Istradefylline, an adenosine A2a receptor antagonist, inhibits the CD4+ T-cell hypersecretion of IL-17A and IL-8 in humans

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ABSTRACT
Extracellular adenosine produced from ATP plays a role in energy processes, neurotransmission, and inflammatory responses. Istradefylline is a selective adenosine A2a receptor (A2aR) antagonist used for the treatment of Parkinson’s disease. We previously showed using mouse models that adenosine primes hypersecretion of interleukin (IL)-17A via A2aR, which plays a role in neutrophilic inflammation models in mice. This finding suggests that adenosine is an endogenous modulator of neutrophilic inflammation. We, therefore, investigated the in vitro effect of istradefylline in humans. In the present study, using human peripheral blood mononuclear cells (PBMCs), we tested the effect of adenosine, adenosine receptor agonists and istradefylline on cytokine responses using mixed lymphocyte reaction (MLR), PBMCs, CD4+ T cells, and Candida albicans antigen (Ag)-stimulated PBMCs. We showed that adenosine and an A2aR agonist (PSB0777) promoted IL-17A and IL-8 production from human PBMCs, and istradefylline suppressed this response. In addition, istradefylline inhibited not only the IL-17A and IL-8 production induced by adenosine but also that from C. albicans Ag-stimulated PBMCs. These results indicate that adenosine-mediated IL-17A and IL-8 production plays a role in neutrophilic inflammation, against which istradefylline should be effective.

1. Introduction
Adenosine is a purine nucleoside formed from the breakdown of adenosine monophosphate and is a molecular moiety of ATP, ADP, and AMP. Extracellular adenosine is produced from ATP secreted by ectonucleotidases, such as ecto-nucleoside triphosphate diphosphohydrolase (E-NTPDase)-1 cluster of differentiation (CD)39, which converts ATP or ADP to ADP or AMP, respectively, and the 5’-nucleotidase CD73, which dephosphorylates AMP to adenosine [1].

Adenosine binds to the adenosine receptors expressed on the cell surface. There are four subtypes of adenosine receptors (A1, A2a, A2b, and A3), all of which belong to the G protein-coupled receptor family. A2aR and A2bR signal the Gs protein, whereas A1R and A3R signal the Gi protein [1]. A1R, A2bR, and A3R are widely expressed in vivo, whereas A2aR is expressed at high levels in only a few regions of the body, such as the striatum, olfactory tubercle, nucleus accumbens, endothelial cells, vascular smooth muscle cells, platelets, and immune cells [2]. A1R and A2aR are high-affinity receptors, whereas A2bR and A3R are low-affinity receptors [3,4]. Adenosine also plays a role as a neurotransmitter [5], and istradefylline is a selective A2aR antagonist used for the treatment of Parkinson’s disease [6]. Adenosine is also a potent endogenous regulator of inflammation and immune reactions [1]. However, the molecular mechanisms underlying these effects are largely unknown. In a previous study, adenosine was reported to induce T-helper (Th)17 differentiation by activating A2bR [7].

Th17 cells are a subset of T-helper cells that differentiate from naïve CD4+ T cells in the presence of tumor growth factor (TGF)-β and interleukin (IL)-6. These cytokines are secreted by antigen-presenting cells in response to stimulation via T cell receptor (TCR) [8-10]. IL-17A production by Th17 cells drives the recruitment of neutrophils and neutrophilic inflammation [11,12]. IL-17A promotes both neutrophil production and chemotaxis via the induction of other proinflammatory cytokines and chemokines, such as IL-6 and IL-8 [13,14]. IL-17A-mediated responses are induced in IL-17 receptor-
Neutrophilic inflammation is associated with many diseases [16], including autoimmune diseases [17–26], neutrophilic airway inflammation [27,28], psoriasis [29,30], and severe atopic dermatitis [31]. There are currently no specific therapies using low-molecular-weight chemicals for neutrophilic inflammation; nevertheless, corticosteroids have proven effective for eosinophilic inflammation. However, recent studies by ourselves and others have suggested that dopamine D1-like receptor antagonists and dopamine D2-like receptor agonists suppress neutrophilic inflammation by suppressing Th17 differentiation and activation [32–34].

We recently reported that adenosine is also produced by activated CD4+ T cells, mainly during T cell-antigen-presenting cell (APC) interactions and primes the hypersecretion of IL-17A by CD4+ T cells, where A2aR plays a pivotal role. Istradefylline, as well as inhibitors of CD39 (ARL67156) and CD73 (AMP-CP), suppressed the adenosine-mediated IL-17A production, and the administration of istradefylline to mice with experimental autoimmune encephalomyelitis led to the marked amelioration of the symptoms [35]. These results suggest that adenosine is an endogenous modulator of neutrophilic inflammation. In addition, we recently reported that adenosine-mediated IL-17A production plays a role in other neutrophilic inflammation models, and istradefylline, ARL67156, and AMP-CP have proven effective in these models in vivo [36]. In the present study, we used human lymphocytes to demonstrate the effect of an A2aR antagonist on human cells.

2. Materials and methods

2.1. Preparation of peripheral blood mononuclear cells (PBMCs)

Heparinized peripheral venous blood was obtained from healthy volunteers under protocols approved by the Saitama Medical University Ethics Committee (#787-III). The blood samples were centrifuged for 10 min at 450 × g and separated into blood cells and plasma. After adding RPMI1640 (Sigma-Aldrich, St. Louis, MO, USA) to the blood cells, the sample was overlayed onto a Ficoll-Paque PLUS (GE Healthcare, Buckinghamshire, England, UK) and centrifuged for 40 min at 450 × g. PBMCs were recovered from the top-most layer of Ficoll-Paque. CD4+ T cells within the PBMCs were isolated by positive selection using magnetic-activated cell sorting (MACS; Miltenyi Biotec, Bergisch Gladbach, Germany), according to the manufacturer’s instructions.

2.2. Mixed lymphocyte reaction (MLR)

Human leukocyte antigen (HLA)-DR-non-shared PBMCs of 2 donors (7.5 × 10^4 cells/individual donor/well of 96-well plates) were cocultured in RPMI 1640 (Sigma-Aldrich) medium containing 10% human serum, 1% L-glutamine, 50 IU/mL penicillin, and 50 μg/mL streptomycin (R10H medium) to induce a 2-way MLR at 37°C in a humidified atmosphere at 5% CO2. The MLR was performed for 7 days in the presence or absence of adenosine (100 μM). After 7 days, the supernatant fluids were then collected for IL-17A, interferon (IFN)-γ, and IL-5 enzyme-linked immunosorbent assays (ELISAs).

2.3. CD3/CD28 stimulation

CD4+ T cells or PBMCs (1.5 × 10^5 cells/well of 96-well plates) were stimulated for 3 days at 37°C with anti-human CD3 (BioLegend, San Diego, CA, USA; 5 μg/mL) and CD28 (BioLegend; 1 μg/mL) antibodies (Abs) (CD3/CD28) in the presence of adenosine (0–300 μM), an A2aR antagonist (istradefylline; Sigma-Aldrich; 0–10 nM) plus adenosine (100 μM), and adenosine receptor agonists (0–10 μM) (AIR: 2-Chloro-N6-cyclopentyladenosine [CCPA], Tocris, Bristol, UK; A2aR: PSB0777, Tocris; A2bR: BAY 60-6583, Tocris; A3R: HEMADO, Tocris) in 200 μL of R10H medium. After stimulation, the supernatants were collected for use in cytokine ELISAs.

2.4. Candida albicans Ag stimulation

PBMCs (1.5 × 10^5 cells/well of 96-well flat-bottomed culture plate) were stimulated at 37°C with C. albicans Ag (15 μg/mL; Torii Pharmaceutical, Tokyo, Japan) with or without istradefylline (at 1 × Cmax= 170 ng/mL= 443pM) in 200 μL of R10H medium. Seven days after the initiation of culture, the supernatants were collected for cytokine ELISAs. Cmax is the maximum plasma concentration in a healthy adult described in an interview form (package insert) for istradefylline as of July 2019 (ver 4) [37].

2.5. Cytokine ELISAs

The concentrations of IFN-γ, IL-5, IL-8, and IL-17A in cell supernatants were measured using specific ELISA kits (DuoSet Kit; R&D, Minneapolis, MN, USA). Any value below the lower limit of detection (15.6 pg/mL) was set to 0. No cytokine cross-reactivity was observed within the detection ranges of the kits. If necessary, samples were diluted appropriately so that the measurements fell within the appropriate detection range for each cytokine.
2.6. Statistical analyses

Differences between the two groups were analyzed using an unpaired Student’s t-test. Differences between three or more groups were analyzed using a one-way analysis of variance with Tukey’s post-hoc test. All calculations were performed using the KaleidaGraph software program (Synergy Software, Reading, PA, USA). P values of <.05 were considered to indicate statistical significance.

3. Results

3.1. Adenosine promotes IL-17A production in MLR

First, we analyzed the effect of adenosine on adaptive Th responses in human two-way MLR. We found that the IL-17A and IFN-γ production was upregulated by the addition of adenosine. IL-5 production was reduced by the addition of adenosine in a dose-dependent manner (Figure 1).

3.2. Adenosine induces hypersecretion of IL-17A and IL-8 by PBMCs in the presence of anti-CD3/CD28 abs

We next addressed whether or not PBMCs respond to adenosine and induce cytokine production. As expected, anti-CD3/28 Ab-stimulated PBMCs produced IL-17A and IFN-γ in the presence of adenosine (Figure 2A). As in the MLR, IL-5 production was reduced by the addition of adenosine in a dose-dependent manner (Figure 2A). PBMCs also upregulated IL-17A after stimulation with anti-CD3/CD28 Abs in the presence of an A2aR agonist, but this was not the case in the presence of A1R, A2bR, or A3R agonists (Figure 2B). In addition, A2aR antagonist istradefylline suppressed adenosine-induced IL-17A secretion (Figure 2C), suggesting that A2aR-mediated signaling plays a pivotal role in adenosine-induced IL-17A secretion. Detailed dose dependency testing for IL-17A response revealed that the IC50 value of istradefylline was 3.4 pM to suppress the effect of 100 μM adenosine in the presence of CD3/28 stimulation (not shown). No IL-5 responses were inhibited at any concentrations tested, suggesting that the suppression of IL-17A is specific. Because IL-17 upregulates the migration of neutrophils by inducing the production of chemokine IL-8, we next addressed whether or not PBMCs responded to adenosine for the induction of IL-8 production. As expected, anti-CD3/28 Ab-stimulated PBMCs produced IL-8, which was further upregulated in the presence of adenosine and an A2aR agonist (Figure 2D, E). In addition, istradefylline suppressed the adenosine-induced IL-8 secretion (Figure 2F).

3.3. Adenosine promotes IL-17 production from CD4+ T cells

In the two-way MLR, CD4+ T cells proliferate in response to antigenic self-peptides in the context of class II major histocompatibility complex (MHC) molecules on antigen-presenting cells. Therefore, we analyzed the IL-17A secretion by stimulating CD4+ T cells with agonistic anti-CD3/CD28 Abs in the presence of adenosine. As in the PBMCs, adenosine and an A2aR agonist upregulated the IL-17A secretion, while istradefylline suppressed the adenosine-induced IL-17A secretion (Figure 3A–C).

3.4. Effects of istradefylline, on the IL-17A and IL-8 production of PBMCs stimulated by C. albicans Ag

Human PBMCs react to C. albicans Ag mainly through Th1/17 responses [38]. PBMCs were therefore stimulated by C. albicans Ag in the presence or absence of istradefylline. After seven days, the IL-17A and IL-8 production was significantly suppressed at 1× Cmax tested compared with the control group (Figure 4). Thus, istradefylline inhibited the production of IL-17A and IL-8 from natural Ag-stimulated PBMCs at a physiologically feasible concentration.
Figure 2. Adenosine and an A2aR agonist promote IL-17A production from PBMCs. (A) PBMCs were stimulated for 3 days with anti-CD3/CD28 Abs in the presence of adenosine (0–300 μM). After 3 days, culture supernatant fluids were then collected for the IL-17A, IL-5, and IFN-γ ELISAs (n = 5). (B) PBMCs were stimulated for 3 days with anti-CD3/CD28 Abs in the presence of each adenosine receptor agonist (CCPA: an A1R agonist, PSB0777: an A2aR agonist, BAY 60-653: an A2bR agonist, HEMADO: an A3R agonist) (0–10 μM). After 3 days, culture supernatant fluids were collected for the IL-17A ELISA. (n = 5). (C) PBMCs were stimulated for 3 days with anti-CD3/CD28 Abs in the presence of istradefylline (0–10 nM) plus adenosine (100 μM). After 3 days, culture supernatant fluids were collected for the IL-17A and IL-5 ELISA. (n = 5). (D) PBMCs were stimulated for 3 days with anti-CD3/CD28 Abs in the presence of adenosine (0–300 μM). (E) PBMCs were stimulated for 3 days with anti-CD3/CD28 Abs in the presence or absence of an A2aR agonist (PSB0777) (0–10 μM) (n = 5). (F) PBMCs were stimulated for 3 days with anti-CD3/CD28 Abs in the presence or absence istradefylline (0–10 nM) plus adenosine (100 μM) (n = 5). After 3 days, culture supernatant fluids were collected for the IL-8 ELISA. (n = 5). Data are expressed as the mean ± SD and were compared using a one-way ANOVA with Tukey’s post-hoc test. *p < .05 and **p < .01, compared with CD3/CD28 stimulation alone (A, B, D, E) or CD3/28 stimulation plus adenosine (100 μM) (C, F).

Figure 3. Adenosine and an A2aR agonist promote IL-17A production from CD4+ T cells. (A) CD4+ T cells were stimulated for 3 days with anti-CD3/CD28 Abs in the presence or absence of adenosine (0–300 μM). After 3 days, culture supernatant fluids were then collected for the IL-17A ELISA. (n = 4). (B) CD4+ T cells were stimulated for 3 days with anti-CD3/CD28 Abs in the presence of each adenosine receptor agonist (CCPA: an A1R agonist, PSB0777: an A2aR agonist, BAY 60–653: an A2bR agonist, HEMADO: an A3R agonist) (0–10 μM). After 3 days, culture supernatant fluids were then collected for the IL-17A ELISA. (n = 4). (C) CD4+ T cells were stimulated for 3 days with anti-CD3/CD28 Abs in the presence of istradefylline (0–10 nM) plus adenosine (100 μM). After 3 days, culture supernatant fluids were collected for the IL-17A ELISA. (n = 4). Data are expressed as the mean ± SD and were compared using a one-way ANOVA with Tukey’s post-hoc test. *p < .05 and **p < .01, compared with CD3/CD28 stimulation alone (A, B) or CD3/28 stimulation plus adenosine (100 μM) (C).
It has been suggested that the concentrations of adenosine are increased as much as 50-fold by physiological stimuli, such as hypoxia, hypoglycemia, and ischemia [39]. In addition, to obtain sufficient adenosine (>100 μM) to trigger hyperssecretion of IL-17A, T cells may need to make contact with other cells to form a microenvironment where a high adenosine concentration can be achieved, as observed during T cell-APC interactions at immunological synapses [36,38,40]. β-D-glucan of C. albicans changes the nature of dendritic cells (DCs) to induce Th17 and is thus designated a Th17 adjuvant [41]. As shown in Figure 4, the inhibition of IL-17A and IL-8 from C. albicans Ag-stimulated PBMCs was augmented by the dopamine D2-like receptor antagonists used to treat Parkinson’s disease [38] and dopamine D2-like receptor agonists both have a pharmacologically similar effect [51,52]. The expression patterns of adenosine receptor subtypes in Th1, Th2, and Th17 cells are being explored in order to explain the differing doseresponse patterns to adenosine.

Neutrophils play a pivotal role in immunity to candidiasis [53]. Adenosine and neuroleptics such as haloperidol enhance neutrophilic inflammation [32,38], thereby expected to ease candida infection. In this relation, numerous studies have reported a reduced risk of rheumatoid arthritis (a typical IL-17A-associated disease) in schizophrenia [54], carrying characteristics opposite to Parkinson’s disease, i.e., excessive stimulation via D2-like receptors [55]. Recent studies by others also pointed out that Parkinson’s disease itself is an autoimmune disease [56]. It is thereby feasible that the medication for Parkinson’s disease is effective not only by neurological but also by immunological mechanisms.

The future research direction using human samples includes: i) autoimmune neutrophilic inflammation such as ulcerative colitis and rheumatoid arthritis; ii) non-autoimmune neutrophilic inflammation such as neutrophilic bronchial asthma and periodontitis; as well as iii) viral infection that activates aryl hydrocarbon receptor such as COVID-19 and dengue fever, which can lead to NETs [50].
Ethical statements

The protocol for this research project has been approved by the ethics committee of Saitama Medical University (#787-III), and it conforms to the provision of Declaration of Helsinki. All informed consents were obtained from the participants.

Disclosure statement

Sho Matsushita is an employee of iMmuno, Inc. The other authors declare no conflicts of interest in association with the present study.

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