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Nicotine Modifies Cytokine Production by Human Mononuclears Stimulated by Colon Cancer Cells

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Abstract

Background: The undesirable effects of prolonged tobacco use and cigarette smoking are well-known and are due to inhalation of a great number of alkaloids including nicotine. Lung cancer is the most feared ailment in chronic smokers and its linkage with nicotine is not always justified. Notably, it has been shown that nicotine possesses anti-inflammatory properties and considering the link between chronic inflammation and cancer it is conceivable to assume that nicotine may reduce tumorigenesis. Our task was to examine the capacity of nicotine to promote peripheral blood mononuclear cells (PBMC) for cytokine production and to assess its ability to modify the cross-talk between immune and colon cancer cells.

Methods: Unstimulated and LPS stimulated PBMC were incubated with various concentrations of nicotine and the generation of the cytokines TNFα, IL-1β, IL-6, IFNγ, IL-2, IL-10, and IL-1ra was detected. In addition, the production of these cytokines was examined in co-cultures of PBMC with HT-29 or RKO colon carcinoma cells in the presence of nicotine.

Results: Nicotine caused inhibition of TNFα, IL-6, IL-1β and IL-1ra secretion by non-stimulated PBMC and reduced IL-6 and IFNγ production by mitogen stimulated cells. The effect of nicotine on the immune function of PBMC became prominent when the cells were triggered for cytokine production by HT-29 colon carcinoma cells. The secretion of the pro-inflammatory cytokines TNFα, IL-1β, IL-2 and IFNγ was inhibited, whereas that of IL-6 was not affected. Cytokine production by PBMC induced by RKO cells was not affected by nicotine at any of the concentrations used, suggesting cell-specific immune response.

Conclusion: Nicotine inhibited the production of proinflammatory cytokines by PBMC. This effect was more conspicuous when PBMC were promoted by HT-29 colon carcinoma cells. It is feasible that nicotine, acting as an anti-inflammatory agent, may modulate the cross-talk between immune and cancer cells and to delay the progress of carcinogenesis.

Keywords: Nicotine; Mononuclears; Colon carcinoma cells; Cytokines; Inflammation; Cross-talk

Introduction

The existence of the of tobacco plant Nicotiana tabacum has been known since the 15th century when Columbus became impressed by the profuse usage of its leaves by the New World population. Although tobacco was initially applied for cure of a long list of diseases reviewed by Charlton [1] the handling of its therapeutic properties was gradually replaced. Research revealed that tobacco leaves contain a great number of ingredients, the most important being nicotine. In times it became clear that this alkaloid is the component responsible for relaxation, sedation and a sense of well-being associated with cigarettes smoking. On the other hand, the dark sides of prolonged smoking and nicotine consumption, above all - addiction and cancer, have been thoroughly debated (Warren and Singh [2]; Sanner and Grimsrud [3]; Dang et al. [4]). There are a few mechanisms by which tobacco smoke may promote tumor development, such as stimulated cell proliferation and migration, angiogenesis, mutation of vital genes, activation of nicotinic acetylcholine receptors (nAChRs), to mention some of them (Warren and Singh [2]; Schaal and Chellapan [5]; Mishra et al. [6]; Dang et al. [4]; Duppont et al. [7]; Xiang et al. [8]). While there is a general agreement as for the carcinogenic effect of tobacco smoke, the concept as for association of nicotine with cancer is rather controversial since there are views that nicotine should not be considered to be a carcinogen. In a comprehensive review on the subject Haussmann and Fariss [9] came to conclusion that the absence

or existence of carcinogenic properties of nicotine should be proved by further research. Considering the well-established connection between chronic inflammation and colorectal cancer development, [10] one may assume that persistent inflammation induced by inhalation of a great number of chemicals including nicotine in the process of long-continuing smocking may serve as an additional way for explanation of cancer development in smokers. Lee et al. [11] reviewed the linkage between cigarette smoking and inflammation and have concluded that the toxins present in the smoke are noxious to both innate and adopted immunity due to their proinflammatory effects. Karavitis and Kovacs [12] asserted that cigarette smoke inhibits macrophage functions such as phagocytosis and their ability to engulf pathogens with a consequent increased morbidity including carcinogenesis. It has been repeatedly shown that nicotine exerts an inhibitory effect on inflammatory responses. Claassen et al. [13] observed a decrease in TNFα, IL-1β and IL-6 in rats with inflammation due to exposure to burn trauma following treatment with nicotine. Similar results have been reported on mice infected with coxsakievirus B_3 [14], as well as in rats with LPS placental inflammation that showed markedly inhibited proinflammatory cytokine TNFα, IL-1β, IL-2, IL-6 and IFNγ production following nicotine administration [15]. The purpose of the present work was to assess the effect of nicotine on the ability of human peripheral blood mononuclear cells (PBMC) to produce inflammatory cytokines and to detect its impact on the immune relationship between PBMC and colon cancer cells from two human lines.

Materials and Methods

Cell preparation

PBMC: Peripheral blood mononuclear cells (PBMC) were separated from venous blood obtained from adult blood donors by Lymphoprep-1077 (Axis-Shield PoC AS, Oslo, Norway) gradient centrifugation. Blood bank donors gave written agreement and informed consent that components of the blood might be used for medical research. The cells were washed twice in phosphate buffered saline (PBS) and suspended in RPMI-1640 medium containing 1% penicillin, streptomycin and nystatin, 10% fetal bovine serum (FBS), (Biological Industries, Beith Haemek, Israel) and was designated as complete medium (CM).

Colon cancer cell lines: HT-29 and RKO human colon cancer cell lines were obtained from American Type Cultural Collection, Rockville, MD. The cells were maintained in CM containing Mc-Coy's 5A medium (Sigma, Israel) and Dulbecco modified eagle medium (DMEM- Biological Industries Co, Beith-Haemek, Israel) respectively, supplemented with 10% FBS, 2 mM L-glutamine and antibiotics (penicillin, streptomycin and nystatin-Biological Industries Co, Beith-Haemek, Israel). The cells were grown in T-75 culture flasks at 37°C in a humidified atmosphere containing 5% CO_2.

Nicotine preparation: Nicotine was purchased from Sigma Aldrich Corporation (Israel). A solution of 100 mM was prepared in ethanol. Further dilutions were made in CM. Nicotine was added at a final volume of 10 µL/mL of culture at concentrations of 0.1 µM, 1.0 µM and 10 µM.

Effect of nicotine on cell proliferation: The effect of nicotine on PBMC and colon cancer cells proliferation was determined using XTT proliferation assay kit (Biological Industries, Beith Haemek, Israel). Briefly: 0.1 mL aliquots of PBMC or colon cancer cells (10^5/mL of CM) were added to each one of 96 well plates and incubated for 24 hrs in absence or presence of nicotine at concentrations as indicated. At the end of the incubation period the cells were stained according to the manufacturer's instructions. The plates were incubated for 2-4 hrs at 37°C in a humidified incubator containing 5% CO_2 and the absorbance was measured at 450 nm using ELISA reader.

Effect of nicotine on cytokine production: For TNFα, IL-1β, IL-6, IL-10, and IL-1ra production 1 mL of PBMC (2×10^6/mL of CM) was incubated without (non-stimulated) or with LPS (50 ng/mL), and for IL-2 and IFNγ secretion the cells were incubated with PMA 1 µg/mL and ionomycin 0.5 µg/mL (Sigma, Israel). In another set of experiments, 0.5 mL of PBMC (4×10^6/mL of CM) was incubated with 0.5 mL of either HT-29 or RKO colon cancer cells (4×10^5/mL) suspended in appropriate CM. Nicotine was added at the onset of cultures at concentrations as indicated. Cultures without nicotine served as controls. The cultures were maintained for 24 hrs at 37°C in a humidified atmosphere containing 5% CO_2. At the end of the incubation period cells were removed by centrifugation at 250 g for 10 min., supernatants were collected and kept at -70°C until assayed for cytokines content.

Cytokine content in the supernatants: The concentration of the following cytokines: TNFα, IL-1β, IL-6, IFNγ, IL-2, IL-10, and IL-1ra in the supernatants was tested using ELISA kits specific for these cytokines (Biosource International, Camarillo, CA) as detailed in the guide-line provided by the manufacturer. The detection level of these kits was 30 pg/mL.

Statistics: A linear mixed model with repeated measures and assumption of compound symmetry (CS) was used to assess the effect of different concentrations of nicotine on cytokine secretion by non-stimulated or stimulated PBMC. SAS vs 9.4 was applied for this analysis. Paired t-test was used to compare between the level of cytokines produced following incubation with various concentrations of nicotine and that found in control cultures. Probability values of $p<0.05$ were considered as significant. The results are expressed as mean ± SEM.

Results

Effect of nicotine on cell proliferation

Nicotine added for 24 hrs to PBMC, HT-29 or RKO cells at concentrations between 0.1 µM and 10 µM had no effect on the cell proliferation rate.

Effect of nicotine on proinflammatory cytokine production

The secretion of TNFα and IL-1 β by non-stimulated PBMC or by cells activated by HT-29 colon cancer cells was significantly reduced following 24 hrs of incubation with nicotine at concentrations between 0.1 µM and 10 µM. However, TNFα and IL-1B production was increased when LPS-stimulated PBMC were incubated with 0.1 µM and 1.0 µM of nicotine, as compared to that produced by cells incubated without nicotine. The production of TNFα or IL-1β by RKO-stimulated PBMC was not affected by nicotine at the same culture conditions. The secretion of IL-6 by non-stimulated and by LPS-stimulated PBMC was significantly reduced following 24 hrs of incubation with nicotine added at concentrations between 0.1 µM and 10 µM. HT-29 or RKO induced IL-6 secretion by PBMC was not affected by nicotine added at the same conditions **(Table 1).**

Table 1 Effect of nicotine on proinflammatory cytokine production by PBMC. Non-stimulated PBMC or cells stimulated with either LPS or with one of the colon cancer cell lines HT-29 or RKO, were incubated for 24 hrs without (0) or with nicotine at concentrations as indicated. The level of cytokines in the supernatants was tested by ELISA. The results are expressed as Mean ± SEM of 3-7 experiments. Asterisks represent statistically significant difference from cells incubated without nicotine ($^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$, †p=0.06).

TNFα, pg/mL				
Nicotine, M	**Non-stimulated**	**LPS-stimulated**	**HT-29**	**RKO**
0	247 ± 42	727 ± 147	748 ± 68	817 ± 125
0.1 µM	124 ± 12**	821 ± 129*	705 ± 108	816 ± 91
1.0 µM	164 ± 32*	775 ± 128	661 ± 82**	884 ± 106
10 µM	156 ± 21*	697 ± 126	697 ± 81*	795 ± 85
Repeated measures	$F_{3,18}$=6.48, P=0.004	$F_{3,18}$=5.52, P=0.007	$F_{3,18}$=1.28, P=0.312	$F_{3,18}$=1.49, P=0.25
IL-1 β, ng/mL				
0	1.27 ± 0.28	3.72 ± 0.48	3.60 ± 0.37	3.19 ± 0.26
0.1 µM	0.48 ± 0.02*	4.97 ± 21***	2.77 ± 0.26***	3.49 ± 0.22
1.0 µM	0.62 ± 0.07*	4.24 ± 0.22†	2.90 ± 0.32***	3.04 ± 0.16
10 µM	0.58±0.04*	4.03±0.22	3.18±0.34*	3.16 ± 0.16
Repeated measures	$F_{3,18}$=7.35, P=0.002	$F_{3,18}$=11.71, P<0.001	$F_{3,18}$=12.3, P<0.001	$F_{3,18}$=1.35, P=0.29
IL-6, ng/mL				
0	8.47 ± 1.5	17.65 ± 1.54	17.48±0.55	15.35 ± 1.09
0.1 µM	3.28 ± 0.56***	16.76 ± 1.83†	17.00±0.19	15.23 ± 2.57
1.0 µM	3.84 ± 0.33**	16.42 ± 1.61**	18.56±0.78	15.68 ± 2.51
10 µM	3.85 ± 0.49**	16.31 ± 1.81**	17.38±0.53	16.43 ± 2.31
Repeated measures	$F_{3,18}$=9.16, P<0.001	$F_{3,18}$=5.65, P=006	$F_{3,18}$=2.74, P=0.072	$F_{5,15}$=0.4, P=0.75

IL-2 and IFNγ

Non-stimulated PBMC did not secret detectable amounts of IL-2 as measured by the kit used in our study. The production of IL-2 by PMA-ionomycin stimulated PBMC was not affected following incubation with 0.1 µM to 10 µM of nicotine. HT-29-induced IL-2 secretion was significantly inhibited at the above mentioned concentrations of nicotine, whereas that of RKO-induced IL-2 generation was significantly elevated at a concentration of 0.1 µM. IFNγ secretion by non-stimulated PBMC or by cells stimulated with RKO colon cancer cells was not affected by nicotine added at the doses applied. However, inhibition of IFNγ secretion was observed when nicotine was added at the above mentioned concentrations to PBMC

activated for 24 hrs with either PMA-ionomycin or with HT-29 colon cancer cells **(Table 2).**

Table 2 Effect of nicotine on IL-2 and IFNγ production by PBMC. Non-stimulated PBMC or cells stimulated with either PMA and ionomycin, or with one of the colon cancer cell lines HT-29 or RKO, were incubated for 24 hrs without (0) or with nicotine at concentrations as indicated. The level of cytokines in the supernatants was tested by ELISA. The results are expressed as Mean ± SEM of 3-7 experiments. Asterisks represent statistically significant difference from cells incubated without nicotine ($^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$).

IFNγ, ng/mL				
Nicotine	**Non-stimulated**	**PMA-stimulated**	**HT-29**	**RKO**
0	1.0 ± 0.09	42.5 ± 5.57	2.23 ± 0.38	5.19 ± 0.72
0.1 μM	0.9 ± 0.00	38.9 ± 5.63*	1.74 ± 0.37***	5.40 ± 0.61
1.0 μM	0.87 ± 0.06	38.6 ± 5.64*	1.65 ± 0.34***	5.25 ± 0.63
10 μM	0.87 ± 0.06	36.8 ± 5.00**	1.74 ± 0.34***	5.19 ± 0.74
Repeated measures	$F_{3,6}$=2.26, P=0.181	$F_{3,18}$=3.61, P=0.034	$F_{3,18}$=17.6, P<0.0001	$F_{3,18}$=0.75, P=0.537
IL-2, ng/mL				
0	-	8.2 ± 0.49	0.61 ± 0.05	0.41 ± 0.02
0.1 μM	-	8.5 ± 0.75	0.41 ± 0.02***	0.51 ± 0.02***
1.0 μM	-	7.8 ± 0.62	0.44 ± 0.03***	0.42 ± 0.02
10 μM	-	7.9 ± 0.61	0.43 ± 0.03***	0.42 ± 0.02
Repeated measures	-	$F_{3,9}$=2.9, P=0.094	$F_{3,18}$=26.6, P<0.0001	$F_{3,18}$=38.1, P<0.0001

Effect of nicotine on anti-inflammatory cytokine production

The production of IL-1ra by non-stimulated PBMC was inhibited when PBMC were incubated for 24 hrs with nicotine at concentrations of 1 μM and 10 μM. However, IL-1ra secretion stimulated by LPS or by HT-29 and RKO cells was not affected. IL-10 secretion either spontaneously or that induced by LPS, HT-29 or RKO cells was not affected by addition of nicotine at concentrations as indicated **(Table 3).**

Table 3 Effect of nicotine on anti-inflammatory cytokine production by PBMC. Non-stimulated PBMC or cells stimulated with either LPS, or with one of the colon cancer cell lines HT-29 or RKO, were incubated for 24 hrs without (0) or with nicotine at concentrations as indicated. The level of cytokines in the supernatants was tested by ELISA. The results are expressed as Mean ± SEM of 3-7 experiments. Asterisks represent statistically significant difference from cells incubated without nicotine (*p<0.05, **p<0.01).

IL-10, ng/mL				
Nicotine, M	**Non-stimulated**	**LPS-stimulated**	**HT-29**	**RKO**
0	026 ± 0.04	1.07 ± 0.25	1.38 ± 0.08	0.96 ± 0.09
0.1 μM	0.18 ± 0.01	1.11 ± 0.21	1.44 ± 0.05	1.00 ± 0.09
1.0 μM	0.18 ± 0.01	1.14 ± 0.25	1.29 ± 0.03	1.05 ± 0.09
10.0 μM	0.18 ± 0.01	1.10 ± 0.25	1.39 ± 0.06	1.00 ± 0.09
Repeated measures	$F_{3,6}$=3.28, P=0.101	$F_{3,6}$=0.28, P=0.84	$F_{3,15}$=2.33, P=0.11	$F_{3,6}$=0.72, P=0.57
IL-1ra, ng/mL				
0	1.08 ± 0.20	1.06 ± 0.10	1.47 ± 0.11	0.87 ± 0.06
0.1 μM	0.84 ± 0.19	0.97 ± 0.07	1.38 ± 0.15	0.88 ± 0.06

1.0 μM	0.71 ± 0.15**	0.97 ± 0.09	1.54 ± 0.20	0.82 ± 0.04
10.0 μM	0.70 ± 0.09**	0.98 ± 0.09	1.52 ± 0.19	0.86 ± 0.04
Repeated measures	$F_{3,18}$=4.17, P=0.02	$F_{3,18}$=, 1.06 P=0.39	$F_{3,18}$=1.86, P=0.173	$F_{3,6}$=1.27, P=0.366

Discussion

The effect of nicotine on the immune function of mononuclear cells has previously been debated. It appears that nicotine modulates the immune function of both M1 and M2 monocytes expressed by inhibition of M1 proinflammatory monocytes with subsequent limited production of the proinflammatory cytokines TNFα, IL-1β, IL-6 and IL-12 and stimulation of anti-inflammatory IL-10 and TGF-β secretion respectively [16]. Similar findings have been reported on activated human astrocytes treated with nicotine and have been explained by activation of alpha 7 nicotinic acetylcholine receptors [17]. Considerable number of evidence supports the importance of proinflammatory cytokines in origination of cancer and its progression [18]. In our hands, nicotine at all concentrations caused inhibited secretion of the proinflammatory cytokines TNFα, IL-1β and IL-6 by non-stimulated PBMC. LPS and PMA primed PBMC showed a decreased production of IL-6 and IFNγ respectively. The secretion of IL-2 was not affected by stimulated PBMC. As for the activity of nicotine on the anti-inflammatory cytokine production there was a slight, but significant inhibition of IL-1ra by non-stimulated cells and only by higher concentrations. These findings are in accordance with those reported in other studies with human nasal epithelial cells [19], dendritic cells [20] and neutrophils [21] supporting the concept that nicotine is an anti-inflammatory promoter. In the present work the effect of nicotine on the immune function of PBMC became prominent when the cells were triggered for cytokine production by HT-29 colon carcinoma cells. In that set of experiments the secretion of the proinflammatory cytokines TNFα, IL-1β, IL-2 and IFNγ was inhibited, whereas that of IL-6 was not affected. On the other hand, cells of the RKO line failed to respond to nicotine by cytokine production at any of concentrations used except for that of IL-2 which was elevated at 10 μM only, findings indicating the existence of cell-dependent PBMC responses. It has been reported that the plasma concentrations of nicotine in habitual tobacco smokers vary between 90 and 1000 nM [22]. Therefore, the nicotine concentrations applied in our study practically imitate the blood values detected in these individuals. Although the dispute about the carcinogenic effect of nicotine appears to be unconcluded and it is still under investigation, our findings support the concept that while nicotine possesses a number of undesirable activities, it cannot be definitely denoted as a carcinogenic culprit. Moreover, the observed increased production of proinflammatory cytokines by PBMC triggered by HT-29 colon carcinoma cells indicates the existence of an immune dialogue between PBMC and cancer cells, as we have previously reported by Bessler and Djaldetti [23] and that this relationship may be affected by a number of mediators [24-26]. It is conceivable to assume that the capacity of nicotine to reduce the production of proinflammatory cytokines by PBMC, stimulated by HT-29 cells will suppress chronic inflammation with a boomerang effect on cancer development. The link between inflammation and colon cancer *in vivo*, based on the existence of cross-talk between cancer cells and their microenvironment containing a number of immune cells and macrophages has been reviewed by Klampfer [27]. Accordingly, the immune cells, and to some extend the tumor cells, are able to produce cytokines that initiate and promote inflammatory processes suitable for tumor development. Fukuyama et al. [28] reported that cells from 31 lines of lung cancer were capable for production of IL-1α, IL-1β, IL-4, IL-6, IL-8, IL-10, TNFα and a number of growth cell mediators. Although it has been observed that Colo 205, Colo 320 and HT-29 colon adenocarcinoma cells can produce IL-10 following stimulation with macrophage-secreted IL-6, co-cultures of macrophages with malignant cells revealed that cancer cells first induce macrophages to produce IL-6, which in turn promotes IL-10 production by cancer cells [29] An attempt to detect cytokine production by HT-29 and RKO cells incubated without or with nicotine in our study did not show any immune activity of the cancer cells. However, incubation of HT-29 cells with PBMC in the presence of nicotine promoted the immune cells for cytokine production reinforcing the concept that the malignant cells are those that stimulate mononuclear cells to became immune-active. Although we cannot rule out the possibility that nicotine may affect cytokine secretion by malignant cells we are confident that the foremost immune activity of nicotine is focused on the secretion of cytokines by PBMC. This concept is based on observations that the extent of cytokines produced by non-stimulated or simulated PBMC is higher than that produced by malignant cells [29]. It is notable that nicotine did not exert any effect on IL-1β and TNFα production by LPS stimulated cells, whereas the inhibitory effect of nicotine on the production of proinflammatory cytokines was remarkable when PBMC were activated by HT-29 cells.

In conclusion, the results of the study indicate that nicotine is able to inhibit the production of proinflammatory cytokines by human peripheral blood mononuclear cells. This activity was more prominent when PBMC were co-cultured with HT-29 colon carcinoma cells, attesting that nicotine, through its capacity to act as an anti-inflammatory agent may modulate the cross-talk between immune and cancer cells and to exert an inhibitory effect on carcinogenesis.

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