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Nickel Increases Chemotactic Activity of Porcine Peripheral Blood Polymorphonuclear Cells

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Abstract : Nickel is a nutritionally essential trace element that plays an important role in the immune system of several animal species. The aim of this study was to examine the effect of nickel chloride on chemotactic activity of peripheral blood polymorphonuclear cells (PMNs) and whether this effect is associated with interleukin (IL)-8 and a nuclear factor-kappa B (NF-κB)-dependent pathway. Peripheral blood mononuclear cells (PBMCs) and PMNs were isolated by Percoll solution (Specific gravity; 1.080) and 1.5% dextran treatment, respectively. A modified Boyden chamber assay was used to measure the chemotactic activity of PMNs. The level of IL-8 in culture supernatant from PBMCs was measured by enzyme-linked immunosorbent assay (ELISA). Both of PBMCs and PMNs exhibited a low viability when cultured with concentration of greater than 1,000 μM of nickel chloride for 24 h. Thus, nickel chloride was used at concentration of 500 μM, which preserved cell viability. Treatment with nickel did not directly affect the chemotactic activity of PMNs. However, the chemotactic activity of PMNs was remarkably increased by culture supernatant from PBMCs treated with nickel chloride (500 μM) for 24 h. Recombinant porcine IL-8 polyclonal antibody (pAb) neutralized the enhancing effect on the chemotactic activity of PMNs by culture supernatant from PBMCs treated with nickel and this culture supernatant had higher IL-8 levels than the culture supernatant from untreated PBMCs. In addition, n-tosyl-l-phenylalanine chloromethyl ketone (TPCK), a NF-κB inhibitor, antagonized the enhancing effect on the chemotactic activity of PMNs by the culture supernatant from PBMCs treated with nickel. These results suggested that nickel stimulates porcine PBMCs to produce IL-8, which increases the chemotaxis of PMNs via NF-κB-dependent pathway.

Key words **:** nickel, chemotactic activity, peripheral blood mononuclear cells, peripheral blood polymorphonuclear cells, interleukin-8, NF-κB inhibitor, porcine.

Introduction

Polymorphonuclear cells (PMNs) are the main effector cells which are involved in the immune response to microorganisms (16). PMNs move to the site of infection or inflammation by factors generated by the interaction of host cells and infecting pathogens (27). They are attracted by soluble factors termed chemoattractants (25). Chemoattractants cause them to migrate and adhere to the endothelium via cell-surface receptors (5). Directed migration of leukocytes along chemical gradient is fundamental to development of lymphatic tissues, lymphocyte recirculation and accumulation of leukocytes at sites of inflammation or tissue injury (20). It is well-known that leukocytes respond to various well-defined chemotactic signals, such as formylated peptides, leukotriens and essential part of the primary inflammatory response to participate in a number of cellular activities (17,19).

The soluble products from activated monocytes and lymphocytes have been also considered to cause a cellular infiltration into inflamed sites such as arthritic joint and shown to directly induce chemotactic response for phagocytes (14). The cytokines such as interleukin (IL)-1 and -8 are also considered to be the predominant neutrophil chemoattractant, which actively participates in the induction of the inflammatory disease (1).

IL-8 is generated as a 99-amino acid precursor with a characteristic leader sequence of 22 amino acids (18). IL-8 induce activation of the motile apparatus, directional migration, expression of surface adhesion molecules, release of storage enzymes, and production of reactive oxygen metabolites in chemotactically stimulated neutrophils (3).

Nickel is essential for maintaining physiological homeostasis and one of the trace mineral in the body (24). Nickel is a pleiotropic cell stimulant that can affect multiple signaling pathways to alter cell phenotype and induces prolonged expression of interleukin (IL)-8 with latent increases in protein release (4). Nickel chloride is able to affect the activation or activity of NF-κB in different cell types such as neutrophils (11). Monocytes and cells differentiated from monocytes play important regulatory and effector roles in both arms of the immune system through the activation of NF-κB and posterior release of cytokines (11). It has been reported that nickel induced inflammatory response through tumor necrosis factor-α (TNF-α) (10), which encourage neutrophil phagocytosis (15). However, the effect of nickel was not investigated on chemotactic activity of PMNs.

The aim of this study is to examine the effect of nickel on chemotactic activity of PMNs and whether this effect is asso-

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ciated with the IL-8 and a NF-κB-dependent pathway. For this purpose, we examined the migration distances of PMNs by culture supernatant of PBMCs treated with nickel chloride. And then, we examined the level of IL-8 in the culture supernatant of PBMCs.

Materials and Methods

Reagents

Nickel(II) chloride-hexahydrate was purchased commercially from Dongyang Chemical (OCI Company Ltd., Seongnam, Korea). Goat-anti-recombinant porcine IL-8 polyclonal antibody (IgG) (R&D systems Inc., Minneapolis, MN, USA), fetal bovine serum (FBS) (Gibco Company, Grand Island, NY, USA), rabbit- anti-recombinant mouse IL-6 polyclonal antibody (IgG), Percoll® and RPMI 1640 medium and n-tosyl-l-phenylalanine chloromethyl ketone (TPCK) (Sigma-Aldrich Co. St. Louis, MO, USA) were also commercially purchased.

Porcine peripheral blood mononuclear cells (PBMCs) and peripheral blood polymorphonuclear cells (PMNs) isolation

Clinically healthy 6-month-old crossbred pigs from slaughterhouse (Donga food Co. Ltd., Cheongju, Korea) were used as blood donors. The peripheral blood drawn from anterior vena cava of pigs was immediately filled in heparinized conical tube. To isolate PBMCs, blood was overlaid on a Percoll® solution (specific gravity, 1.080) and centrifuged at 400 ×g for 45 min at room temperature. The remaining PBMCs in the space between plasma and Percoll® solution layer were harvested, and treated with RBC lysis buffer (iNtRON biotechnology, Seongnam, Korea) for 5 min to lyse remaining erythrocytes. The PMNs were obtained from the upper layer of sedimented erythrocytes after the removing the PBMCs layer. Three ml of the upper part of the erythrocytes were mixed with 10 ml of 1.5% dextran (molecular weight, 200,000; Wako Ltd., Japan) in PBS and allowed to sediment for 45 min. The residual erythrocytes were lysed by brief treatment with RBC lysis buffer for 5 min. After that, PMNs were washed three times with PBS.

PBMCs culture supernatant

The isolated PBMCs at a density of 2×10^6 cells/ml in a twenty-four-multi well plate (Nunc company, Naperville, IL, USA) were incubated with a concentration of nickel chloride (0-500 μM) for 24 h at 37°C in a 5% CO_2-humidified atmosphere. After an incubation, culture supernatant were centrifuged at 14,000 ×g for 10 min, filtered through a 3.0 μm-pore size and 120 μm thick membrane filter and stored at −70°C until used.

Cytotoxicity assay

PBMCs and PMNs were plated onto 24-well plates. Nickel chloride (0-500 μM) were added to each well and incubated for 24 h at 37°C in a 5% CO_2-humidified atmosphere. After 24 h, cell viability was tested by Trypan blue assay (23).

NF-κB inhibitor assay

N-tosyl-l-phenylalanine chloromethyl ketone (TPCK), an irreversible inhibitor of serine proteases with chymotrypsin-like specificity, was prepared as 10 mM stock in methanol and stored at 4°C. TPCK (25 μM) in RPMI 1640 medium was used as NF-κB inhibitor. PBMCs cultures were pretreated with TPCK (25 μM) for 20 min at room temperature, then stimulated with nickel (500 μM) and incubated in medium with TPCK (25 μM) for up to 24 h. TPCK effects was measured by modified Boyden chamber assay.

Chemotaxis assay

The chemotactic activity of PMNs was determined as migration distance through Millipore membrane filters by modified Boyden chamber assay (21). The chemotaxis chambers (Neuro probe, Gaithersburg, MD, USA) were used to determine directional migration distance of PMNs. Shortly, chemotaxis chambers, RPMI 1640 medium and culture supernatant from PBMCs were pre-warmed at 37°C incubator for 2 h. Two hundreds μl of nickel solution or culture supernatant from PBMCs treated with nickel (50-500 μM) or culture supernatant (100%) pretreated with TPCK which is NF-κB inhibitor were placed in lower chamber of device. A nitrocellulose filter (125 μm thick and 3.0 μm pore size; Merk-Millipore Corporation, Frankfurter, Darmstadt, Germany) was placed on top of the well of the lower compartment. And then, 200 μl of PMNs suspension (4×10^5 cells/200 μl) was put into the upper compartment. The chambers were incubated for 45 min at 37°C in 5% CO_2-humidified atmosphere. After incubation, the membrane filters were immediately removed by pincette, fixed for 20 sec in 70% ethyl alcohol and washed for 2 sec in 100% ethyl alcohol, dried for 1 h and stain with harris-hematoxylin for 4 min, decolorized with 70% ethyl alcohol for 20 sec, dried on kims-wipe paper. After 1 day, filter were mounted on a slide glass and treated with cytoseal XYL (Thermo-Fisher scientific, Waltham, MA, USA).

A bright field microscopy at 400 × magnification was used to determine the directional migration distance of cells. Five fields per filter were selected randomly to examine migration distance of cells in triplicate assay. The chemotactic response of PMNs was evaluated as the absolute distance (μm/45 min) in the directional migration of PMNs in response to chemoattractant.

Neutralization test

Anti-rpIL-8 pAb diluted with various concentrations (0-100 μg/ml) were added to the culture supernatant from PBMCs treated with nickel. As a control isotype IgG, anti-rmIL-6 antibody instead of anti-rpIL-8 pAb was added to the well. The mixed samples were settled for 1 h at room temperature. The effect of this mixture to stimulate the chemotactic activity of PMNs was also evaluated as described above.

Enzyme-linked immunosorbent assay (ELISA)

The culture supernatant of PBMCs treated with or without nickel (500 μM) was collected after 24 h incubation. The IL-8 levels in the culture supernatant from PBMCs were determined by the direct sandwich enzyme-linked immunosorbent assay (ELISA) in the porcine IL-8 ELISA kit (Thermo-Fisher scientific, Waltham, MA, USA) according to the manufacturer's- protocol. All samples, standard and controls were

Table 1. Cell viability (%) of PBMCs and PMNs exposed to nickel chloride for 24 h

Cells	Nickel chloride concentration (μM)					
	0	50	100	200	500	1000
PBMCs	97.67 ± 0.44	97.33 ± 0.47	97.00 ± 0.4	96.67 ± 0.47	96.27 ± 0.47	82.33 ± 1.45***
PMNs	97.43 ± 0.75	97.23 ± 0.52	97.20 ± 0.31	96.90 ± 0.38	96.43 ± 0.39	81.00 ± 2.08**

The value represent means ± S.D (n = 3). One-way ANOVA was used for statistical analysis, followed by a Dunnett's post hoc test. Comparison of two groups was made by t-test. **p < 0.01, ***p < 0.001, vs untreated group (0 μm nickel chloride).

assayed in triplicate. The optical density was determined using an automated microplate reader (Bio-Tek Instruments Inc., Winooski, Vermont, USA) at 450 nm. The IL-8 levels in the samples were quantified from standard curves generated with purified porcine IL-8 tested at eight titration points.

Statistical analyses

All statistical analyses were carried out by using GraphPad prism 6 software (GraphPad software, San Diego, CA, USA). Comparisons of two groups were done using the t-test. One-way analysis of variance (ANOVA) was used to investigate differences between the control and treatment groups, followed by Dunnett's post hoc test. P value of < 0.05 was considered to be statistically significant. Results are expressed as means ± standard deviations (S.D).

Results

Effect of nickel on viability of PBMCs and PMNs

PBMCs and PMNs with > 96% viability were cultured for 24 h with nickel chloride at concentrations ranging from 0 to 1,000 μM and then their viability was assessed by Trypan blue dye exclusion. As shown in Table 1, both PBMCs and PMNs exhibited high viability at concentrations from 0 to 500 μM nickel chloride. However, viability was decreased significantly ($p < 0.001$) by nickel chloride at a concentration of 1,000 μM. Subsequently, nickel chloride was used at concentrations below 500 μM, which preserved cell viability.

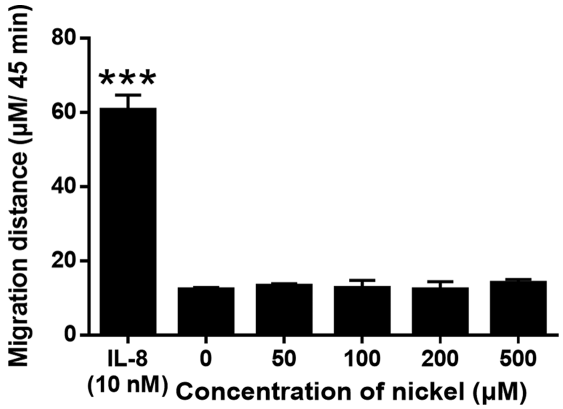

Fig 1. Direct effect of nickel chloride on chemotactic activity of porcine PMNs. Freshly isolated PMNs (4×10^5 cells/200 μl) were placed in the upper chamber. Nickel chloride (0-500 μM) and rpIL-8 (10 nM) were placed in the lower chamber. After 45 min incubation, the migration distance by the cells through the filter was measured. The value represent means ± S.D (n = 3). One-way ANOVA was used for statistical analysis, followed by a Dunnett's post hoc test. Comparison of two groups was made by t-test. ***P < 0.01 vs. vs untreated group (0 μm nickel chloride).

Nickel does not affect directly the chemotaxis of PMNs

To examine the direct effect of nickel chloride on chemo-

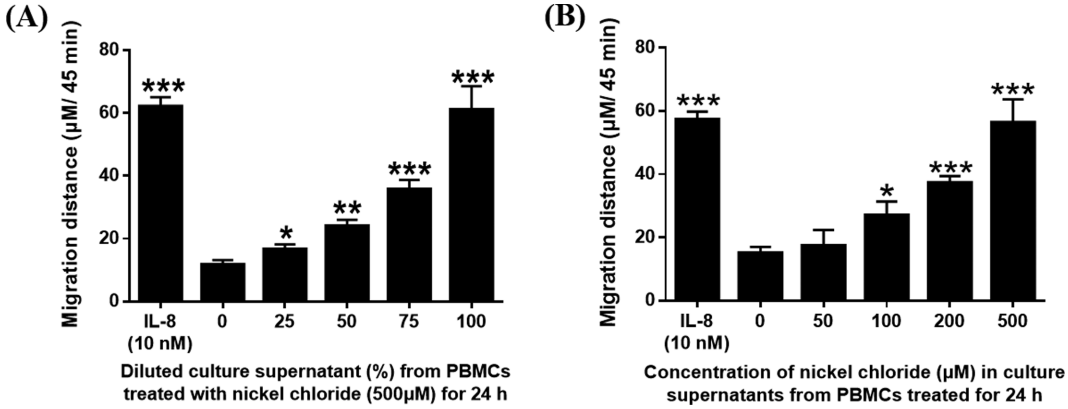

Fig 2. Chemotactic activities of porcine PMNs by culture supernatants from PBMCs exposed to nickel chloride. Freshly isolated PMNs (4×10^5 cells/200 μl) were placed in the upper chamber. IL-8 (10 nM), culture supernatant from PBMCs (2×10^6 cells/ml) treated with nickel chloride (0-500 μM) for 24 h (A) and diluted culture supernatant (0-100%) from PBMCs (2×10^6 cells/ml) treated with nickel chloride (500 μM) for 24 h (B) were placed in the lower chamber. After 45 min incubation, the migration distance by the cells through the filter was measured. The value represent means ± S.D (n = 3). One-way ANOVA was used for statistical analysis, followed by a Dunnett's post hoc test. Comparison of two groups was made by t-test. *P < 0.05, **p < 0.01, ***P < 0.01 vs. untreated group (0 μm nickel chloride).

tactic activity of PMNs, the migration distance of PMNs to nickel chlroide was measured. IL-8 in lower chamber, as a positive control, increased significantly ($p < 0.001$) the chemotactic activity of PMNs compared to untreated control. However, nickel chloride at concentration of 0 to 500 μM in lower chamber showed no effects on chemotaxis of PMNs as compared to untreated control (Fig 1).

Culture supernatant from PBMCs treated with nickel chloride increases the chemotactic activity of PMNs

To examine the effect of culture supernatant from PBMCs treated with nickel chloride on chemotaxis of PMNs, the migration distance of PMNs to culture supernatant was measured. The chemotaxis of PMNs was increased significantly (100 μM; $p < 0.05$, 200 and 500 μM; $p < 0.001$) by culture supernatant from PBMCs with nickel chloride as compared with control (0 μM) (Fig 2A). The chemotaxis of PMNs was also increased significantly (25%; $p < 0.05$, 50%; $p < 0.01$, 75 and 100%; $p < 0.001$) by diluted culture supernatant from PBMCs with nickel chloride (500 μM) as compared with control (0%) (Fig 2B).

Anti-rpIL-8 pAb neutralizes the increased chemotactic activity of PMNs

To examine whether the increased chemotactic activity of PMNs by the culture supernatant from PBMCs treated with nickel chloride is due to IL-8, the neutralization effect of anti-rpIL-8 pAb was examined. The increased chemotactic activities of PMNs by culture supernatant from PBMCs treated with nickel chloride were inhibited significantly by the addition of anti-rpIL-8 pAb (50 μg/ml; $p < 0.05$, 100 μg/ml; $p < 0.001$) as compared with that of culture supernatant (100%) from PBMCs treated with nickel chloride (500 μM). However, in the examination of the possibility of nonspecific inhibition for immunoglobulin isotype, IgG, any chemotactic activity of PMNs by culture supernatant (100%) from PBMCs treated with nickel chloride (500 μM) was not inhibited by the addition of high concentration (100 μg/ml) of control IgG, anti-rmIL-6 pAb (Fig 3).

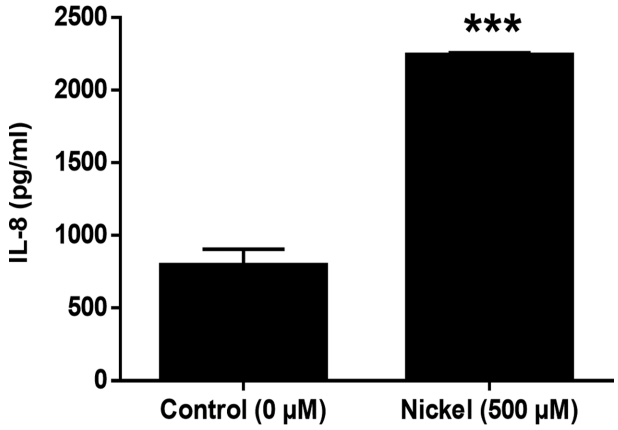

Fig 4. Amount of IL-8 in the culture supernatant from PBMCs treated with nickel chloride (500 μM). The levels of IL-8 in culture supernatant from PBMCs (2×10^6 cells/ml) treated with or without nickel chloride (500 μM) were measured by ELISA. The value represent means ± S.D (n = 3). One-way ANOVA was used for statistical analysis, followed by a Dunnett's post hoc test. Comparison of two groups was made by t-test. ***P < 0.01 vs. control (0 μM).

Nickel increases the production of IL-8 from PBMCs

The amount of IL-8 in the culture supernatant from PBMCs treated with nickel (500 μM) was measured by ELISA. The level of IL-8 in culture supernatant from PBMCs treated with nickel chloride (500 μM) was significantly ($p < 0.001$) higher than untreated control (0 μM) (Fig 4).

TPCK, an inhibitor of NF-κB, antagonizes the enhancing effect on the chemotactic activity of PMNs

To investigate whether the chemotactic activity of PMNs is related with NF-κB-dependent pathway, the effect of TPCK on chemotactic activity of PMNs was examined. The chemotactic activites of PMNs by culture supernatant from PBMCs treated with or without nickel were inhibited significantly (100%; $p < 0.001$, 0%; $p < 0.05$) by addition of TPCK (25 μM), respectively (Fig 5).

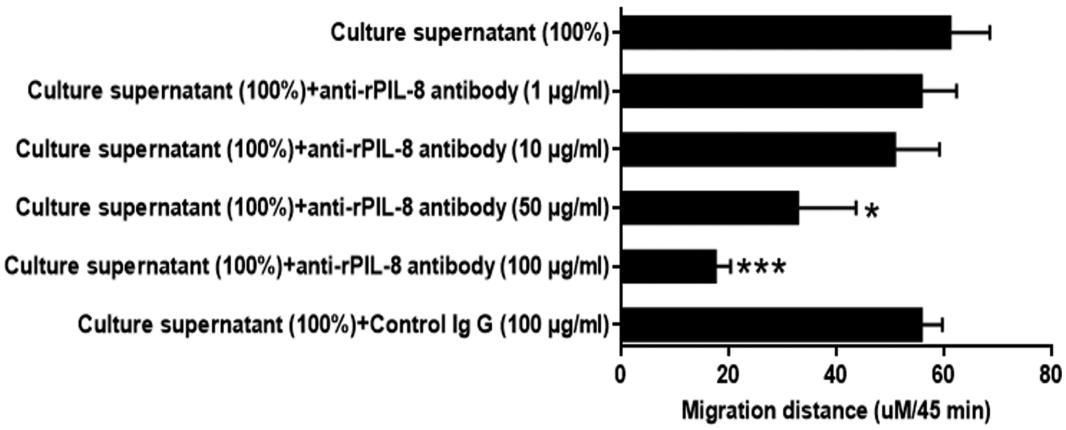

Fig 3. Neutralization effect of anti-rpIL-8 pAb on chemotactic activity of PMNs by culture supernatant from PBMCs treated with nickel chloride (500 μM). Anti-rpIL-8 pAb (IgG) (0-100 μg/ml) and anti-rmIL-6 pAb (100 μg/ml) were mixed to the culture supernatant (100%) from PBMCs treated with nickel chloride (500 μM) for 1 h. As a control isotype IgG, anti-rmIL-6 pAb (IgG) was used. The value represent means ± S.D (n = 3). One-way ANOVA was used for statistical analysis, followed by a Dunnett's post hoc test. Comparison of two groups was made by t-test. *P < 0.05, ***P < 0.01 vs. culture supernatant (100%) alone.

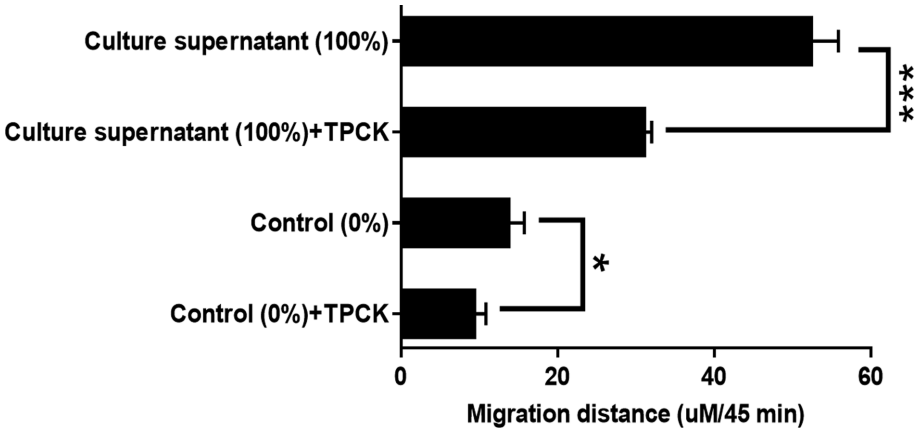

Fig 5. Effect of TPCK, an inhibitor of NF-κB, on the chemotactic activity of PMNs by culture supernatant from nickel-treated PBMCs. Culture supernatant (0 and 100%) from PBMCs treated with nickel chloride (500 μM) was treated with n-tosyl-l-phenylalanine chloromethyl ketone (TPCK) (25 μM). The value represent means ± S.D (n = 3). One-way ANOVA was used for statistical analysis, followed by a Dunnett's post hoc test. Comparison of two groups was made by t-test. *P < 0.05 vs. control (0%), ***P < 0.01 vs. culture supernatant (100%) alone.

Discussion

In the present study, nickel chloride at concentration of 1,000 μM reduced the cell viablitiy of PBMCs and PMNs for 24 h incubation. However, 500 μM had no apparent effects on their viability. In addition, it was reported that nickel did not decrease the viability of THP-1 monocytic cells at concentration of 250 μM for 24 h incubation (7) and human neutrophils at concentration of 500 μM for 18 h incubation (8). Therfore, based on the viability result, nickel chloride was used at concentration of 500 μM, which preserved cell viability.

We examined the effect of nickel on chemotactic activity of PMNs. The data revealed that nickel chloride as a chemoattractant on PMNs has no effect. This result indicated that nickel chloride do not directly affect the chemotactic activity of PMNs. However, the chemotactic activity of PMNs was increased remarkably by culture supernatant from PBMCs treated with nickel chloride. It was, therefore, hypothesized that the chemotactic factor(s) may be existed in soluble products from PBMCs treated with nickel chloride. In the previous study, nickel stimulated human monocyte to produce a variety of chemotactic factors, such as c-c motif chemokine ligand 5 (CCL5)/RANTES, and chemokine ligand 8 (CXCL8)/IL8 (13). Among of these chemotactic factors, IL-8 is a powerful PMNs priming agent that increase the chemotaxis of neutrophils (1). IL-8 had been shown to be more selective for neutrophils than other chemotactic factors and was a specific neutrophil chemoattractant with only minor effects on eosinophils, monocytes and basophils (28). Also, IL-8 has effect on neutrophils such as shape change and directional migration, exocytosis of storage protein, respiratory burst and leak out from vessel wall to site of inflammation (1,12). IL-8 plays important roles in local accumulation of neutrophils (2). We hypothesized that the soluble factor in the culture supernatant from PBMCs stimulated by nickel chloride may be IL-8. We examined whether rpIL-8 pAb neutralizes the enhancing effect on the chemotactic activity of PMNs by culture supernatant from PBMCs treated with nickel chloride. Our data showed that anti-rp IL-8 pAb neutralized the enhanced chemotactic activity of PMNs by culture supernatant from PBMCs stimulated by nickel chloride. This finding suggested that nickel chloride induces the increasing effect on chemotactic activity of PMNs, which is mediated by IL-8 produced by nickel-stimulated PBMCs.

Also, we found that IL-8 level of culture supernatant from PBMCs treated with nickel were higher than the culture supernatant from untreated PBMCs, as expected. These findings suggested that nickel stimulates porcine PBMCs to produce IL-8, which increased the chemotactic activity of PMNs.

We examined whether n-tosyl-l-phenylalanine chloromethyl ketone (TPCK), a NF-κB inhibitor, antagonizes the enhancing effect on the chemotactic activity of PMNs by the culture supernatant from PBMCs treated with nickel. TPCK antagonized chemotactic activity of PMNs by culture supernatant from PBMCs treated with or without nickel chloride. In previous study, nickel chloride elevates the protein expression of NF-κB (6). NF-κB can stimulate the synthesis of proinflammatory mediators, such as tumor necrosis factor-α (TNF-α), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), IL-1β, IL-6, and IL-8 (26). In addition, NF-κB is a ubiquitous transcription factor whose activation is crucial in a series of cellular processes, such as inflammation, immunity, cell proliferation and apoptosis (9). This finding was suggested that nickel increases the chemotactic activity of PMNs by activation of NF-κB pathway which is related with production of IL-8.

Essentiality of nickel has been also studied. Nickel deprived pigs had delayed estrus and progeny of nickel-deficient sows had an increased neonatal mortality and a decreased growth rate (22). Nickel-deficient pigs also had lower concentrations of calcium in bone tissue and decreased concentrations of zinc in liver, hair, rib and brain (22). Therefore, nickel chloride may have immunoenhancing effect and also be used for feed additives.

In conclusion, the data supported our hypotheses that the increasing chemotactic effect of porcine PMNs is related with IL-8 produced by nickel-stimulated PBMCs and with activation of NF-κB pathway. Therefore, this study suggested that

nickel stimulates porcine PBMCs to produce IL-8, which increases the chemotaxis of PMNs via NF-κB-dependent pathway.

Acknowledgments

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