Catecholamines—Crafty Weapons in the Inflammatory Arsenal of Immune/Inflammatory Cells or Opening Pandora's Box§?

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It is well established that catecholamines (CAs), which regulate immune and inflammatory responses, derive from the adrenal medulla and from presynaptic neurons. Recent studies reveal that T cells also can synthesize and release catecholamines which then can regulate T cell function. We have shown recently that macrophages and neutrophils, when stimulated, can generate and release catecholamines *de novo* which, then, in an autocrine/paracrine manner, regulate mediator release from these phagocytes via engagement of adrenergic receptors. Moreover, regulation of catecholamine-generating enzymes as well as degrading enzymes clearly alter the inflammatory response of phagocytes, such as the release of proinflammatory mediators. Accordingly, it appears that phagocytic cells and lymphocytes may represent a major, newly recognized source of catecholamines that regulate inflammatory responses.

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INTRODUCTION

Norepinephrine and epinephrine are key hormones to prepare the body for one of its most primeval reactions: the "fight or flight" response. Catecholamines (CAs) increase the contractility and conduction velocity of cardiomyocytes, leading to increased cardiac output and a rise in blood pressure, which leads to increased vascular tone and resistance. This results in an increased "pre-load" in the right atrium, causing the heart rate to drop due to the Starling-mechanism. Moreover, catecholamines facilitate breathing (bronchi become dilated), and the body's metabolic reserves are mobilized (lipolysis and glycogenolysis) to provide vital energy. Past concepts held the adrenal medulla and the nervous system to be responsible for the production, storage, and release of catecholamines. Recent findings suggest that such assertions need to be re-evaluated. Because the brain and the immune system are some of the body's major adaptive systems (1) and communicate with each other extensively in an attempt to regulate body homeostasis (2), a common "language" is needed to facilitate this crosstalk. Key systems involved in this crosstalk are the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system, consisting of the adrenergic sympathetic nervous system, the vagus-mediated parasympathetic nervous system, and the enteric nervous system (1-3). Over many decades, an increasing body of evidence has accumulated demonstrating that lymphocytes and phagocytes not only are capable of synthesizing and releasing neuropeptides, but also neurotransmitters and hormones. Furthermore, these cells express adrenergic and cholinergic functions. Thus, coexisting in the nervous as well as in the immune system, these mediators become an universal language of a neuro-endocrine-immune modulating network (4), which enables the nervous, endocrine, and immune system to regulate and fine-tune their functional responses positively or negatively, and thereby allows the body to adapt rapidly to various changes of internal and external environments. We are beginning now to understand that catecholamines are an integral part, and potent modulators, of these neuro-endocrine-immune/inflammatory interactive networks. Through direct communication via sympathetic nerve fibers that innervate lymphoid organs (5), catecholamines can modulate mouse lymphocyte proliferation, differentiation, (6) and cytokine pro-

Footnote §: *Zeus ordered Hephaestus to create the first woman on earth, Pandora. She was bestowed with exceptional beauty and many talents by the Greek Gods. When Prometheus stole fire from heaven, furious Zeus provided Pandora with a jar (Pandora's box) and gave her to Epimetheus, Prometheus' brother. Not under any circumstances was she to open that box, but intrigued by natural inquisitiveness, she did, and all evil contained escaped and spread over the earth. The only thing remaining at the bottom of the box was Hope.*

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duction of rodent Th cells (7) and human peripheral blood mononuclear cells (PBMCs) (8). These interactions are facilitated by adrenergic receptors expressed on murine lymphocytes (7), rat natural killer (NK) cells (9), rodent macrophages and neutrophils (10,11), and human PBMCs (12). Consequently, we need to understand better the sources, distribution, and roles of catecholamines and their receptors in immunity and inflammation.

IMMUNE CELLS—A NEW, DIFFUSELY EXPRESSED ADRENERGIC ORGAN

The first evidence that catecholamines might originate from sources other than neuronal or endocrine tissue was reported more than ten years ago when the presence of endogenous catecholamines was reported in human lymphocytes (13). Lymphocytes were described not only to contain intracellular levels of catecholamines, but these catecholamines were secreted, negatively regulating lymphocyte proliferation, differentiation, and apoptosis via an autocrine loop in mice and humans (13,14). Shortly thereafter, parallel experiments identified dopamine and norepinephrine in human PBMCs (15,16). In line with these findings, additional studies confirmed the presence of catecholamines in various other cells, including murine bone marrow derived mast cells (17), rodent macrophages and neutrophils (11,18), and in a macrophage cell line (19). Surprisingly high levels of the epinephrine-synthesizing enzyme, phenylethanolamine-*N*-methyl transferase (PNMT), were found in the thymus of young mice, which were comparable to levels in the brainstem (Figure 1A; 20). Interestingly, PNMT levels were found to be two-fold higher in the lymphocyte-harboring cortex of the thymus than in the medulla. Low PNMT activity and PNMT mRNA also could be detected in the marginal zone of the white pulp of the spleen (20), which contains significant amounts of lymphocytes also, suggesting the presence of epinephrine-generating cell population(s) in lymphoid organs. As the morphology of these findings correlate perfectly with the lymphocyte-rich sites of lymphoid organs, it is reasonable to assume that the epinephrine-producing cell population might be lymphocytes. The mere presence of catecholamines in cells, however, left the unanswered question as to whether these catecholamines originated from extracellular sources and simply were taken up actively and stored by lymphocytes and phagocytes or whether such cells might have synthesized catecholamines *de novo*. Affirmation of the presence of the intracellular machinery for catecholamine production in human lymphocytes was obtained indirectly when human hematopoietic cell lines and human T and B cell hybridomas were cultured over a long period of time, with subsequent detection of catecholamines inside the cells. Based on the cell culture protocols, it was highly unlikely that these intracellular catecholamines could have originated from extracellular sources (21).

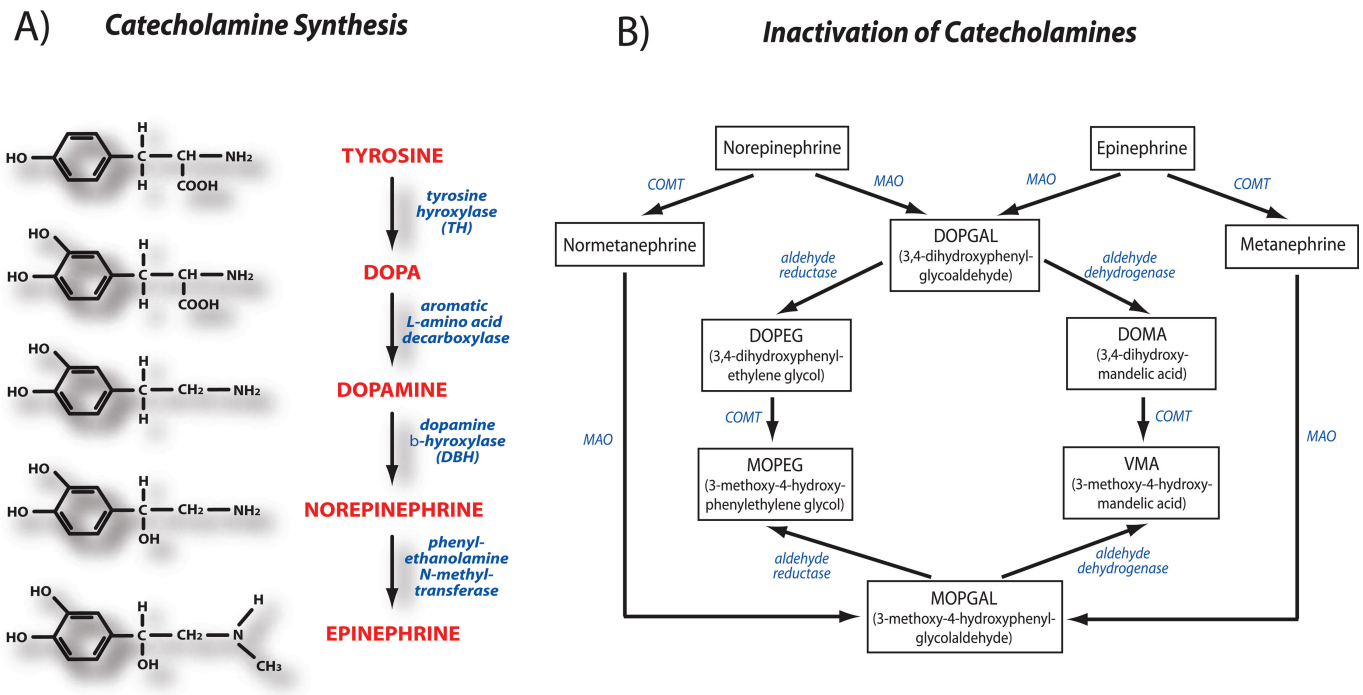

Figure 1. Pathways for synthesis of catecholamines (A) and various metabolizing pathways of catecholamines (B).

Evidence for *de novo* Synthesis, Storage, Release, and Inactivation of Catecholamines by Immune/ Inflammatory Cells

Synthesis. The synthesis of catecholamines relies on two key enzymes: tyrosine-hydroxylase (TH), which is known to be the rate-limiting step in catecholamine synthesis, and dopamine-β-hydroxylase (DBH), which converts dopamine to norepinephrine (3; Figure 1A). The intracellular presence of these hydroxylases and changes in expression of these enzymes strongly implies the ability of cells to synthesize catecholamines *de novo*. Recently, rat phagocytes were found to contain mRNA for both TH and DBH, which clearly were inducible by cell contact with bacterial lipopolysaccharide (LPS) (11). In parallel, rat lymphocytes (22,23) and human PBMCs (24) contain inducible mRNA for these catecholamine-generating enzymes, upregulation of which results in increased levels of dopamine, norepinephrine, and epinephrine when rat lymphocytes were stimulated (22). In contrast, pharmacological inhibition of TH and DBH in rat and human lymphocytes decreased intracellular catecholamine levels in a dose-dependent manner (22,25). Blockade of the conversion of dopamine to norepinephrine (by DBH-inhibition) increased intracellular levels of dopamine and other norepinephrine precursor molecules in human PBMCs (25). Therefore, it is not surprising that the addition of tyrosine and *L*-DOPA to lymphocyte cultures increases catecholamine levels in these cells in a dose-dependent manner (25). Shortly after exposure of human PBMCs to [^{3}H]-*L*-DOPA, [^{3}H]-norepinephrine, and [^{3}H]-dopamine were detected in these cells, suggesting an active uptake mechanism of catecholamine-precursor molecules from the extracellular fluids into human PBMCs (25). Interestingly, these metabolic events are highly selective, because, in contrast to *L*-dopa, *D*-dopa failed to alter catecholamine synthesis in human PBMCs (25). However, human PBMC presents a highly heterogenous group of cells (lymphocytes, monocytes, etc.), making it difficult to draw definitive conclusions about its various cell types.

In summary, these findings suggest that, like neurons and endocrine cells, lymphocytes actively transport tyrosine and *L*-dopa from extracellular sources into the cell to produce catecholamines via catalysis by TH and DBH. Thus, it now is becoming clear that lymphocytes and phagocytes not only possess the ability to produce, store, release, and reuptake catecholamines *de novo*, but that these cells also are capable of exquisitely regulating their catecholamine-synthesis in response to various extracellular stimuli. But, the question remains: how significant is the relative abundance of immune cell-derived catecholamines in comparison to the main catecholamine-producing organ, the adrenal medulla or presynaptic neurons? The adrenomedullary baseline production of epinephrine and norepinephrine in rodents is about 730pg/mL/min and 102pg/mL/min, respectively (26). In a recent study, 10^7 rat neutrophils produced about 100pg/mL and 20pg/mL while 10^7 rat macrophages released nearly 375pg/mL of epinephrine and 50pg/mL of norepinephrine when stimulated with 50ng/mL LPS (11). However, it is important to note that the kinetics of phagocytic catecholamine release is biphasic due to release of stored material versus *de novo* biosynthesis (11). This means that, during inflammatory processes, phagocytic catecholamine levels are linked to a very delicate and dynamic regulation within a local milieu, making it difficult to determine precisely the relative contributions to catecholamines by phagocytes as opposed to the adrenal medulla during inflammation. There do not appear to be definitive publications describing the amount of catecholamines secreted by lymphocytes or presynaptic neurons.

Storage and release of catecholamines. Catecholamines are found throughout adrenergic neurons, but the highest concentrations of these biogenic amines are found in the peripheral presynaptic nerve terminals where these amines are stored in membrane-bound granules and protected from enzymatic destruction (27,28). After depolarizing stimulation of these neurons, rapid secretory release of stored catecholamines occurs. One of the main modes to remove catecholamines that have been released by presynaptic neurons is cellular reuptake of these amines (*see* below). In neurons, this process is known to be inhibited by reserpine. In rodent and human lymphocytes, trace amounts of intracellular catecholamines have been found. In the resting rodent lymphocyte, norepinephrine was the highest content (2.53×10^{-20} M/cell), followed by dopamine (1.29×10^{-20} M/cell) and epinephrine (1.00×10^{-20} M/cell) (22). To date, it seems unclear which role these intracellular baseline catecholamine stores play, because it is only after mitogen stimulation such as phytohaemagglutinin (PHA) (29), concanavalin A (conA) (22), or lipopolysaccharide (LPS) (11), that lymphocyte- or phagocyte-derived catecholamines increase to significant amounts for secretion, affecting cells in an autocrine/ paracrine fashion. Incubation of human PBMCs with reserpine markedly reduced intracellular accumulation of catecholamines, while catecholamine levels in culture supernatant fluids significantly increased (21), suggesting that human PBMCs employ a mechanism similar to neurons, resulting in catecholamine release followed by reuptake. Moreover, studies have revealed that, in accordance with chromaffin cells from the adrenal medulla, secretion of norepinephrine by human lymphocytes depends on acetylcholine and calcium (30,31). Acetylcholine (ACh) facilitated norepinephrine release from peripheral human lymphocytes, as did inflow of calcium into human lymphocytes. Yet, in clear contrast to mechanisms employed by chromaffin cells, blockade of nicotinergic receptors on lymphocytes blocked ACh-induced release of norepinephrine release only by about 50% and blocking of Ca^{2+}-channels attenuated the ACh-induced norepinephrine release by no more than 30% (30,31). Therefore, it is clear that we lack a detailed understand-

ing of the molecular mechanisms involved in catecholamine release by lymphocytes. A recent report identified interferons (IFNs) as molecular regulators of catecholamine synthesis in human PBMCs (29). When human PBMCs were stimulated with phytohaemagglutinin, catecholamine production and release was increased by addition of IFNβ, while the opposite was the case when stimulated PBMCs were exposed to IFNγ which reduced even the mRNA expression of TH. In turn, stimulation with norepinephrine caused mouse Th1 cells to produce two- to four-fold more IFNγ(6), suggesting a negative feedback loop of IFNγ on norepinephrine production. Thus, IFNs seem to emerge as the first physiological compounds that mediate production of catecholamines by human PBMCs. However, PBMCs are a highly heterogenous population of various cell types, making it difficult to draw definitive conclusions from these findings. Thus, achieving a more complete comprehension of the involvement of various ion channels, neurotransmitters, and other mediators triggering catecholamine-release clearly is needed.

Reuptake and degradation of catecholamines by immune/inflammatory cells. Following release of epinephrine and norepinephrine, their activities are terminated by (1) reuptake into nerve terminals, (2) dilution into extracellular fluids and uptake at extraneuronal sites, and (3) metabolic transformation (inactivation) of these catecholamines (32). Two enzymes are essential in the initial steps of metabolic inactivation (Figure 1B): monoamine oxidase (MAO) and catechol-*O*-methyl transferase (COMT) (33,34). MAO and COMT produce physiologically inactive catecholamine-metabolites, but neither of these enzymes plays an important role in the rapid termination of the physiological actions of secreted catecholamines. Rather, this is achieved by active reuptake into presynaptic nerve terminals (27). Human lymphocytes also have been shown to express some of these reuptake transporters. Dopamine-specific binding sites, as well as a dopamine-selective reuptake system, have been demonstrated on human lymphocyte membranes (35,36). Selective blockade of these monoamine transporters suppressed both the dopamine binding to the specific sites and the uptake of [^{3}H]-dopamine. Dopamine-transporter (DAT) mRNA, DAT immunoreactivity, and vesicular monoamine transporter immunoreactivity have been detected on cell membranes and in vesicle-like structures of human lymphocytes (37,38), suggesting DAT on lymphocytes similar to that on neurons. There is some evidence that, in addition to DATs, human PBMCs also may express a norepinephrine transporter (NAT), which would allow for active uptake of catecholamines (12). Nevertheless, the presence of NAT on immune cells remains debatable and additional confirmation is needed for definitive proof (39,40).

As mentioned above, the physiological actions of released catecholamines are terminated primarily by rapid cellular reuptake. Yet, their final intracellular inactivation still relies on the mitochondria-bound MAO and the cytosolic COMT. Several studies have demonstrated the presence of MAO and COMT in human lymphocytes (34,41). Furthermore, metabolites of dopamine, norepinephrine, and epinephrine have been detected in rat lymphocytes (21). Recently, both mRNA and protein for MAO and COMT were found in rat macrophages and rat neutrophils and could be induced by LPS (11). When MAO was inhibited by pargyline, the content of intracellular dopamine, norepinephrine, and epinephrine levels increased in activated human and rat lymphocytes, while intracellular catecholamine metabolites decreased (12,22). Thus, immune cells seem to possess not only the full cellular machinery for *de novo* synthesis, release, and inactivation of catecholamines, but also are capable of intracellular catecholamine-inactivation by MAO and COMT, utilizing the same classical metabolic pathway described in nervous and endocrine systems.

Modulation of Immune/Inflammatory Cell Functions by Catecholamines

Endogenous catecholamines as modulators of immune/inflammatory cells. There is a large body of evidence indicating that, in addition to being crucial neurotransmitters and hormones, catecholamines are important immunomodulators during health and disease (3,42-45; Figure 2). Surprisingly, first reports of the immunomodulating functions of catecholamines were published as early as 1904, describing a robust leukocytosis following subcutaneous administration of epinephrine (46). However, it was not until the mid 1990s that it was reported that lymphocyte-derived catecholamines modulate lymphocyte functions in an autocrine and paracrine manner, providing these cells with a potent tool to fine tune their actions and crosstalk with nearby cells (13). Because the expression of TH and DBH mRNA has been found to be inducible by various stimuli when compared with non-stimulated lymphocytes, it seems likely that the catecholamine synthesis in lymphocytes and phagocytes depends on the functional state of these cells, and that there are diverse cell triggers (11,19,22,23). These auto-regulatory interactions between endogenous catecholamines and immune/inflammatory cells can alter a wide array of cell functions, in part through adrenoceptors or dopaminergic receptors expressed on these cells (10,11,47,48) (*see* below). For instance, it has been observed that the neurotransmitter dopamine, at physiological concentrations, inhibits the proliferation (by downregulating tyrosine kinases) (49-51) and the cytotoxicity of human $CD4^+$ and $CD8^+$ T cells in vitro by acting through the D1/D5, D2, and D3 receptors, making dopamine an important regulator of human T cell functions (52,53). Moreover, exposure of human PBMCs to norepinephrine triggered a very distinct profile of mRNA expression and cytokine production in individual lymphocyte populations, augmenting Th1 (IL-2) and Th2 (IL-4, IL-5, IL-13) type cytokine production, while expression of MIP-1α and

MCP-1 mRNA remained unaffected (8). Similar results were obtained when cells were exposed to dopamine. Thus, it seems likely that catecholamines very selectively activate different lymphocyte subpopulations, leading to a pattern of very distinct expression of inflammatory mediators. It also was demonstrated that catecholamines activate resting T cells by stimulating the release of pro- and anti-inflammatory mediators and alter the expression of surface integrins.

Regulation of immune cell-derived catecholamines. Immune cells seem to regulate their activity and the function of surrounding cells via endogenous catecholamines by two different mechanisms: (a) released catecholamines act in an autocrine/paracrine feedback fashion and (b) catecholamines produced by the adrenal medulla directly activate and modulate intracellular functions of immune/inflammatory cells.

Receptor-mediated autocrine/paracrine mechanisms. It is well established now that immune/inflammatory cells express multiple receptors for catecholamines. Numerous types of adrenergic receptors have been identified on human and rodent PBMCs, macrophages, neutrophils, and lymphocytes (10,11,48,54,55). Dopamine receptor subtypes also have been described on these cells (50,56,57). Adrenoceptors are G-protein coupled, seven-transmembrane spanning receptors (58). Upon interaction with their ligand, intracellular second messengers such as cyclic AMP, calcium ions, diacylglycerol, and inositol 1,4,5-triphosphate become activated and/or inhibited. Therefore, secreted endogenous catecholamines are able to activate the releasing cell itself as well as nearby cells in an autocrine/paracrine manner, stimulating cellular adrenergic/dopaminergic receptors, activating intracellular second messengers, and ultimately regulating cell functions (18,59). Rodent phagocytes have been demonstrated to regulate their release of inflammatory mediators via autocrine/paracrine interactions of endogenous catecholamines with adrenergic receptors expressed on their cell surfaces (10,11,18). Blockade of α- and β-adrenoceptors on human or rodent macrophages, neutrophils, and lymphocytes significantly inhibited the cytokine/chemokine production of these cells (10,11,18,60). These findings make it tempting to speculate that the inflammatory cytokine/chemokine network might be one of the important mediator systems tightly controlled by catecholamines via adrenergic receptors. Yet, it remains to be determined if catecholamine secretion by immune cells is a ubiquitous phenomenon or if it is, rather, an ultimate weapon of immune cells facing overpowering pathogenic insults. The physiological counterpart of the adrenergic system, the cholinergic system, also is known to be an integral part of human macrophage and lymphocyte regulation. Human macrophages are known to control their cytokine release via interactions of acetylcholine with nicotinic acetylcholine receptors expressed on cell membranes (61,62). Stimulation of the α7 subunit of the nicotinic acetylcholine receptors on macrophages greatly inhibited production of tumor necrosis factor (TNF)α, interleukin- (IL-)1β, HMGB1 (and other cytokines), by transducing a cellular signal that inhibits the nuclear activity of NF-κB and activates the transcription factor STAT3 via phosphorylation by JAK2 (63). Human peripheral blood lymphocytes also have been shown to express various cholinergic products including acetylcholine, choline acetyltransferase (ChAT), acetylcholinesterase (AChE), and vesicular acetylcholine transporter (VAChT), as well as M_2-M_5 muscarinic cholinergic receptors (38). As evaluated by confocal microscopy, acetylcholine and VAChT were clustered in punctiform intracellular areas (which most likely correspond to cytoplasmic storage vesicles), while ChAT and AChE were spread diffusely throughout the cytoplasm. As expected, muscarinic receptors were localized in the cell membranes (38). To date, however, it is not clear how these lymphocytic cholinergic markers may contribute to the regulation of immune functions.

Receptor-independent intracellular regulatory mechanisms. Following termination of their actions and cellular reuptake, catecholamines are oxidized intracellularly by the mitochondrion-associated MAO and the ubiquitous cytosolic COMT. During inactivation, catecholamines are degraded into various products including large quantities of reactive oxygen species and other cytotoxic oxidative metabolites, which are known to induce cellular apoptosis in mouse lymphocytes, human PBMCs, and PC12 cell lines (14,64-67). Newly synthesized intracellular catecholamines might not be released immediately but stored inside the cells, which may put cells in jeopardy of receptor-independent and oxidative stress-induced apoptosis (39). This theory is supported by the finding that stress-induced apoptosis can be blocked by the anti-oxidant ascorbic acid (19). Therefore, it seems likely that catecholamines use intracellular oxidative mechanisms to exert autoregulatory functions on immune cells. Even more importantly, a catecholamine-specific transporter has been described on nuclear membranes of lymphocytes, which actively transports catecholamines from the cytoplasm into the cell nucleus where catecholamines interact with nuclear receptors such as steroid receptors (16,68), influence transcription processes via interaction with nuclear factor (NF-)κB, and modulate apoptosis (69) by facilitating the expression of proto-oncogene *Bax* while attenuating *Bcl-2* expression (16,17). It is noteworthy that the mitochondria-associated MAO and the cytosolic COMT fail to enter the nucleus, posing the important but so far unanswered question of how and by what mechanism intranuclear actions of catecholamines are terminated.

IMMUNE CELL-DERIVED CATECHOLAMINES DURING SHOCK AND SEPSIS

Foolishly Unlocking Pandora's Box?

Even though catecholamines are used frequently, sometimes even as last-resort

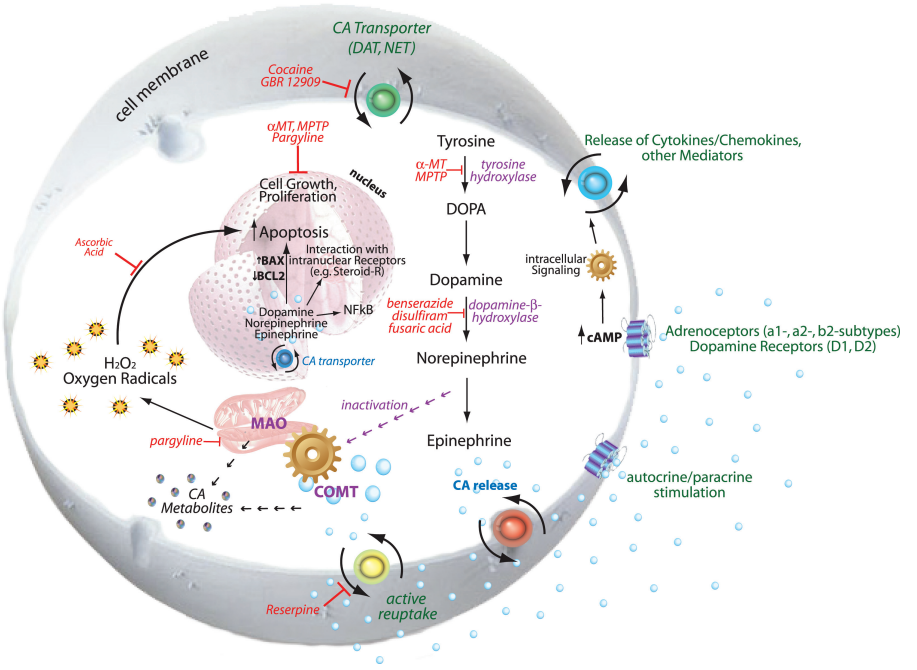

Figure 2. Summary of the various interactions between catecholamines and lymphocytes/phagocytes. Most of these actions have been demonstrated in lymphocytes (*see* text).

drugs to stabilize cardiovascular functions in the critically ill patient, there are several potentially fatal consequences of lymphocyte/phagocyte-derived or exogenously administered catecholamines, in addition to the above described immunomodulatory properties, that need to be taken into account.

Shock. The state of shock leads to a strong activation of the sympathetic nervous system resulting in a massive increase of circulating catecholamines. When endogenous catecholamine-release fails to stabilize cardiovascular parameters, therapeutic catecholamines frequently are administered. Therefore, it is essential to understand the immunomodulatory effects of endogenously released or administered catecholamines in the setting of shock. As expected, hemorrhagic shock induces a robust increase of circulating epinephrine and norepinephrine in an experimental animal model (70). While these increases were paralleled by an elevated number of circulating natural killer (NK) cells and an elevated $CD4/CD8^-$ ratio, levels of circulating $CD8^+$ lymphocytes significantly decreased. Moreover, an increased rate of splenocyte apoptosis was noted 24 h after induction of hemorrhage. All of these effects could be abolished by administration of nonselective or β_1-selective adrenergic blockade without affecting serum cytokine concentrations of TNFα or IL-10 (70). In addition, when noradrenergic neurons were depleted within the central nervous system, cellular cytokine release was affected significantly during hemorrhagic shock (71-73). Thus, hemorrhagic shock leads to vigorous increases in circulating catecholamines, which finally modulate immune cell functions via adrenergic receptors expressed on these cells. Surprisingly, it has been shown that massive, trauma-induced activation of the sympathetic nervous system with subsequent robust release of norepinephrine leads to increased in vivo growth of bacteria within the gastrointestinal system in an experimental animal model, which most likely contributes to the high incidence of systemic bacterial inflammation and sepsis following trauma hemorrhage (74). Most importantly (or shockingly), it was discovered that catecholamines *directly* stimulate bacterial growth. It was reported that catecholamines enhanced growth of several gram-negative bacteria and the production of bacterial growth factor in cultured *E. coli* (75-77). However, to date, it is unclear under precisely what conditions catecholamines inhibit or augment bacterial growth, because norepinephrine and epinephrine failed to demonstrate uniform effects on bacterial growth (78).

Sepsis and septic shock. One of the most challenging subtypes of shock clinically is the septic shock, which is characterized by impaired functions of heart and vessel tone, despite high concentrations of circulating catecholamines (79). Yet, administration of catecholamines often becomes the choice of last resort to maintain blood pressure in patients with septic shock (80). In an experimental model of sepsis, infusion of epinephrine was associated with profound alterations of cellular immune functions analogous to those observed in hemorrhagic shock: all lymphocyte subsets decreased, while the splenocyte apoptosis rate and number of circulating NK cells increased (81). Moreover, splenocyte proliferation and cytokine release was inhibited, whereas apoptosis-rate of splenic lymphocytes was increased (81). In parallel, infusion of dopamine decreased the survival rate of septic mice. Thus, there seems to be a universal pattern for catecholamine effects during sepsis, which might be modulated by cellular adrenoceptors: splenocytes are driven into apoptosis, lymphocyte counts decrease (perhaps due to apoptosis), while NK cell numbers increase. Dopamine is another commonly used drug to prevent renal failure and treat moderate hypotension in the critically ill (82). Dopamine also is an agonist of α- and β-adrenergic receptors, but exerts its effects mainly via

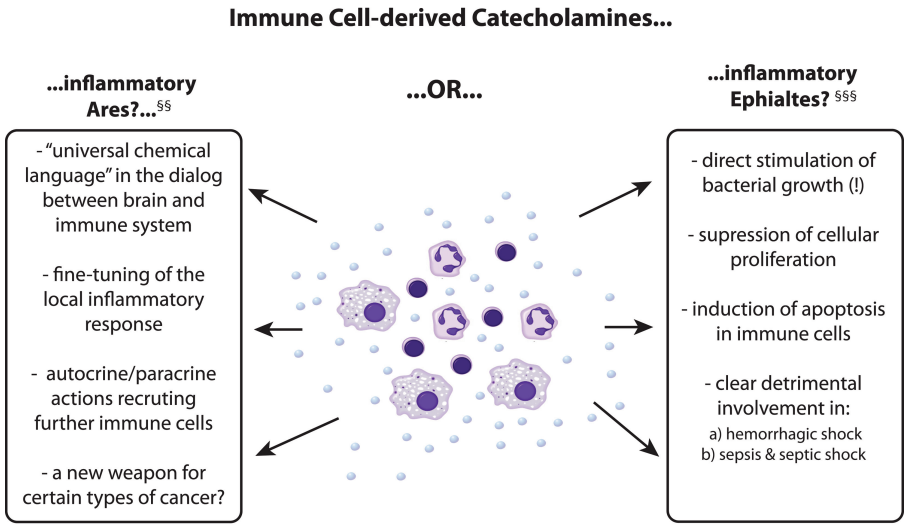

Figure 3. Lymphocyte- and phagocyte-derived catecholamines seem to be a double-edged sword. Some of these bidirectional actions during inflammation are listed.

specific dopaminergic receptors that can be found on a large number of cells including lymphocytes (83). In physiological concentrations, dopamine inhibits the proliferation and cytotoxicity of human $CD4^+$ and $CD8^+$ lymphocytes in vivo and in vitro via the dopamine receptors (52,84-86), paralleling the adverse effects of epinephrine and norepinephrine.

Lately, the gut has also been identified as an alternate source of catecholamines during sepsis in rodents, releasing norepinephrine into the portal vein and thereby altering the functional state of hepatocytes and Kupffer cells, unexpectedly contributing to hepatocellular dysfunction during sepsis (87-90). This mechanism also seems to be mediated via α_2-adrenoceptors (88).

Unfortunately, there are only a few human studies investigating the immunomodulatory effects of catecholamines in septic patients. Yet, evidence now is emerging that the pro- and anti-inflammatory "cytokine-/chemokine storm" occurring in septic patients seems to be modulated, at least in part, by epinephrine. In parallel to various animal studies, immunosuppressive actions of catecholamines seem to be co-regulated by the β-adrenoceptor in humans (91,92). Thus, catecholamines clearly contribute to the severe immunodysregulation occurring during septic shock.

It is important to be aware of these adverse effects of catecholamines in critically ill patients. Although catecholamines are textbook drugs for various settings in patients suffering from severe trauma, hemorrhagic shock, sepsis or septic shock, their administration needs to be evaluated carefully on an individual basis to maximize benefit and minimize adverse effects of catecholamine administration.

Or Skilled Hephaestus§§§§ Going to Work?

Despite all these potentially harmful actions described above, there are several benefits of endogenous catecholamines (Figure 3). First of all, in addition to neuropeptides, the neuro-endocrine-immune network produces powerful mediators enabling rapid communication and fine-tuning of the nervous, endocrine, and immune systems. A recent report allows a brief foretaste of how exquisite this fine-tuning might in fact be. Blockade of diverse adrenoceptors on rat phagocytes variably inhibited expression of different cytokines and chemokines (11). TNFα production was inhibited completely by blockade of the α_2-adrenoceptor or high-dose blockade of the β_2-adrenoceptor, while remaining completely unaffected by α_1- or β_1-adrenoceptor blockade. In sharp contrast, IL-1β levels were suppressed greatly by pharmacological blockade of either α_1-, α_2-, β_1-, or β_2-adrenoreceptors. IL-6 and CINC-1 production by phagocytes was regulated by either α_2-, β_1-, or β_2-adrenoreceptors, respectively. Because norepinephrine has higher affinity for the α-adrenergic receptors and epinephrine for β-adrenoceptors, it might well be that these two catecholamines display dissimilar effects on phagocytes which could define a very distinct inflammatory mediator pattern best suited for a particular inflammatory setting. A better understanding of these observations might provide us with many new pharmacological targets to dampen inflammation. Finally,

Footnote §§: *Ares, son of Zeus and Hera, is the Greek God of savage war, bloodlust and slaughter.*

Footnote §§§: *Ephialtes guided Xerxes' Persian forces around the allied Greek troops who were blocking the pass of Thermophylae in 480 BC, leading to the last stand of the Leonidas and his 500 Spartans. The malicious treacherousness of this ancient character is still being remembered today, as Ephialtes literally means "nightmare" in Modern-Greek.*

Footnote §§§§: *Hephaestus, son of Zeus and Hera, is the Greek God of technology, blacksmiths, metallurgy and fire. His skilled craftsmanship is thought to have created many of the splendid equipment of the Greek Gods, and most of the power-imbued metalworks that appear in Greek mythology: Hermes' winged helmet and sandals, Aegis' breastplate, Aphrodite's legendary girdle, Achilles' armor, Heracles' bronze clappers, Helios' chariot and Eros' famed bow and arrow.*

recent research reports suggest that catecholamines might be cytotoxic for human neuroblastoma cells (93,94). While specific types of cancer might present an appealing new target for catecholamine-dependent immunomodulation, this needs to be further evaluated.

CONCLUSIONS

Besides the adrenomedullary chromaffin cells and neurons, lymphocytes, and phagocytes represent a third category of catecholamine-producing cells. They are able to synthesize and release endogenous catecholamines *de novo* which can modify various pathological responses, all of which challenges traditional paradigms. The wide distribution of immune cells throughout the body, combined with their ability to migrate to the site of inflammation, underscores the dynamic role of immune/inflammatory cells. Targeting lymphocyte/phagocyte-derived catecholamines will pose an extremely challenging quest for researchers. Because catecholamines are not proteins, usage of neutralizing antibodies seem an unlikely strategy. The fact that immune cells utilize the very same molecular pathways as the adrenal medulla and neurons defies classical immunological approaches such as blocking catecholamine-producing enzymes by antibodies or RNA-silencing to inhibit immune/inflammatory cell-derived catecholamines. Moreover, myriad actions of endogenous catecholamines occur inside the cell and perhaps even in the nucleus, further complicating a selective targeting attempt. However, extending our understanding for extra- and intracellular adrenergic regulation of lymphocytes and phagocytes, its implications and its possibilities might deepen our understanding of the pathogenesis of diverse diseases and ultimately might result in great curative advances.

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