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COMMENTARY

Regulation of Cytokine and Chemokine Production by Transmitters and Co-transmitters of the Autonomic Nervous System

György Haskó† and Csaba Szabó†‡*

*Inotek Inc., and ‡Division of Critical Care, Children's Hospital Medical Center, Cincinnati, OH, U.S.A.

ABSTRACT. The sympathetic nervous system innervates immune organs and, when activated, releases its signaling molecules in the vicinity of immune cells. The released molecules include the "classical" transmitters norepinephrine and epinephrine and the co-transmitters ATP and adenosine. Immune cells express various adrenergic and purinergic receptors that are sensitive to these molecules, and the production of immune/inflammatory mediators (cytokines, chemokines, and free radicals) is modulated by activation of these receptors. Notably, the production of tumor necrosis factor-α, interleukin-6, -10, and -12, and the chemokine macrophage inflammatory protein 1α and the production of the free radical nitric oxide, produced by the inducible nitric oxide synthase, have been shown to be altered by activation of these receptors. Alterations in the production of the immune mediators may contribute to the development of various diseases. On the other hand, novel experimental therapies based on the modulation of adrenergic or purinergic receptors on immune cells are emerging. Such approaches may have beneficial effects in limiting tissue injury and suppressing symptoms in certain pathophysiological states. BIOCHEM PHARMACOL **56**;9:1079–1087, 1998. © 1998 Elsevier Science Inc.

KEY WORDS. epinephrine; norepinephrine; sympathetic nervous system; tumor necrosis factor; interleukin; ATP; purinergic; neurotransmission

Immune functions have traditionally been thought to be regulated by signals originating within the immune system. Recently, however, increasing attention is being paid to those regulatory pathways that control the immune system from "outside," most notably from the brain and the endocrine system. The first evidence for such an interaction between the nervous, the endocrine, and the immune systems dates back to the 1930s, when Selye in his pioneering work demonstrated that in rats subjected to various stressors, the adrenal gland became enlarged and the thymus underwent involution [1]. On the other hand, the immune system itself can be a stressor influencing the activation state of the central nervous and the endocrine systems, as demonstrated by the ability of immune stimuli to increase blood corticosterone [2] and catecholamine [3] levels. The temporal and spatial organization of this complex system of interactions is governed mainly by communication, using specific signaling molecules. In the context of signaling from the brain to the immune system, information is transmitted mainly via (a) the HPA§ axis with the steroid hormones, its effector signaling molecules, and (b) the SNS originating from the brainstem, hard-wiring the immune system, and releasing its various transmitters. On the other hand, cells of the immune system communicate with each other, or with the neuroendocrine system, by secreting a wide range of molecules such as cytokines, chemokines, arachidonate metabolites, and diffusible free radicals.

RELEASE OF TRANSMITTERS OF THE SYMPATHETIC NERVOUS SYSTEM IN THE VICINITY OF IMMUNE CELLS

The autonomic nervous system consists of two major components that originate in the CNS: the sympathetic and parasympathetic division. The sympathetic division sets out from nuclei within the brainstem and gives rise to preganglionic efferent fibers that terminate in the paravertebral or prevertebral ganglia. The postganglionic noradrenergic fibers innervate a wide variety of target organs

† Corresponding authors: Dr. György Haskó, Inotek Inc., 3rd Floor, 3130 Highland Ave., Cincinnati, OH 45219-2374 [Tel. (513) 475-6655; FAX (513) 221-1891]; and Dr. Csaba Szabó, Children's Hospital Medical Center, Division of Critical Care, 3333 Burnet Ave., Cincinnati, OH 45229 [Tel. (513) 636-8714; FAX (513) 636-4892].

§ *Abbreviations:* ADO, adenosine; cAMP, cyclic adenosine monophosphate; EAE, experimental allergic encephalomyelitis; EPI, epinephrine; HPA, hypothalamo-pituitary-adrenal; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; NE, norepinephrine; MIP, macrophage inflammatory protein; SNS, sympathetic nervous system; and TNF, tumor necrosis factor.

including the heart, gastrointestinal tract, blood vessels, and lymphoid organs. These fibers give rise to widespread arborizations and release NE as the principal neurotransmitter. In addition, EPI, a methyl derivative of NE, and neuropeptide Y are released from the sympathetic nerve terminals in response to neuronal activity. Adrenal medullary cells, innervated by the SNS, are embryologically analogous to postganglionic sympathetic neurons, and release mainly EPI, and, to a lesser extent, NE. ATP is co-stored and co-released with catecholamines in both the noradrenergic nerve endings and the adrenal medulla [4]. The ATP released is promptly degraded to ADO by the extracellular enzymes ecto-ATPase, ecto-ADPase, and ecto-5′-nucleotidase [5].

Once the transmitters of the SNS are released, they can reach their target cells, by (1) neural communication, in which neurotransmitters are released at synaptic junctions from the terminals and act across a narrow synaptic cleft on the postsynaptic cell, (2) nonsynaptic communication, in which the transmitter diffuses in the vicinity of the nerve terminal, and reaches target cells at more distant sites than in the case of synaptic transmission, and (3) endocrine communication, in which these molecules (now termed hormones) reach cells via the circulating blood.

For any putative neurotransmitter to be accepted as a *bona fide* neurotransmitter by classical evaluation, it must meet some major criteria. These are: (1) the presence and localization of nerve fibers in the region where the target cells reside, (2) the synthesis and release of the neurotransmitter, and (3) the presence of receptors sensitive to the neurotransmitter on the target cells. As far as the immune system is concerned, it is now well-established that both primary lymphoid tissues (thymus and bone marrow) and secondary lymphoid tissues (spleen, lymph nodes, and gut-associated lymphoid tissue) are innervated by noradrenergic sympathetic nerve fibers [6–10]. These fibers are associated with blood vessels and specific cellular elements, including lymphocytes and macrophages, forming very tight "synaptic-like" appositions with immune cells, as demonstrated in the spleen [8, 11], or providing the basis for nonsynaptic transmitter release, as observed in the thymus [9]. There is now good evidence that in response to neuronal firing, NE can be released from the sympathetic nerve terminals of both the thymus [9, 12] and the spleen [13]. Moreover, other nonspecific stimuli, such as hypoglycemia, hypoxia, or ischemia can also induce the release of NE in lymphoid tissues (Haskó G, unpublished observation). Another aspect of the communication between sympathetic nerve terminals and immune cells is that the release of transmitters from nerve endings is subject to an additional level of modulation, through various receptors located presynaptically. Most importantly, the transmitters released from these nerve terminals can exert positive or negative feedback effects on their own release. In the thymus and spleen, the release of NE is inhibited by the stimulation of presynaptic α_2-adrenoceptors and ADO receptors, and is propagated through β-adrenoceptors [9, 12, 13].

Several lines of evidence indicate that immune/inflammatory processes activate the sympathetic nervous system. Stimulation of the immune system by a variety of agents including bacterial LPS, concanavalin A, pokeweeed mitogen, influenza, and Newcastle disease viruses increases plasma catecholamine levels [3, 14, 15], triggers the activation of cerebral and splenic catecholamine metabolism [16–18], and enhances sympathetic nerve firing rates in the kidney [14]. The release of catecholamines under conditions of immunostimulation is paralleled by the release of ATP and ADO [19–24]. It is now well accepted that the activation by antigenic stimulation of the SNS, as well as of the HPA axis is due mainly to mediators (cytokines, chemokines, platelet-activating factor, arachidonate metabolites) released from cells of the immune system and is integrated at the hypothalamic level. IL-1 was the first cytokine shown to be responsible for mediating the activation of the CNS by antigenic challenge [25], which was later followed by the demonstration that a host of other cytokines including TNF-α, IL-6, IL-2, IL-12, IFN-γ, and MIP-1α are also involved in triggering the stimulation of the CNS [26–28].

Taken together, antigenic challenge of the immune system activates immune cells to secrete cytokines, chemokines, and other peptide and non-peptide mediators, which stimulate the sympathetic nervous system, resulting in the release of its transmitters. In the latter parts of this review, we will attempt to summarize the physiological significance of the increased SNS activation during an immune response, namely, how transmitters of the SNS affect immune cell functions. No comprehensive summary is available on how transmitters of the SNS regulate the production of mediators of the immune system, although various specific aspects of these interactions have been the subject of recent overviews [26, 29–32].

ROLE OF ADRENERGIC RECEPTORS IN THE MODULATION OF CYTOKINE, CHEMOKINE, AND FREE RADICAL PRODUCTION

The catecholamines NE and EPI exert their effects by binding to 7 transmembrane spanning G-protein-coupled cell surface receptors termed adrenoceptors. Adrenoceptors can be classified into three major groups: α_1-, α_2-, and β-adrenoceptor types. Each of these three major types can be subdivided further into at least three subtypes: α_{1A}, α_{1B}, α_{1C}; α_{2A}, α_{2B}, α_{2C}; and β_1, β_2, and β_3.

α_1-Adrenoceptors

There is only limited evidence for the expression of α_1-adrenoceptors on immune cells. For example, radioligand binding studies failed to detect α_1-adrenoceptors on resting murine lymphocytes [33] or on circulating human blood cells [34]. In line with these observations, α_1-

adrenoceptor stimulation failed to affect TNF-α or IL-6 secretion and α_1-adrenoceptor-mediated mechanisms only marginally contributed to the enhancement of IL-10 production by EPI in LPS-stimulated human whole blood [35, 36]. Although α_1-adrenoceptor activation does not appear to play a major role in the regulation of immune function under physiological conditions, this may not necessarily be the case in inflammation. Notably, α_1-adrenoceptor expression has been shown to increase with cellular activation: selective stimulation of this receptor type enhances IL-6 production in peripheral blood mononuclear cells from arthritic but not healthy patients [37].

α_2-Adrenoceptors

In contrast to α_1-adrenoceptors, α_2-adrenoceptors appear to have a substantial modulatory role in cytokine production both *in vitro* and *in vivo*. In the earlier reports of α_2-adrenergic effects on cytokine production by immune cells, Spengler *et al.* [38, 39] demonstrated that stimulation of this receptor subtype by exogenous or endogenous NE increases TNF-α release by murine peritoneal macrophages stimulated with LPS. The same investigators also demonstrated that macrophages possess an endogenous pool of NE, which can be released upon stimulation of the cells with LPS [39]. Subsequently, these *in vitro* data were confirmed by *in vivo* studies, in which the α_2-adrenoceptor antagonists idazoxan [40], CH-38083 [41, 42], or rauwolscine [43] inhibited TNF-α production in endotoxemic rodents, suggesting that endogenous NE enhances TNF-α production via α_2-adrenoceptors. An important aspect of the immunomodulation by α_2-adrenoceptor blockade *in vivo* is that the α_2-adrenoceptor on the immune cell is only one of the targets of these drugs. Another mechanism that might contribute to the alteration of cytokine expression by α_2-adrenoceptor blockade involves the presynaptic α_2-adrenoceptor. Figure 1 shows that inhibition of presynaptic α_2-adrenoceptors results in an enhanced release of NE in various lymphoid organs such as the spleen [13] and thymus [12], and this NE being present in high concentrations can stimulate β-adrenoceptors on macrophages, thereby decreasing TNF-α production by these cells (see below).

While stimulation of α_2-adrenoceptors has no effect on LPS-induced IL-10 production by human whole blood [36], α_2-adrenoceptor blockade greatly enhances the release of IL-10 in endotoxemic mice [44]. Furthermore, α_2-adrenoceptor inhibition increases IL-6 [41] and decreases IL-12 and MIP-1α [44] in LPS-challenged mice.

Although the α_2-adrenoceptors are consistently associated with inhibition of adenylyl cyclase and suppression of intracellular cAMP levels [45], the signal transduction mechanisms of the immunomodulatory action of occupation of this receptor are unknown. Considering the well-known modulatory effects of alterations of intracellular cAMP levels on cytokine production [46–50], it is possible that blockade of α_2-adrenoceptors influences cytokine production through elevation of cAMP (Fig. 2). A further possibility is that α_2-adrenoceptor blockade, which can also inhibit calcium flux into the cell [45], decreases intracellular calcium concentrations in immune cells, resulting in an altered cytokine profile. Indeed, a decrease in intracellular calcium concentration elicited by calcium entry blockers or inhibitors of intracellular calcium mobilization is known to affect pro- and anti-inflammatory cytokine production in a fashion that resembles the effect of α_2-adrenoceptor antagonists [51–53].

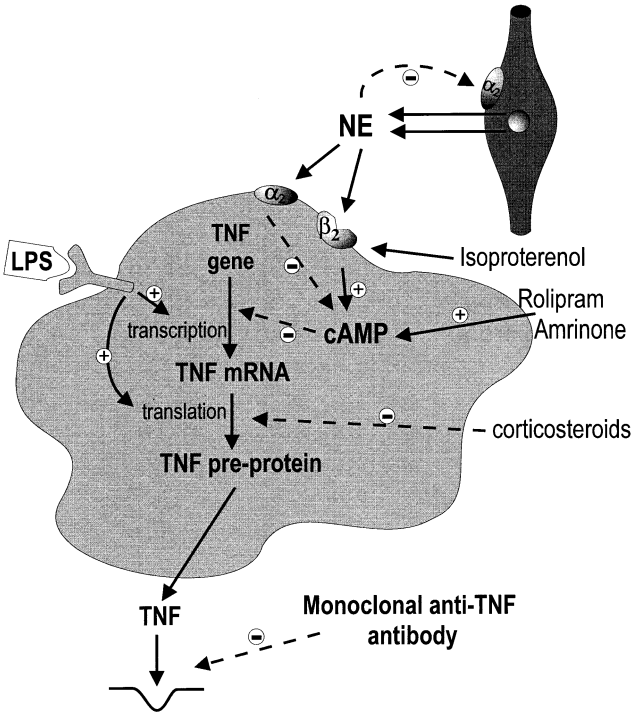

FIG. 1. Modulation of TNF-α production in macrophages by presynaptic and postsynaptic adrenoceptors in the spleen or thymus.

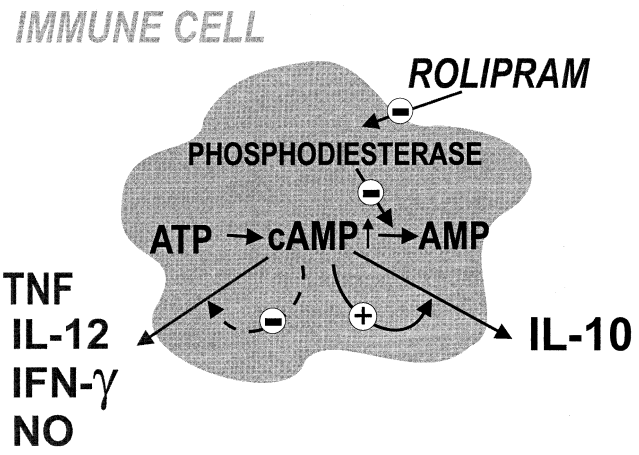

FIG. 2. Modulation of cytokine production in macrophages by intracellular cAMP. Changes in cAMP can exert opposing effects on the production of pro-inflammatory (e.g. TNF and IL-12) and certain anti-inflammatory (e.g. IL-10) cytokines.

β-Adrenoceptors

β-Adrenoceptors are expressed by various immune cells, such as lymphocytes, macrophages, neutrophils, eosinophils, and basophils. Upon stimulation, these receptors cause increased intracellular cAMP levels that can lead to the modulation of various immunologic functions, including proliferation of lymphocytes, antibody secretion, and production of pro-inflammatory cytokines [32]. The first evidence for inhibition of LPS-induced TNF-α production by rat spleen macrophages in the presence of NE, EPI, and isoproterenol, agents able to stimulate β-adrenergic receptors, was described by Hu and colleagues [54]. Another *in vitro* study reported that both EPI and isoproterenol inhibited the production of TNF-α by human whole blood and THP-1 (monocyte) cells stimulated with LPS, and that this inhibition was prevented by the β-receptor antagonist oxprenolol [55]. The inhibition of TNF-α production was exerted at the post-transcriptional level, while in murine peritoneal macrophages, β-adrenoceptor stimulation decreased TNF-α release by inhibiting the accumulation of TNF-α mRNA [55, 56]. In RAW 264.7 macrophages, isoproterenol, a selective β-receptor agonist, decreased TNF-α and NO production and simultaneously elevated intracellular cAMP accumulation [57]. Importantly, isoproterenol did not affect the nuclear translocation of NF-κB, a transcription factor involved in TNF-α gene expression, suggesting that pathways other than NF-κB are affected by β-receptor stimulation, resulting in the suppression of TNF-α [57]. In addition to causing decreases in LPS-induced TNF-α production, activation of β-receptors enhances IL-6 production in both isolated perfused rat liver and isolated Kupffer cells [58].

Stimulation of β-receptors has a dual effect on chemokine production. While it has been shown to augment the release of the CXC chemokine IL-8 [59–61], we recently observed that stimulation of this receptor type suppresses production of the CC chemokine MIP-1α at both the protein and the mRNA levels [62].

Recent *in vitro* findings show that stimulation of β-adrenoceptors enhances IL-10 and inhibits IL-12 production by human whole blood and dendritic cells [36, 63, 64]. In conjunction with its ability to suppress IL-12 production, salbutamol, an agonist of β_2-receptors, inhibits the development of Th1-type cells, while promoting Th2 cell differentiation [63]. On the other hand, Th1 but not Th2 clones express β_2-receptors, and stimulation of these receptors inhibits IL-2, IFN-γ, and IgG2 production, but Th2 responses (IL-4 and IgG1 production) remain unaffected [65, 66].

In vivo, in agreement with the *in vitro* data, β-receptor stimulation blocks the LPS-induced plasma TNF-α, IL-12, IFN-γ, MIP-1α, and NO production [42, 62, 67–69] but elevates plasma IL-6 and IL-10 [67, 70]. Similarly, in a mouse model of hemorrhagic shock, the expression of TNF-α, IL-1, and TGF-β is inhibited by stimulation of β-adrenoceptors [71].

Since in endotoxemic mice IL-10 inhibits the production of pro-inflammatory cytokines [72], it would be conceivable that *in vivo* stimulation of β-adrenoceptors decreases TNF-α, IL-12, and IFN-γ by augmenting IL-10. This, in turn, would down-regulate the release of the pro-inflammatory mediators. However, this is not the case, because isoproterenol is able to inhibit the production of the pro-inflammatory mediators even in IL-10-deficient mice, indicating that its effects on TNF-α, IL-12, IFN-γ, and NO are independent of the increased release of IL-10 [73].

In conclusion, β-receptor stimulation has mainly anti-inflammatory effects by inhibiting the production of the pro-inflammatory mediators TNF-α, IL-12, IFN-γ, MIP-1α, and NO and by enhancing the production of the anti-inflammatory IL-6 and IL-10. As far as specific immunity is concerned, β-adrenoceptor stimulation causes a shift towards a Th2 versus a Th1 phenotype and to humoral from cellular immunity.

REGULATION OF CYTOKINE AND NO PRODUCTION BY PURINORECEPTORS

Immune cells express plasma membrane receptors for extracellular ATP and ADO. Receptors for ATP are termed P_2 purinoceptors, while ADO-sensitive receptors are called P_1 or ADO receptors. Both ATP and ADO can be present at physiologically relevant concentrations in the vicinity of immune cells [74–76] and can exert their effects at various subtypes of purinoceptors. ATP receptors are classified as metabotropic (G-protein-coupled) P_{2y} or ionotropic (ion channel) P_{2x} receptors. ADO interacts with at least four different G protein-coupled receptors, namely A_1, A_{2A}, A_{2B}, and A_3 receptors, all of which are expressed on various immune cells [77–79].

P_2 Receptors

The processing and release of pro-IL-1β are highly ineffective in macrophages treated with LPS alone. However, this process can be promoted by adding ATP to the cells, which results in high levels of secreted IL-1 protein in the supernatants [80]. This process is also operational *in vivo*, as ATP induces the release of IL-1 in LPS-treated mice [81]. Recent evidence indicates that the interleukin-1 release triggered by ATP is due to an effect on the pore-forming P_{2X7} receptor [82, 83]. Although the mechanisms coupling P_{2X7} activation and IL-1 release are far from being understood, it has been suggested that stimulation of this receptor might activate interleukin-1 converting enzyme, the cytoplasmic enzyme responsible for the maturation and release of IL-1 [75].

ATP can also influence inflammatory processes by acting on the P_{2Y} receptor: 2-methylthio-ATP, a partial agonist of P_{2Y} receptors suppresses TNF-α, IL-6, IL-1α, and NO release [84, 85] and protects mice from endotoxemic death.

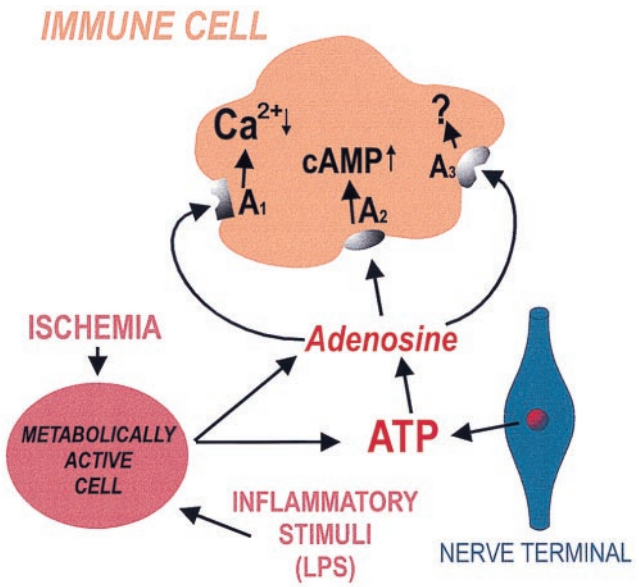

FIG. 3. Modulation of cytokine production in macrophages by the three adenosine receptor subtypes. Activation of A_1 receptors affects cytokine responses via changes in intracellular calcium levels, while changes in cAMP mediate the effects of A_2 receptors. The intracellular signal transduction pathways associated with A_3 receptor activation are not fully characterized.

ADO Receptors

In an early study, ADO, and its structurally related analog MDL201112 (9-[(1*S*, 3*R*)-*cis*-cyclopentan-3-ol] adenine) were shown to inhibit TNF-α, but not IL-1 production by activated mouse peritoneal macrophages and the macrophage-like cell line J774 and RAW 264 [86]. In the same study, the authors demonstrated that MDL201112, and to a lesser extent ADO, decreased LPS-induced plasma levels of TNF-α in mice. Furthermore, ADO inhibited the production of TNF-α, IL-6, and IL-8 by LPS-activated human monocytes [87]. The A_2 receptor-specific ADO analogs 2-chloroadenosine and 5′-*N*-ethylcarboxamidoadenosine were most effective in attenuating LPS-induced cytokine production, whereas the A_1 selective ADO analog N^6-cyclopentyladenosine was less effective, indicating that inhibition of cytokine production by ADO was primarily an A_2 receptor-mediated event. In LPS-stimulated Kupffer cells, ADO, 5′-*N*-ethylcarboxamidoadenosine, 2-chloroadenosine, and *R*(−)-N^6-phenylisopropyladenosine suppressed the release of TNF-α with an order of potency characteristic of A_2 receptors [88]. The mechanism by which A_2 receptor agonists affect cytokine release is most probably related to accumulation of intracellular cAMP [89] (Fig. 3).

In other studies, it was found that both A_1 and A_2 receptor agonists inhibited TNF-α production by RAW 264.7 macrophages or human monocytes, and the rank order of potency of agonists was characteristic of neither A_1 nor A_2 receptors [90, 91], suggesting a possible involvement of the A_3 receptor. Moreover, ADO but not selective A_1 and A_2 receptor agonists enhanced IL-10 production in human monocytes [92]. In a recent study using specific A_1, A_2, and A_3 receptor agonists and antagonists, it was demonstrated that inhibition of TNF-α production by LPS-stimulated U937 (human monocyte) cells was mainly an A_3 receptor-mediated process [93]. Similarly, ADO receptor agonists, in a concentration-dependent manner characteristic of the A_3 receptor, blocked endotoxin induction of the TNF-α gene and protein expression in the murine J774.1 macrophage cell line [79]. Recently, we reported that stimulation of A_3 receptors by the selective A_3 receptor agonist N^6-[3-iodobenzyl]-adenosine-5′-*N*-methyluronamide (IB-MECA) decreased plasma TNF-α, IL-12, IFN-γ, and NO, and increased IL-10 in LPS-treated mice [91, 94]. Furthermore, activation of A_3 and A_2, but not A_1 receptors inhibits MIP-1α mRNA and protein accumulation in immunostimulated macrophages and fibroblasts [95]. A_3 receptor stimulation in macrophages does not involve cAMP, protein kinase A, or the transcription factor NF-κB, while the composition of the AP-1 transcription complex can be altered by stimulation of this receptor subtype [93].

In summary, ADO receptor stimulation can potently and selectively alter the production of various immune mediators, and, overall, these effects (increase in IL-10 and decrease in TNF-α, IL-1, IFN-γ, IL-12, MIP-1α, IL-8, and NO) point towards an anti-inflammatory action of ADO receptor activation.

MODULATION OF THE COURSE OF INFLAMMATION BY LIGANDS OF ADRENERGIC OR PURINERGIC RECEPTORS

Endotoxic Shock

The management of severe sepsis includes the administration of ligands of both α- and β-adrenoceptors, aiming to provide cardiovascular support. Such support includes the administration of α-adrenergic agonists to maintain perfusion pressure, and the use of β-adrenergic agonists to improve cardiac output. As discussed above, accumulating evidence shows that these agents can affect the production of inflammatory mediators, which are responsible for the deleterious effects of shock-inducing microorganisms. In this respect, β-adrenergic stimulation or α_2-adrenergic antagonism seems to shift the inflammatory process to an anti-inflammatory direction, as these agents inhibit the release of pro-inflammatory mediators (TNF-α, IL-12, IFN-γ, MIP-1α, and NO) while increasing the production of the anti-inflammatory IL-10. In line with the observations showing a beneficial effect of such a shift in the cytokine response in septic shock [96], administration of β-adrenergic agonists or α_2-adrenergic antagonists has been shown to exert protective effects in animal models of endotoxic shock [43, 69, 97, 98]. Similarly, methylthio-ATP and ADO receptor agonists improve survival in lethal rodent models of endotoxemia [84, 86, 90, 94].

It is important to stress that some of these pharmacological agents are known to have harmful or unwanted

side-effects. For example, ADO agonists exert vasodilatory effects, which are unwanted during septic shock, where the vasculature is in an already dilated state. Moreover, the rodent endotoxemic models do not fully mirror the pathophysiological events occurring during human sepsis. Therefore, it will require further studies to establish a therapeutic rationale for these agents in human septic shock.

Autoimmune Diseases

Autoimmune diseases are characterized by specific alterations in the expression of the above inflammatory mediators. In some of these diseases, a clear polarization of cytokine expression can be observed, either to the Th1 (multiple sclerosis, EAE, autoimmune thyroid disease, non-insulin-dependent diabetes mellitus) or to the Th2 direction (systemic lupus erythematosus, autoimmune hemolytic anemia). In a Th1 cytokine response, IL-12, IFN-γ, IL-2, and TNF-α are the key players, while a Th2 profile is often associated with increased expression of IL-10, IL-4, IL-13, and transforming growth factor-β. Consequently, an approach to inhibit Th1 cytokines and potentiate Th2 cytokines would be desirable in Th1 diseases, and the opposite would be required in Th2-mediated disorders. The data available regarding the modulatory affects of the SNS and adrenergic agents on the course of EAE, an animal model of human multiple sclerosis (Th1), appear to be in accord with the effects of these drugs on the cytokine profile: β-agonists and prazosine, an α_1 and α_{2B} antagonist, which inhibit Th1 cytokines, ameliorate the symptoms of disease [99, 100]. Also, β-receptor agonists suppress experimental allergic neuritis [101] and acute passive transfer of experimental autoimmune myasthenia gravis [102].

The regulation of rheumatoid arthritis by the SNS appears to be a controversial issue: in some studies the SNS exerts anti-inflammatory effects as shown by the exacerbation of the disease after sympathectomy [103], while in others, chemical sympathectomy or β-adrenergic blockade prevents joint injury [104, 105]. According to Levine and co-workers [106], epinephrine at low doses exacerbates arthritis, acting on presynaptic β-adrenoceptors located on sympathetic nerve terminals. However, at high doses, epinephrine inhibits inflammation through stimulation of α_2-adrenoceptors located presynaptically [107] and decreasing the release of some unidentified mediator. The downstream mechanisms of these effects are unclear, and are complicated by the fact that both ATP and ADO, which are released by the sympathetic nerve endings, have substantial inhibitory activity in experimental arthritis [108]. Recently, we provided evidence that stimulation of A_3 receptors attenuates collagen-induced arthritis in mice [109], which is in agreement with the ability of A_3 receptor stimulation to inhibit the production of pro-inflammatory mediators. In this respect, it is important to note that the anti-inflammatory effects of several drugs used in the treatment of rheumatoid arthritis (e.g. methotrexate, sulfasalazine, and sodium salicylate) may involve a mechanism involving increased levels of extracellular ADO [110, 111]. Clearly, further studies will be needed to determine the positive or negative contribution of the different transmitters of the SNS in the development and symptomatology of rheumatoid arthritis.

CONCLUSIONS

Immune cells express various adrenergic and purinergic receptors that are sensitive to transmitters of the SNS. The production of immune/inflammatory mediators (cytokines, chemokines, and free radicals) is modulated by activation of these receptors. The investigations are only at the initial stages of exploring the complex regulation of the production of pro- and anti-inflammatory mediators by various receptor subtypes of the adrenergic and purinergic receptors. Continuing work in this area is necessary and may lead to a better explanation of the contribution of the alterations in the production of the immune mediators to the development of various diseases. In addition, novel experimental therapies can be designed which will be based on the modulation of specific adrenergic or purinergic receptors on immune cells. Exploitation of these mechanisms by pharmacological means may provide novel means for the experimental therapy of a variety of immune and inflammatory disorders.

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