exposure to dopamine may increase susceptibility to HIV [20,21]. Macrophages are the main cell type in the CNS that are infected with HIV, and recent studies showed that dopamine treatment of human peripheral blood monocyte-derived macrophages led to a twofold increase in CCR5-mediated HIV entry and increased HIV replication. Supportive of these studies, another group reported a positive correlation between dopamine levels and CNS viral loads in SIV-infected macaques [22]. These studies implicate catecholamines as immunomodulatory molecules and elucidate a potential role for these neurotransmitters in HIV-associated neurocognitive disorders. Since therapeutic drugs, such as ritalin and some antidepressants, and illicit drugs, such as cocaine, can lead to increased CNS dopamine, these drugs may contribute to increased HIV virulence.

Catecholamine signaling also negatively impacts the rate of wound repair. The stress induced by injury can lead to a surge in catecholamines, with 10-fold increases in circulating adrenaline in severe burn injuries [23]. Macrophages and neutrophils that are recruited to the injury respond to and produce catecholamines.