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The immunosuppressive effects of nicotine during human mixed lymphocyte reaction

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Abstract

Cell-to-cell interaction through binding intercellular adhesion molecule (ICAM)-1, B7.1, B7.2 and CD40 on monocytes and their ligands on T-cells plays roles in cytokine production and T-cell proliferation. Interleukin (IL)-18, which is elevated in the plasma during acute rejection after organ transplantation, induces the expression of ICAM-1, B7.1, B7.2 and CD40, production of interferon (IFN)-γ and IL-12 and proliferation of lymphocytes during human mixed lymphocyte reaction. Nicotine is known to inhibit the production of pro-inflammatory cytokines from macrophages through the stimulation of nicotinic acetylcholine receptor α7 subunit. In the present study, we examined the effect of increasing concentrations ranging from 0.1 to 100 μM of nicotine on the expression of ICAM-1, B7.1, B7.2 and CD40, production of IFN-γ and IL-12 and proliferation of lymphocytes during mixed lymphocyte reaction treated with IL-18 at 100 ng/ml for 48 h. Nicotine inhibited the expression of adhesion molecules, cytokine production and lymphocyte proliferation. The IC50 values of nicotine for inhibition of the IL-18-enhanced ICAM-1 expression, IFN-γ production and proliferation were 1, 1 and 2 μM, respectively. A non-selective and a selective antagonist for nicotinic acetylcholine receptor α7 subunit, mecamylamine and α-bungarotoxin abolished the effects of nicotine. The actions of nicotine might depend on stimulation of nicotinic acetylcholine receptor α7 subunit. Nicotine induced prostaglandin E_2 production during mixed lymphocyte reaction. The inhibitors of cyclooxygenase (COX)-2 and protein kinase A (PKA) at 100 μM inhibited the actions of nicotine, suggesting that the endogenous prostaglandin E_2 might be, at least, partially involved the actions of nicotine.

Keywords: Nicotine; Interleukin-18; Monocytes; Prostaglandin E_2

1. Introduction

Interleukin (IL)-18, a pro-inflammatory cytokine with potent Th1 immune response-promoting, is strongly induced in mouse or human acute graft-versus-host-disease, and it may be involved in the pathogenesis of acute graft-versus-host-disease and increased in acute graft-versus-host-disease after bone marrow transplantation (Fujimori et al., 2000; Reddy et al., 2001; Shaiegan et al., 2006). Moreover, serum levels of IL-18 are significantly elevated in patients with acute rejection of human or mouse kidney allograft (Striz et al., 2005) and cardiac transplantation (Affleck et al., 2001). IL-18-induced IL-12 production by antigen presenting cells in turn promotes the proliferation of alloantigen-responsive Th1-cells during mixed lymphocyte reaction (Ohshima and Delespesse, 1997). IL-18 induces IFN-γ production by T- and B-cells in the presence of IL-12 (Okamura et al., 1995; Matsui et al., 1997; Yoshimoto et al., 1997; Kohno et al., 1997). Blockade of the costimulatory signals, including, intercellular adhesion molecule (ICAM)/lymphocyte function-associated antigen-1 (LFA-1), B7/CD28 and CD40/CD40 ligand (CD40L) has considerable therapeutic potential for

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controlling inflammatory and immune responses, and has been shown to prolong allograft survival in a variety of animal models and human patients (Fabrega et al., 2000; Park et al., 2000; Zhang et al., 2000; Zhu et al., 2000; Sayegh and Turka, 1998; Shimizu et al., 2000). The interactions of ICAM-1/LFA-1, B7/CD28 and CD40/CD40L play an important role in the IL-18-initiated production of interferon (IFN)-γ and IL-12 and lymphocytes proliferation during an mixed lymphocyte reaction as an *in vitro* model that is useful for studying alloresponsiveness in T-cells, including proliferation and cytokine production (Tamura et al., 2004; Morichika et al., 2003; Takahashi et al., 2005).

Among the endogenous mechanisms that regulate the inflammatory response, cross-talk between the immune and nervous systems play an important role. It has been shown that acetylcholine, the main parasympathetic neurotransmitter, effectively deactivates peripheral macrophages and inhibits the release of proinflammatory mediators, including tumor necrosis factor (TNF)-α. Nicotinic acetylcholine receptor α7 subunit is thought to be involved in the nicotine-induced decrease in proinflammatory cytokine production by stimulated human and mouse macrophages (Wang et al., 2003), and this receptor is described as essential for the so called "cholinergic anti-inflammatory pathway" (Wang et al., 2003; Tracey, 2002). However, little is known about the effect of stimulation of nicotinic acetylcholine receptor α7 subunit on immune response during mixed lymphocyte reaction.

Prostaglandin E_2 is a major product of the cyclooxygenase (COX)-2-initiated arachidonic acid metabolism. Among the four subtypes of prostaglandin E_2 receptors, prostanoid EP_1, EP_2, EP_3, and EP_4 (Coleman et al., 1994), the stimulation of prostanoid EP_2- and EP_4-receptor leads to an increase in the activation of cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) pathway (Coleman et al., 1994). We recently demonstrated that prostaglandin E_2 strongly inhibited mixed lymphocyte reaction regarding the expression of ICAM-1, B7.1 and B7.2 via the prostanoid EP_2- and EP_4-receptors, irrespective of the presence of IL-18 (Morichika et al., 2003). In a previous study, we found that nicotine induced prostaglandin E_2 production in human monocytes through the stimulation of nicotinic acetylcholine receptor α7 subunit, thus leading to an elevation in the intracellular cAMP levels, and such prostaglandin E_2 production was involved in the inhibitory effect of nicotine on the expression ICAM-1, B7.2 and CD40 in the presence of IL-18 (Takahashi et al., 2006).

In the present study, we examined the effect of nicotine on immune response during mixed lymphocyte reaction in the presence or absence of IL-18 and the involvement of nicotinic acetylcholine receptor α7 subunit in the actions of nicotine. In addition, to investigate the mechanism of nicotine action, the effect of COX-2 and PKA inhibitors on the nicotine-treated mixed lymphocyte reaction was determined.

2. Materials and methods

2.1. Reagents

Recombinant human IL-18 was purchased from MBL (Nagoya, Japan), and nicotine (1-methyl-2-(3-pyridyl)pyrrolidine), α-bungarotoxin, mecamylamine and H-89 were purchased from Sigma Chemical (St. Louis, MO). NS398 (*N*-(2-cyclohexyloxy-4-nitrophenyl)-methanesulphonamide) and indomethacin were purchased from Cayman Chemical (Ann Arbor, MI). For the flow cytometric analysis, fluorescein isothiocyanate (FITC)-conjugated mouse IgG1 monoclonal antibody (mAb) against ICAM-1 and phycoerythrin-conjugated anti-CD14 mAb were acquired from DAKO (Glostrup, Denmark). FITC-conjugated anti-B7.1 mAb (mouse IgG1) was purchased from IMMUNOTECH (Marseille, France), and FITC-conjugated anti-B7.2 and anti-CD40 mAbs (mouse IgG1) were obtained from Pharmingen (SanDiego, CA). Finally, FITC-conjugated IgG1 isotype-matched control was purchased from Sigma Chemical, and [^{3}H]-thymidine was purchased from Amersham (Braunschweig, Germany).

2.2. Culture conditions during mixed lymphocyte reaction

Normal human peripheral blood mononuclear cells were obtained from ten healthy volunteers after acquiring IRB approval (Okayama Univ. IRB No.106). Samples of 20 to 50 ml of peripheral blood were withdrawn from a forearm vein, after which the Peripheral blood mononuclear cells were prepared and suspended at a final concentration of 1×10^6 cells/ ml in the medium as previously described (Tamura et al., 2004; Morichika et al., 2003). The peripheral blood mononuclear cells, which were mismatched for all the HLA alleles, were mixed with cells from an unrelated person (mixed cells), and the final concentration of the cells was adjusted to 2.0×10^6 cells/ml. Triplicate wells were incubated under various conditions for 48 h at 37 °C in a humidified atmosphere of 5% CO2 in air. All reagents were added to the media at the start of mixed lymphocyte reaction.

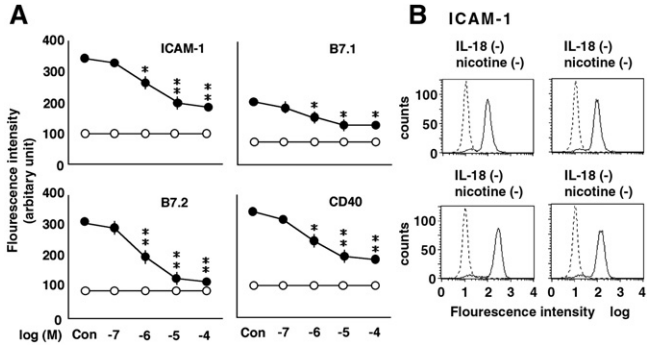

Fig. 1. The effects of nicotine on the expression of ICAM-1, B7.2, B7.2 and CD40 on monocytes during mixed lymphocyte reaction (A) The mixed cells at 2×10^6 cells/ml were incubated with increasing concentrations ranging from 0.1 to 100 μM of nicotine in the presence (filled circles) or absence (open circles) of 100 ng/ml IL-18 for 48 h. After treatment, the expression of ICAM-1, B7.1, B7.2 and CD40 on monocytes was determined by flow cytometry. Con, 0 M. The results are expressed as the means±S.E.M. of triplicate findings from five distinct responder stimulator pairs. *$P<0.05$, **$P<0.01$ compared with the value for IL-18. When an error bar was within a symbol, the bar was omitted. (B) The mean fluorescence intensities are shown in the histogram plots for ICAM-1. The mixed cells were treated with nicotine at 100 μM in the presence or absence of IL-18 at 100 ng/ml, and then incubated for 48 h. The dotted lines represent the mean fluorescence intensities of FITC-conjugated IgG1 as an isotype-matched control.

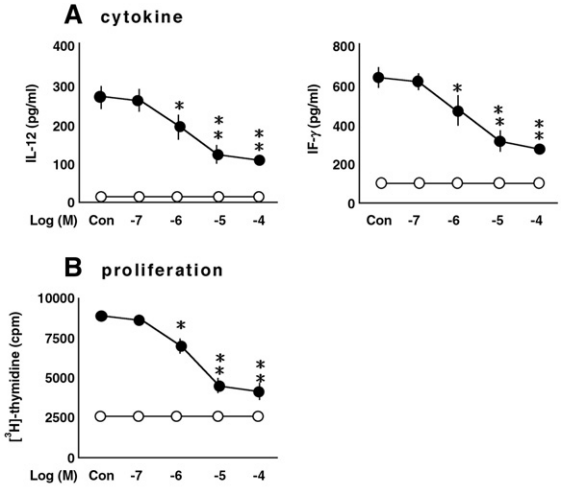

Fig. 2. The effects of nicotine on the production of IL-12 and IFN-γ and proliferation of lymphocytes during mixed lymphocyte reaction. The mixed cells at 2×10^6 cells/ml were incubated with increasing concentrations ranging from 0.1 to 100 μM of nicotine in the presence (filled circles) or absence (open circles) of 100 ng/ml IL-18 for 48 h. (A) After the treatment, IL-12 and IFN-γ productions in the condition media were determined by ELISA. (B) The [^{3}H]-thymidine uptake by lymphocytes during mixed lymphocyte reaction was determined. Con, 0 M. The results are expressed as the means±S.E.M. of triplicate findings from five distinct responder stimulator pairs. *$P<0.05$, **$P<0.01$ compared with the value for IL-18. When an error bar was within a symbol, the bar was omitted.

2.3. Flow cytometric analysis

Changes in the expression of human leukocyte antigens, ICAM-1, B7.1, B7.2 and CD40, on monocytes were examined by multi-color flow cytometry using a combination of anti-CD14 Ab with anti-ICAM-1, anti-B7.1, anti-B7.2 or anti-CD40 Ab. Cultured cells at 5×10^5 cells/ml were prepared for flow cytometric analysis as previously described (Tamura et al., 2004; Morichika et al., 2003) and analyzed with a FACSCalibur (BD Biosciences, San Jose, CA). The data were processed using the CELL QUEST program.

2.4. ELISA assay

Cell-free supernatant was assayed for IL-12, IFN-γ and prostaglandin E_2 protein by enzyme-linked immunosorbent assay (ELISA) employing the multiple Abs sandwich principle (IL-12 (p70) and IFN-γ from R&D Systems, Minneapolis, MN, PGE2 from Cayman Chemical). The detection limits of the ELISA for IL-12, IFN-γ and prostaglandin E_2 were 10 pg/ml.

2.5. Proliferation assay

Cultures were incubated for 48 h, during which time they were pulsed with [^{3}H]-thymidine (3 Ci/well) for the final 16 h. The cells were then divided into 96-well microplates, 200 μl/well, resulting in 1 μCi [^{3}H]-thymidine per well, and harvested by the Micro-Mate 196 Cell Harvester (Perkin Elmer Life Science Inc., Boston, MA, USA). Thymidine incorporation was measured by a beta-counter (Matrix 9600, Perkin Elmer Life Science Inc.).

2.6. Statistical analysis

The results are expressed as the means±S.E.M. of at least triplicate findings from five distinct pairs. The averages of the mean fluorescence intensity in a FACS analysis, mean cytokine production in ELISA and mean proliferation of each experiment were tested for significance using the ANOVA followed by Dunnett's test. Values of $P<0.05$ were considered to be significant.

3. Results

3.1. The effects of nicotine on the expression of ICAM-1, B7.2, B7.2 and CD40 on monocytes, the production of IL-12 and IFN-γ and the proliferation of lymphocytes during mixed lymphocyte reaction

A previous study indicated the proper incubation time when investigating whether nicotine affects the costimulatory molecule

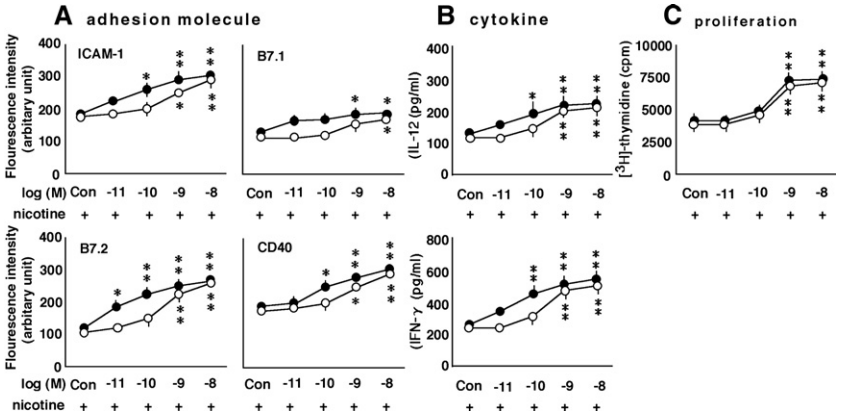

Fig. 3. The effect of antagonists for nicotinic acetylcholine receptor α7 subunit on the action of nicotine The mixed cells at 2×10^6 cells/ml were incubated with increasing concentrations ranging from 0.01 to 10 nM of a non-selective antagonist for nicotinic acetylcholine receptor α7 subunit, mecamylamine (open circles) or a selective antagonist for nicotinic acetylcholine receptor α7 subunit, α-bungarotoxin (filled circles) in the presence of 100 ng/ml IL-18 and 100 μM nicotine for 48 h. (A) After treatment, the expression of ICAM-1, B7.1, B7.2 and CD40 on monocytes was determined by flow cytometry. (B) IL-12 and IFN-γ concentrations in the conditioned media were determined by ELISA. (C) The [^{3}H]-thymidine uptake by lymphocytes during *mixed* lymphocyte reaction was determined. Con, 0 M. The results are expressed as the means±S.E.M. of triplicate findings from five donors. *$P<0.05$, **$P<0.01$ compared with the value for nicotine and IL-18. When an error bar was within a symbol, the bar was omitted.

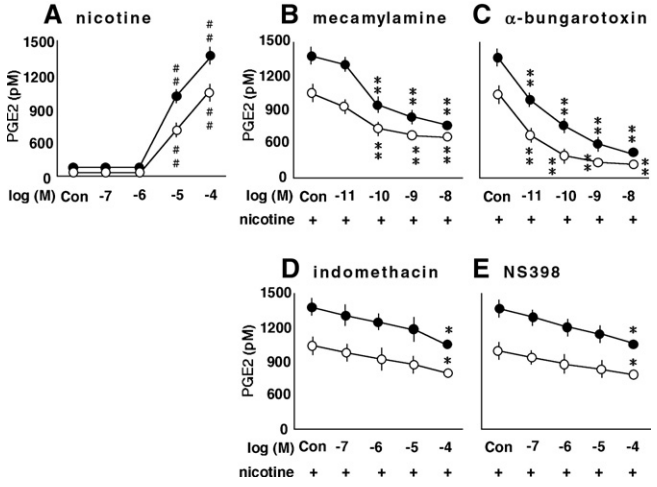

Fig. 4. The effect of nicotine on the production of prostaglandin E_2 during IL-18-treated mixed lymphocyte reaction (A) The mixed cells at 2×10^6 cells/ml were incubated with increasing concentrations ranging from 0.1 to 100 μM of nicotine in the presence (filled circles) or absence (open circles) of 100 ng/ml IL-18 for 48 h. After treatment, the concentration of prostaglandin E_2 in the conditioned media was determined by ELISA. The results are expressed as the means±S.E.M. of triplicate findings from five donors. ##$P<0.01$ compared with the value in the absence of nicotine. When an error bar was within a symbol, the bar was omitted. (B) (C) The mixed cells treated with 100 μM nicotine were incubated with increasing concentrations ranging from 0.01 to 10 nM of a non-selective antagonist for nicotinic acetylcholine receptor α7 subunit, mecamylamine (B) or a selective antagonist for nicotinic acetylcholine receptor α7 subunit, α-bungarotoxin (C) in the presence (filled circles) or absence (open circles) of 100 ng/ml IL-18 for 48 h. (D) (E) The mixed cells treated with 100 μM nicotine were incubated with increasing concentrations ranging from 0.1 to 100 μM of a non-selective COX-2 inhibitor, indomethacin (D) and a selective COX-2 inhibitor, NS398 (E) in the presence (filled circles) or absence (open circles) of 100 ng/ml IL-18 for 48 h. *$P<0.05$, **$P<0.01$ compared with the value for nicotine. Con, 0 M.

expression, cytokine production and proliferation during mixed lymphocyte reaction (Katsuno et al., 2006). The results suggested that the effects of nicotine should be determined after 48 h incubation. As shown in Figs. 1 and 2, we established the effect of nicotine on the expression of ICAM-1, B7.1, B7.2 and CD40 on monocytes and its impact on the production of IL-12 and IFN-γ and the proliferation of lymphocytes during mixed lymphocyte reaction. Nicotine had no effect on the expression of adhesion molecules, cytokine production or proliferation in the absence of IL-18. IL-18 induced the expression of ICAM-1, B7.1, B7.2 and CD40 on monocytes, the production of IL-12 and IFN-γ and the proliferation of lymphocytes (Katsuno et al., 2006). Nicotine inhibited the IL-18-enhanced expression of ICAM-1, B7.1, B7.2 and CD40 and production of IL-12 and IFN-γ and the proliferation of lymphocytes. The IC50 values of nicotine for inhibition of the IL-18-enhanced ICAM-1 expression, IFN-γ production and proliferation were 1, 1 and 2 μM, respectively.

3.2. The effects of nicotinic acetylcholine receptor α7 subunit antagonists on the action of nicotine

To determine the involvement of nicotinic acetylcholine receptor α7 subunit in nicotine activity, we examined the effect of a non-selective antagonist for nicotinic acetylcholine receptor α7 subunit, mecamylamine and a selective antagonist for nicotinic acetylcholine receptor α7 subunit, α-bungarotoxin on the nicotine-induced inhibition of ICAM-1, B7.1, B7.2 and CD40 expression on monocytes, production of IL-12 and IFN-γ and proliferation of lymphocytes during mixed lymphocyte reaction in the presence of IL-18 (Fig. 3). Mecamylamine and α-bungarotoxin both prevented nicotine inhibition of adhesion molecule expression and cytokine production but had no effects in the absence of nicotine (data not shown).

3.3. The effects of nicotine on the production of prostaglandin E2 during IL-18-treated mixed lymphocyte reaction

As shown in Fig. 4A, nicotine induced prostaglandin E_2 production in the presence of IL-18. Mecamylamine and α-bungarotoxin prevented nicotine-stimulated prostaglandin E_2 production (Fig. 4B and C). A non-selective COX-2 inhibitor,

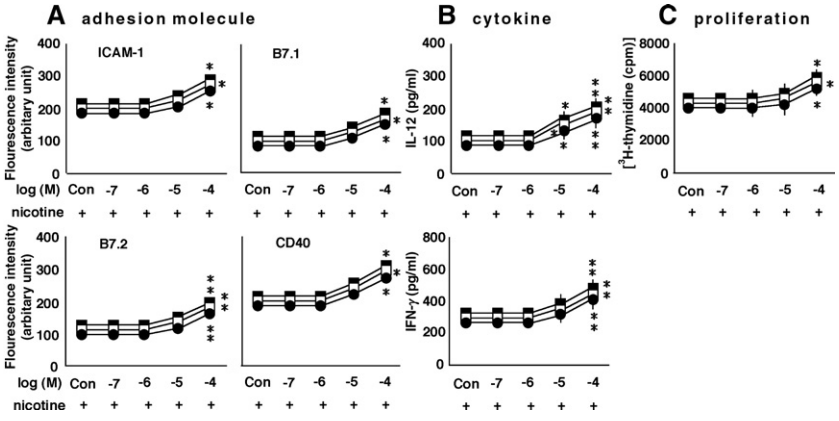

Fig. 5. The involvement of COX-2 and PKA in the action of nicotine The mixed cells at 2×10^6 cells/ml were incubated with increasing concentrations ranging from 0.1 to 100 μM of the COX-2 inhibitors, indomethacin (filled circles) or NS398 (open circles), or a PKA inhibitor, H89 (filled squares) in the presence of 100 ng/ml IL-18 and 100 μM nicotine for 48 h. (A) After treatment, the expression of ICAM-1, B7.1, B7.2 and CD40 on monocytes was determined by flow cytometry. (B) IL-12 and IFN-γ concentrations in the conditioned media were determined by ELISA. (C) The [^{3}H]-thymidine uptake by lymphocytes during mixed lymphocyte reaction was determined. Con, 0 M. The results are expressed as the means±S.E.M. of triplicate findings from five donors. *$P<0.05$, **$P<0.01$ compared with the value for nicotine and IL-18. When an error bar was within a symbol, the bar was omitted.

indomethacin and a selective COX-2 inhibitor, NS398 again suppressed nicotine-initiated prostaglandin E_2 production (Fig. 4D and E). Without nicotine, neither antagonists for nicotinic acetylcholine receptor α7 subunit nor the COX-2 inhibitors had any effects on prostaglandin E_2 production (data not shown).

3.4. The involvement of COX-2 and PKA in the action of nicotine

In the previous study, we found that nicotine activated intracellular cAMP in monocytes in the presence of IL-18 (Takahashi et al., 2006). The antagonists for nicotinic acetylcholine receptor α7 subunit and COX-2 inhibitors prevented this nicotine-induced activation of cAMP (Takahashi et al., 2006). To investigate the involvement of COX-2 and PKA in the nicotine-induced regulation of ICAM-1, B7.1, B7.2 and CD40 expression, production of IL-12 and IFN-γ and proliferation of lymphocytes in the presence of IL-18, we examined the effect of COX-2 and PKA inhibitors (Fig. 5). Indomethacin, NS398 and the PKA inhibitor, H89 at 10 or 100 μM reversed the inhibitory effect of nicotine on the expression of adhesion molecules, cytokine production and proliferation of lymphocytes, respectively.

4. Discussion

Acetylcholine is known to cause endothelium dependent vessel relaxation (Furchgott and Zawadzi, 1980; Hodgson and Marshall, 1989), suggesting that acetylcholine might improve graft survival. On the other hand, there is evidence that cigarette smoking may contribute to poor graft function, cardiovascular disease and the development of secondary malignancies after transplantation (Pungpapong et al., 2002; Sung et al., 2001; Ramsay et al., 2000; Arcasoy et al., 2001). However, the data are scant regarding the effect of nicotine on immune response after the transplantation. Ullola (Ulloa, 2005) reviewed that nicotine inhibited the production of pro-inflammatory cytokines from macrophages through nicotinic acetylcholine receptor α7 subunit. In the previous study, we found that nicotine abolished the expression of ICAM-1, B7.2 and CD40 on monocytes and production of IL-12, IFN-γ and TNF-α in IL-18-treated peripheral blood mononuclear cells (Takahashi et al., 2006). The present study is the first study to our knowledge to demonstrate that the effects of nicotine on the IL-18-enhanced expression of adhesion molecules, cytokine production and proliferation of lymphocytes during mixed lymphocyte reaction. Nicotine inhibited the IL-18-enhanced expression of ICAM-1, B7.2 and CD40, production of IL-12 and IFN-γ and proliferation of lymphocytes (Figs. 1 and 2). In the absence of IL-18, nicotine had no effect on the expression of adhesion molecules, cytokine production and proliferation of lymphocytes, which is consistent with the actions of nicotine in peripheral blood mononuclear cells (Takahashi et al., 2006), suggesting that nicotine might regulate the IL-18-elicited signal transduction. Therefore, further study should be continued. Moreover, the actions of nicotine were reversed by the antagonists for nicotinic acetylcholine receptor α7 subunit (Fig. 3). The results suggested that the stimulation of nicotinic acetylcholine receptor α7 subunit might inhibit the IL-18-enhanced expression of adhesion molecules, cytokine production and proliferation of lymphocytes during mixed lymphocyte reaction.

The stimulation of nicotinic acetylcholine receptor α7 subunit by nicotine is reported to induce the expression of COX-2 and the synthesis of one of its major products, prostaglandin E_2 in macrophages (Saareks et al., 1998). As shown in Fig. 4, the production of prostaglandin E_2 was detected in the incubated medium of nicotine-treated mixed lymphocyte reaction. We also determined the levels of other COX-2 metabolites, including PGE_1, PGD_2, PGF_2, PGI_2, PGJ_2 and thromboxane, in media of monocytes treated with nicotine with or without IL-18, but all were under the level of detection (data not shown). In the previous study, we suggested that the endogenous prostaglandin E_2 induced by nicotine might activate the cAMP and PKA pathway in monocytes via nicotinic acetylcholine receptor α7 subunit (Takahashi et al., 2006). The endogenous prostaglandin E_2 was thought to be involved in the effects of nicotine on the IL-18-enhanced expression of adhesion molecules on monocytes and cytokine production in peripheral blood mononuclear cells (Coleman et al., 1994). An analog of cAMP, dibutyryl cAMP mimicked the effect of prostaglandin E_2 on adhesion molecule expression and cytokine production during mixed lymphocyte reaction (Morichika et al., 2003). As shown in Fig. 5, the COX-2 and PKA inhibitors antagonized the actions of nicotine only when applied in high concentration, 10 or 100 μM, suggesting that the endogenous prostaglandin E_2 and the cAMP and PKA pathway might be, at least, partially involved in the effects of nicotine during IL-18-treated mixed lymphocyte reaction.

Wang (Wang et al., 2003) proposes that there is significant potential for developing cholinergic agonists that target α7 subunits on peripheral immune cells for use as anti-inflammatory agents to inhibit release of proinflammatory cytokines. The design of selective agonists for nicotinic acetylcholine receptor α7 subunit could represent a promising pharmacological strategy against rejection after transplantation. While the therapeutic potential of nicotinic agonists has been limited by the characterization of the specific receptors for drug development, the present characterization of nicotinic acetylcholine receptor α7 subunit in monocytes might support the design of selective nicotine agonists that can overcome the toxic effect of nicotine mediated by other receptors. In conclusion, we found that nicotine inhibited IL-18-elicited adhesion molecule expression, cytokine production and proliferation of lymphocytes during mixed lymphocyte reaction through stimulation of nicotinic acetylcholine receptor α7 subunit. Moreover, we demonstrated that the actions of nicotine might be due to the endogenous PGE2 and the activation of cAMP and PKA pathway.

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