INTRODUCTION

Diabetes has become an increasingly prevalent disease worldwide. According to the WHO, there are more than 220 million diabetics worldwide, and it is estimated that this number will double by 2030. Increased susceptibility to infection is one of the pathological alterations associated with diabetes, apart from changes to the kidneys and cardiovascular system (1-3). Certain types of infections are more commonly found in patients with diabetes, while some types of infections are almost exclusive to diabetic patients. Studies on the impaired function of immune cells in diabetes are conducted for a long time, but the etiology of alterations in the functioning of T and B lymphocytes is still poorly understood. The impaired function of lymphocytes in diabetes may be attributed to the direct effect of hyperglycemia and/or hypoinsulinemia that alters the regulatory network of immune cells. Adenosine is an endogenous nucleotide that modulates the immune response. Its immunosuppressant and anti-inflammatory effects are recognized universally (4).

Alterations in T lymphocyte function and an increased risk of lower respiratory tract, urinary tract, skin and mucous membrane infections are common features of both type 1 and type 2 diabetes in humans (5). There is a strong correlation between the one’s increased susceptibility to infections and poor metabolic control in diabetes (6, 7). Patients with insulin-dependent diabetes mellitus (DM1) display a suppressed proliferative response of CD4+ T-cells to primary antigens (8, 9). Studies on peripheral blood mononuclear cells from diabetic patients demonstrate a decreased basal production of cytokines (10, 11). Moreover, it was revealed that the impaired proliferation of lymphocytes in type 2 diabetes patients couldn’t be ameliorated by interleukin-2 (IL-2) during phytohemagglutinin (PHA) treatment (12). Nervi et al. (13) showed that TCR/CD3-mediated proliferation of polymorphic nuclear blood cells from DM1 patients was markedly impaired compared to control subjects. Decreased thymidine uptake by lymphocytes, along with a lower percentage of IL-2 receptor positive cells and increased plasma levels of tumor necrosis factor were also observed in type 2 diabetes 2 (11, 12, 14). In diabetic mice, in turn, the secretion of IL-4 was markedly reduced, in contrast to the secretion of IL-2 and interferon-gamma, which remains unaffected (15). A high rate of apoptosis was observed in lymphocytes obtained from diabetic patients and isolated from alloxan-induced diabetic rats (16). So far, however, there is no consensus as to the occurrence of a reduction in the humoral immune response (function of B cells) in diabetic patients since previous studies revealed both definitive (17-19) and normal (20-22) antibody production following vaccination. These ambiguities may result from the heterogeneity of the groups compared in terms of diabetes type or the antigen used for immunization. Recently Ebil et al. (9) revealed that the primary antibody response to T cell dependent antigens is

ALTERED FUNCTION OF LYMPHOCYTES IN DIABETES

Adenosine plays an important role in physiology of several organs. Its turnover inside and outside of the cell is controlled by several enzymes and transport processes. The action of extracellular adenosine is mediated via at least four receptors named $A_1$, $A_2a$, $A_2b$, and $A_3$. Recent studies have reported that adenosine is a significant mediator of regulatory lymphocyte function. Numerous data indicates that adenosine affects T lymphocyte activation, proliferation and lymphocyte-mediated cytolysis. Impaired lymphocyte functioning and enhanced susceptibility to infections is a common feature of human diabetes. This review collects data bringing us closer to understanding the disturbances in lymphocytes adenosine homeostasis in diabetes. Adenosine receptors and nucleoside transporters are targets for potential drugs in many pathophysiological situations. Therefore, action of adenosine on lymphocyte function in diabetes may be important target for modulation of immune responses and understanding of mechanisms leading to several pathologies of immune cells observed in diabetes.

Keywords: adenosine, diabetes, glucose, insulin, lymphocytes
reduced in patients with type 1 rather than type 2 diabetes. Rubinstein, who analyzed the effect of diabetes on the generation of an antibody response in vivo, suggested that diabetes induces significant decreases in IgG levels after six months of diabetic induction and during the early secondary response (23).

The reasons behind the increased susceptibility of diabetic patients to persistent infections and impaired lymphocyte proliferation are not fully understood. Some of the altered functions of diabetic lymphocytes (such as a reduction in the production of IL-2, IL-6 and IL-10) may result from elevated glucose concentrations (24), and normal proliferation of lymphocytes has been restored following insulin administration (2, 3). One can assume that elevated glucose concentration affects the action of factor(s) that regulate the lymphocyte function. It was observed that adenosine metabolism and release from various cells is altered in diabetes (25).

THE ADENOSINE EFFECTS ON T AND B CELL FUNCTION

The regulatory role of adenosine in the immune system has been documented by many experimental and clinical observations (26, 27). Years of studies have revealed that adenosine can modulate lymphocyte T activation and proliferation, production of pro-inflammatory cytokines, and cell mediated cytolysis (39-42). Activation of A2A-ARs inhibits the TCR-triggered up-regulation of the IL-2 production and lymphocyte proliferation, whereas activation of both A2A and A1-ARs can induce apoptosis in T cells (49-51).

Under normal physiologic conditions, the level of adenosine in the tissue microenvironment is relatively low and increases during hypoxia, ischemia, inflammation, infection and metabolic stress (52). The main source of extracellular adenosine during metabolic stress is extracellular catabolism of released from the cell purine nucleotides by a cascade of ectonucleotidases. The second major source of extracellular adenosine is intracellular adenosine, which is released by nucleoside transporters, when intracellular adenosine levels rise (e.g., degradation of intracellular ATP in ischemic conditions). In patients with septic shock, plasma adenosine reaches levels of 4–10 µM, whereas such high values are not observed in healthy individuals (53). Furthermore, in prolonged and/or inappropriate inflammatory diseases, adenosine concentrations in the range of 100 µM have been found (e.g., in synovial fluid of patients with atherosclerosis). Adenosine levels below 1 µM have little influence on immune cells, but at concentrations of 3 µM and higher this molecule is an important and strong immunosuppressor of T cells.

DISTURBANCES OF ADENOSINE HOMEOSTASIS IN DIABETIC LYMPHOCYTES

SYNTHESIS AND METABOLISM OF ADENOSINE

Adenosine is both a metabolic precursor for nucleic acids and an important signalling molecule. It is continuously generated inside the cell as well as extracellularly. Adenosine concentration and its net release or uptake by lymphocytes depends on the activity of several enzymes. On the cell surface adenosine is generated during ecto-enzymatic hydrolysis of purine nucleotides by ecto-nucleotidase. This pathway comprises at least three ectoenzymes: ecto-NNP (EC 3.1.4.1), ecto-NTPase-1 (CD39, EC 3.6.1.5) and ecto-5'-nucleotidase (EC 3.1.3.5) and regulates local and pericellular concentration of adenosine (54, 55). Ecto-5'-nucleotidase (CD73) that hydrolyse adenosine to adenine is up-regulated during T cell activation events results in significant reduction of IL-2 production in activated human cells (47). Recent findings presented by Zarek at al. demonstrate that stimulation of A2A-ARs by adenosine promotes long-term T-cell anergy and leads to generation of adaptive regulatory T cells (48). It seems that A2A and A1-ARs mediate the effects of adenosine on IL-2 production and lymphocyte proliferation, whereas activation of both A2A and A1-ARs can induce apoptosis in T cells (49-51).

Adenosine is an endogenous nucleoside formed both in the extracellular space and inside the cell. Metabolic changes that occur in the course of diabetes are reflected by elevated adenosine concentrations in some tissues (34, 35). Increased intracellular levels of adenosine may lead to its release into the extracellular space and consequent activation of the receptors located on the surface of the same or surrounding cells. Therefore, adenosine generated under diabetic conditions may modulate lymphocyte function in an autocrine or paracrine fashion. It is proposed that adenosine receptors could be promising therapeutic targets in autoimmune diseases (36). This proposition based on observation that NECA, an adenosine receptor (AR) agonist ameliorated the course of diabetes and protected the pancreas from immune-mediated β-cell destruction in animal models of type 1 diabetes. The multiple effects of purinergic (P1) receptors on T cell effector function and the modulation of immune cell activation have been studied since the 1970s. Many of the adenosine effects on thymocytes and T cells were solved during studies in patients with adenosine deaminase (ADA) severe combined immunodeficiency. The lack of ADA activity results in elevated level of intracellular and extracellular adenosine and derived compounds, which leads to the severe depletion and functional defects of T and B cells. Adenosine plays a potential role in the regulation of thymocyte differentiation by elevating CAMP in immature thymocytes and inducing their apoptosis (37). On the other hand, adenosine can regulate the positive and negative selection of thymocytes by providing a TCR-inhibiting signal to immature CD4+CD8+ thymocytes (38).

Numerous observations have revealed that adenosine can inhibit peripheral T cell activation, proliferation, the production of pro-inflammatory cytokines, and cell mediated cytology (39-42). Activation of A2A-ARs inhibits the TCR-triggered up-regulation of the IL-2 receptor (4). Moreover, exposure to extracellular adenosine blocks FasL mRNA up-regulation (43). This decrease in FasL expression after A2A-AR stimulation protects CD4+ T lymphocytes against activation-induced cell death (44). A2A-ARs may regulate cytokine production in activated T lymphocytes. An example of such an effect is the inverse relationship between elevated plasma concentrations of adenosine and decreased ratios of IFN-gamma to IL-4-producing CD4+ T cells observed in pregnancy (45). Also, A2A-AR activation was recently shown to inhibit Th1- and Th2- cell development by decreasing the proliferation and IL-2 production of naive T cells (46). Furthermore, activation of A2B-ARs that are up-regulated during T cell activation events results in significant reduction of IL-2 production in activated human cells (47). Recent findings presented by Zarek at al. demonstrate that stimulation of A2A-ARs by adenosine promotes long-term T-cell anergy and leads to generation of adaptive regulatory T cells (48). It seems that A2A and A1-ARs mediate the effects of adenosine on IL-2 production and lymphocyte proliferation, whereas activation of both A2A and A1-ARs can induce apoptosis in T cells (49-51).

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production under normoxic, but not hypoxic conditions (59). Intracellular level of adenosine depends not only on reactions producing adenosine, but also on its conversion to other compounds. One of such a reaction is the formation of SAH from adenosine and L-homocysteine in a SAH hydrodrolase reversible reaction. Adenosine can be converted into AMP by cytoplasmic adenosine kinase (AK) (EC 2.7.1.20) and/or be transformed into inosine by adenosine deaminase (ADA) (EC 3.5.4.5) (60-62). Inosine is further degraded to uric acid or returned to the pool of purine nucleotides in the reaction catalyzed by the hypoxanthine-guanine phosphoribosyltransferase (EC 2.4.2.8). There are two different types of ADAs: ADA1 and ADA2 (63). ADA1 is present in the cytoplasm, but also is found on the cell surface. Ecto-ADA1 is anchored on T cell surface by integrating with CD26 (dipeptidylpeptidase IV, EC 3.4.14.5) (64, 65). The activity of membrane bound ADA in T lymphocytes is lower than in B lymphocytes (66, 67). It has been demonstrated that this enzyme plays a putative role in the lymphocyte differentiation (68). Moreover ecto-ADA1 interacts with A1 and A2B-Ar, changing their affinity for adenosine (68, 69). Membrane ADA1 in activated human lymphocytes is regulated by cytokines. The level of ecto-ADA1 and CD26 expression is up-regulated by IL-2 and IL-12. In contrast, IL-4 leads to the down regulation of ADA on lymphocyte surface (70). ADA2 is secreted by dendritic cells or monocytes differentiating into macrophages and is anchored on the cell surface via proteoglycans and adenosine receptors. This enzyme has low ADA activity (100-fold higher Km comparing to that of ADA1), but exhibits a growth factor-like activity and stimulates proliferation of T helper cells (71).

A comparison of adenosine-metabolizing enzymes operating in B and T cells shows a similar activity of AMP deaminase, but higher AK and ADA activities in cytoplasm of T cells. On the other hand B cells are able to release higher quantities of adenosine because of high 5'-NT and low AK and ADA activities (72). Moreover, comparing to T cells B cells exhibit a higher extracellular level of nucleotide-hydrolysing activity (73). Barankiewicz et al. suggested that B lymphocytes are the only source of adenosine, while T lymphocytes being the recipients of adenosine generated signal (73). Extracellular catabolism of ATP (e.g. circulating in plasma) proceeds via sequential ecto-enzymatic nucleotide breakdown to AMP and adenosine. The expression of ecto-nucleotidases is associated with B cell development. It is observed that expression of ecto-ATPase, ecto-ADPase and ecto-AMPase increases continuously with maturation of B cells reaching maximal activity level in late pre-B-cells. Recently we demonstrated that ATP continuously released from B cells constitutes the primary source of peripheral adenosine (74). Thus, the activities of ecto-enzymes and efficiency of adenosine uptake by the nucleoside transporters determine the adenosine level in lymphocyte periphery. The work performed on laboratory animals and observations in humans indicate that both these factors are altered in diabetes. Increased blood level of ADA activity was demonstrated that the activity of 5'-NT increases in lymphocytes of diabetic patients (78). We observed that incubation of rat T cells or human B lymphocytes at high glucose concentrations (25 mM) results in elevation of both cytosolic and ecto 5'-NT activities (66, 67). The mechanism by which high glucose induces the activity of 5'-NT is largely unknown. Stefanovic and coworkers demonstrated that administration of gliclazide (but not glibenclamide) to obese type 2 diabetic patients leads to the reduction of lymphocyte 5'-NT activity (78). Since, gliclazide (but not glibenclamide) owing to its unique aminoazabicyclo-octane ring has free-radical-scavenging ability it might be assumed that elevated 5'-NT activity in diabetics is related to the oxidative stress. However, the precise mechanism of gliclazide-induced reduction of 5'-NT activity in diabetic lymphocytes remains unknown. Rucker et al. demonstrated an increase in ATP, ADP, AMP and 5'TMP hydrolysis in the serum of diabetic rats (79). However, the hydrolysis returned to normal levels following insulin therapy. Authors suggested that increased hydrolysis of extracellular ATP is the leading cause of the elevated level of adenosine in the blood of diabetic animals. Although, in another study no significant differences in ATP, ADP and AMP levels in resting rat T cells cultured at various glucose and insulin concentrations were observed (66). However, in the absence of insulin, T lymphocytes became more susceptible to metabolic stress releasing higher quantities of adenosine. Moreover, changes in the concentrations of insulin did not influence the activities of AMP deaminase, 5'-nucleotidase and adenosine deaminase in rat T lymphocytes. The only enzyme whose activity was dependent on insulin concentrations was adenosine kinase (80). In the absence of insulin the activity of this enzyme in T lymphocytes decreased by ~75%, independently of glucose concentrations. In turn, changes in glucose concentrations modulated the activity of ecto-5'-nucleotidase and level of ADA bound to the plasmatic membrane of T lymphocytes. Both, the ecto-5'-NT and membranous ADA activities were 2-fold higher in cells cultured at 20 mM glucose compared to those cultured at 5 mM glucose, independent of insulin concentrations (66). Proliferating T lymphocytes in response to stimulation with Con-A exhibited marked changes in the activities of AMP deaminase, ADA and 5'-NT, but no changes in AK activity were observed in these cells. This suggests that adenosine metabolism in T lymphocytes depends both on the phase of the cell cycle and the concentrations of glucose and insulin. T lymphocytes cultured in 20 mM glucose and the absence of insulin secrete significant amounts of adenosine into the culture medium. Conversely, the concentration of adenosine is hundreds times lower in the media of cells cultured in 5 mM glucose and the presence of insulin (66). Studies on human B lymphocytes revealed that the activities of ADA and 5'-NT, but not AK depended on glucose and insulin concentrations in the culture media (67). However, changes in these enzymes activities do not correlated with adenosine level in the cell media during accelerated ATP catabolism (67), impaling a rate-limiting role of nucleoside carriers in adenosine outflow from the cell.

ADENOSINE TRANSPORT

The extracellular concentration of adenosine depends on the balance between its release from the cells, generation by ecto-nucleotidases on the cell surface, and its re-uptake by the bi-directional adenosine transport processes. Thus, adenosine transport seems to be an important regulator of adenosine action, since the efficiency of this process may determine adenosine availability either to receptors or to metabolizing enzymes. Two types of nucleoside transport systems are known to mediate nucleoside transport across the plasma membrane: the equilibrative facilitated-diffusion type (ENT) and the concentrative Na+-dependent one (CNT) (81, 82). Other non-specific candidates for nucleoside carriers across plasma membranes are the organic anion and cation transporters, peptide transporters, and ABC protein family members (83). In human peripheral blood lymphocytes the expression of hCNT2, hCNT3, hENT1 and hENT2 transporters has been reported (84). Human leukocytes uptake adenosine predominantly (55%) by ENT1 transporter (84). Many studies have demonstrated that the expression level of nucleotide transporters depends on the type...
of cell and its physiological status. Moreover, exposition of the cell to various hormones (triiodo-L-thyronine, glucagon, insulin), glucose, cytokines (M-CSF, INF-gamma) and/or activators such as PMA, and LPS modulates the expression and activity of nucleoside transporters NT (85). Our knowledge on the regulatory properties of nucleoside transporters in T and B cells is limited. Proliferation of activated T cells involves the synthesis of new RNA and DNA and utilization of the intracellular pool of nucleotides and deoxynucleotides, which originates from de novo synthesis and/or from the nucleoside salvage pathway. In immune cells, de novo synthesis is limited, and the salvage pathway predominates, relying on the cell’s ability to uptake nucleosides from the extracellular milieu (86). It is known that resting human peripheral blood lymphocytes (PBL) have low transport rates of nucleotides and a low density of nitrobenzylthioninose (NBMPR) binding sites. However, about a 30-fold increase in the density of NBMPR binding sites occurs after stimulation with PHA or anti-CD3 (87, 88). The tight relationship between the proliferation rate and the number of NT confirm observations performed on lymphocytes from patients with lymphomas and myeloid leukemias (89). In diabetes the adenosine transport in lymphocytes is altered due to the changes in expression level of NT (90, 91). In rat T lymphocytes the expression level of rENT2 and rCNT2 highly depends on insulin, whereas the expression of rENT1 is sensitive to glucose. In T cells cultured at high glucose (25 mM) and the absence of insulin, the expression level of rENT1 and rENT2 decreases while expression level of CNT2 increases significantly (90). These alterations in NT expression leads to the reduction of adenosine transport rates and depletion of its intracellular level. Diabetic B lymphocytes displayed similar changes in NT to that observed in T lymphocytes. An elevated level of glucose suppresses expression of the rENT1 transporter in B lymphocytes through the MAP kinase pathway, whereas transmission of insulin signaling necessary to maintain rENT2 expression depends on phosphorylation and 3-kinase PI3K activity. The effect of insulin on rCNT2 expression relays on MAP kinase and to a lesser extent on PI3K.

In summary, the increase in glucose levels independently of insulin significantly reduces the expression of ENT1 transporter, which in T and B cells accounts for 80% of adenosine transport. While the ENT2 and CNT2 expression is regulated only by insulin.

ADENOSINE RECEPTORS

Adenosine exerts its biological effect by coupling to cell-surface receptors. To date four adenosine receptors (ARs) have been identified namely A1-AR, A2A-AR, A2B-AR, and A3-AR (92). Adenosine is the major ligand for these receptors however, recently it has been demonstrated that also inosine a metabolite of adenosine is able to activate some ARs effectively (93). It has been observed that extracellular inosine has anti-inflammatory and immune suppressive effects, which could be blocked partially by A1-AR and A2A-AR antagonists (94). Each of the four adenosine receptor subtypes is coupled to a cell protein called a G-protein, which is capable of stimulating (Gs protein) or inhibiting (Gi protein) the production of intracellular cAMP. Changes in the levels of cAMP influence the activity of intracellular protein kinases that phosphorylate intracellular proteins or transmembrane ion channels during physiological responses (95). Adenosine at physiological levels (below 1 μM) can activate A1-AR, A2A-AR, and A3-AR, whereas much higher concentrations of this nucleoside generated under pathophysiological conditions are required to stimulate A2B-AR (96-98). In lymphocytes all four ARs are expressed, although to different extend. It has been demonstrated that the A2A-AR, A3-AR and A1-AR are expressed on human and rodent T lymphocytes (4, 45, 47-51, 69, 97, 98), whereas the expression of A2A-AR on these cells is low or it is not expressed at all (4, 42, 99). Expression of A2A receptors is much stronger on peripheral T lymphocytes compared to B lymphocytes (4, 97). Under in vitro and in vivo conditions activation of A2A-AR and A3-AR negatively regulates pro-inflammatory and anti-tumor effects of activated T cells (100). Development of diabetes results in an altered expression of ARs in many types of cells including lymphocytes (101-104). In experimentally induced diabetes, the expression level of adenosine receptors on T cells is altered, except for the A1-AR. In diabetic T lymphocytes there is a significant increase in level of A1-AR mRNA and a slight increase in A3-AR mRNA, whereas a level of A2A-AR mRNA significantly decreases. These changes in expression of ARs in diabetic T cells depend on hyperglycemia and/or hypoinsulinemia. Studies on the expression of ARs in B lymphocytes cultured at different insulin concentrations showed that the presence of this hormone in the culture medium resulted in an increase of A2A-AR and A2B-AR mRNA and protein levels, along with a decrease in A1-AR mRNA and protein levels. The expression level of A1-AR was significantly decreased in diabetic T lymphocytes cultured at different insulin concentrations showed that the presence of this hormone in the culture medium resulted in an increase of A2A-AR and A2B-AR expression through Ras/RAF-1/MEK/ERK and suppressed A2A-AR expression by activation of p38 MAP kinase (103). On the other hand increased glucose concentration suppressed the expression of A2A-AR, A2B-AR and A1-AR, but had no effect on A2A-AR level (104). Moreover, it appears that high glucose suppresses expression of adenosine receptors in B lymphocytes utilizing some elements of MAPK signaling pathway and different protein kinase C isoforms. It is generally believed that activation of A1, A2A, and A2B AR stimulates immune cell function, whereas ligation of A2A, A3, and A2B receptors is reflected by immunosuppression. Comparison of changes in expression level of ARs in B lymphocytes induced by low insulin level and high glucose suggests that A2B-AR may become the predominant adenosine receptor found on B cells during the course of diabetes. Consequently, B cells might be more sensitive to suppression by adenosine, released by interacting T lymphocytes.

In conclusion, the quantitative and qualitative expression levels of adenosine receptors differ significantly between T and B lymphocytes, and glucose and insulin regulate expression of adenosine receptors in these two types of cells in a different manner.

THE ADENOSINE EFFECT ON LYMPHOCYTE FUNCTION IN DIABETES

Proliferation of lymphocytes is a crucial step in cell-mediated immunity. A reduction in the proliferation potential is one of the most widely observed T cell functional defects associated with diabetes. However, the mechanisms responsible for impaired lymphocyte proliferation in diabetic patients remain largely unclear. Some reports point to disturbances in cytokines production and reduction in number of cell bearing their receptors and decreases in the expression of complement receptor CR-3 (7, 12). Our studies showed that suppressed proliferation of diabetic T lymphocytes is the result of reduced expression of AK, which leads to increased outflow of adenosine from the cells. Outside the cell adenosine by stimulating A2A-AR leads to increase of cAMP synthesis in the cell and suppression its proliferation in a PKA-dependent manner. Moreover, the level of A2A-AR expression increases in diabetic T lymphocytes (99). In diabetic B lymphocytes the expression level of AR changed differently compared to T cells. The level of A1-AR, A2A-AR, and A3-AR expression decreases, whereas level A2B-AR
remains unchanged (103, 104). This might suggest that the sensitivity of diabetic B cells to adenosine decreases. Moreover, adenosine transport in diabetic B lymphocytes is significantly impaired due to the reduction of ENT1 expression (91). However, we have demonstrated that under normal conditions little adenosine is released from B lymphocytes and that ATP released from the cell is the primary source of peripheral adenosine (74). Thus, reduced uptake of adenosine by diabetic B cell with concomitant decrease of ADA activity might result in ATP released from the cell is the primary source of peripheral adenosine as well as the expression level of adenosine receptors in T and B lymphocytes. These changes have functional impact on B and T lymphocytes that display lowered proliferative potential and decreased synthesis of immunoglobulin by B cells in response to stimulation with an antigen. Therefore, it might be assumed that disturbed homeostasis of adenosine greatly contributes to pathomechanism leading to impaired function of immune cells in diabetes.

Conflict of interest: None declared.

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