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Ketamine Decreases Phagocytic Capacity of Canine Peripheral Blood Phagocytes *In Vitro*

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Abstract : Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist and a short-acting general anaesthetic agent for human and veterinary use. We previously reported that treatment with ketamine impairs oxidative burst activity of canine peripheral blood leukocytes. In this study, the effect of ketamine on phagocytic capacity of canine peripheral blood leukocytes was examined *in vitro*. Phagocytic capacity was analyzed by using a flow cytometry. Ketamine directly decreased the phagocytic capacity of peripheral blood polymorphonuclear cells (PMN) and monocytes but not total peripheral blood mononuclear cells (PBMC). In addition, the phagocytic capacity of PMN and monocytes was inhibited by the ketamine-treated PBMC but not PMN culture supernatant. These results suggest that ketamine has a direct inhibitory effect on the phagocytic capacity of canine peripheral blood phagocytes and involves the production of soluble factor(s) from canine PBMC, which may suppress the phagocytic capacity.

Key words **:** canine, ketamine, peripheral blood phagocytes, phagocytic capacity.

Introduction

Peripharal blood phagocytes, including neutrophils and monocytes, have crucial roles in the host defense against infection. They recognize microbes by expressing a broad spectrum of receptors and initiate not only engulfing and microbial killing but also the production of cytokines via in a variety of signal pathways (20). These responses are modulated by prostaglandins and cytokines including interlukin (IL)-1, IL-2, IL-8, interferons and tumor necrosis factors (TNFs) released from peripheral blood mononuclear cells (PBMC), similar to a paracrine manner (4,19).

Intravenous anesthetics may influence the host defense system. It has been reported that the application of intravenous anesthetics, including thiopental, midazolam, and ketamine, induces the decrease of chemotaxis, phagocytosis and reactive oxygen species (ROS) production of human neutrophils (17). Especially, ketamine (a non-competitive N-methyl-D-aspartate receptor antagonist), which has been widely used intravenous anesthetic agent in human and veterinary medicine, has been shown to impair immune functions of patient (1). It has been reported that ketamine attenuates cell adherence and migration of lipopolysaccharide (LPS)-stimulated leukocytes (9,18). Ketamine was also shown to suppress chemotactic activity of human neutrophils (22). Recently we reported that the oxidative burst activities of canine peripheral blood polymorphonuclear cells (PMN) and monocytes are inhibited by the culture supernatant collected from canine peripheral blood mononuclear cells (PBMC) treated with ketamine (12). Therefore, in the present study we examined whether ketamine affects the phagocytic capacity of canine peripheral blood phagocytes *in vitro*.

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Materials and Methods

Animals

Clinically healthy Beagle dogs were used as blood donors. All dogs were housed in room temperature (22 ± 2°C) conditions with a light cycle of day (12 h) and night (12 h). All dogs were individually managed in cages and fed on pellet diet (ProPlan, Purina Korea, Seoul, Korea). All experimental procedures and animal use were approved by the ethics committee of the Chungbuk National University.

Canine PBMC and PMN isolation

Peripheral blood drawn in a heparinized tube from jugular vein was layered 1 : 1 on Percoll solution (GE Healthcare Bio-Science AB, Uppsala, Switz) adjusted to 1.077 of specific gravity and centrifuged at 400 × g for 40 min at room temperature. The resulting layer of PBMC isolated at the interface between plasma and Percoll solution was harvested, and treated with 0.83% NH_4Cl Tris-base buffer (pH 7.2) for 5 min to lyse remaining erythrocytes. The PBMC layer was composed of approximately 30% monocytes and 70% lymphocytes as determined in cell counting by Wright-Giemsa staining. PMN was obtained from the cen-

trifuged gradient layer of erythrocyte sediment after collection of PBMC. One milliliter taken from the upper portion of the erythrocytes layer was mixed with 10 mL of 1.5% dextran (molecular weight, 200,000; Wako Ltd., Osaka, Japan) in PBS, and allowed to sediment for 45 min. Residual erythrocytes were lysed by treatment with 0.83% NH_4Cl in Tris-base buffer solution (pH 7.2) for 5 min, and then cells were washed three times with PBS. The purity of neutrophils in the final canine PMN suspension was routinely greater than 96%, as determined by cytospin smear and Wright-Giemsa staining analyses. The viability of PBMC and PMN, as determined by trypan blue dye exclusion, exceeded 97% in every case. All cells were resuspended in RPMI 1640 medium (Sigma-Aldrich Co. St Louis, MO, USA) supplemented with 2 mM L-glutamine, 0.02 mg/mL gentamicin and 5% heat-inactivated fetal bovine serum (Gibco Co., Grand Island, NY, USA). The cell concentration was finally adjusted to 2×10^6 cells/mL for making culture supernatant or to 1×10^6 cells/mL for evaluating phagocytic capacity.

Culture supernatant

Isolated PMN and PBMC at a density of 2×10^6 cells//mL were placed in wells of a 24-multiwell plate (Nunc Co., Naperville, IL, USA) and incubated with different concentrations of ketamine (Ketamine 50, Yuhan, Korea) for 24 h at 37°C in a 5% CO_2-humidified atmosphere. After 24 h incubation, culture supernatants were collected, centrifuged at 5,000 × g for 30 min, filtered through a 0.45 μm pore size membrane filter (Milipore Co., Bedford, Mass, USA) and stored at −70°C until used.

Phagocytic capacity analysis

One hundred microliter of the cells adjusted to 1×10^7 cells/mL was added into each well of a 24-well plate. The PMN and PBMC were incubated with ketamine (10, 100 and 500 μM) treated media or with culture supernatant collected from ketamine (10, 100 and 500 μM)-treated cells for 12 h at 37°C in a 5% CO_2-humidified atmosphere. Twenty microliter of 1×10^9 beads/mL fluorescein isothiocyanate (FITC)-latex beads (size, 2.0 μm; Sigma-Aldrich Co.) was added into each well for the final 1 h of incubation. PMN or PBMC incubated without FITC-latex beads were used as negative controls. The cultured cells were harvested gently by slow pipetting, centrifuged at 400 × g for 3 min, and washed three times with PBS containing 3 mM ethylenediamine tetraacetic acid (EDTA). The phagocytic capacity was measured by using a flow cytometry (BRYTE HS, Bio-Rad Micro-science Ltd., Hertfordshire, UK). FITC (green) fluorescence was measured on 5,000 cells per sample. For analysis, the monocyte-rich cell population was identified by its typical location on the PBMC scattergram and was selected by gating. The results were expressed as percentages of total phagocytic capacity.

Statistical analysis

All statistical analyses were carried out using SigmaStat version 2.03 (SPSS Inc., Chicago, IL, USA). One-way analysis of variance (ANOVA) was used to investigate differences between control and concentrations of ketamine treatment, followed by Dunnett's post hoc test. $P < 0.05$ was considered statistically significant. All data were expressed as mean values and standard errors (SE).

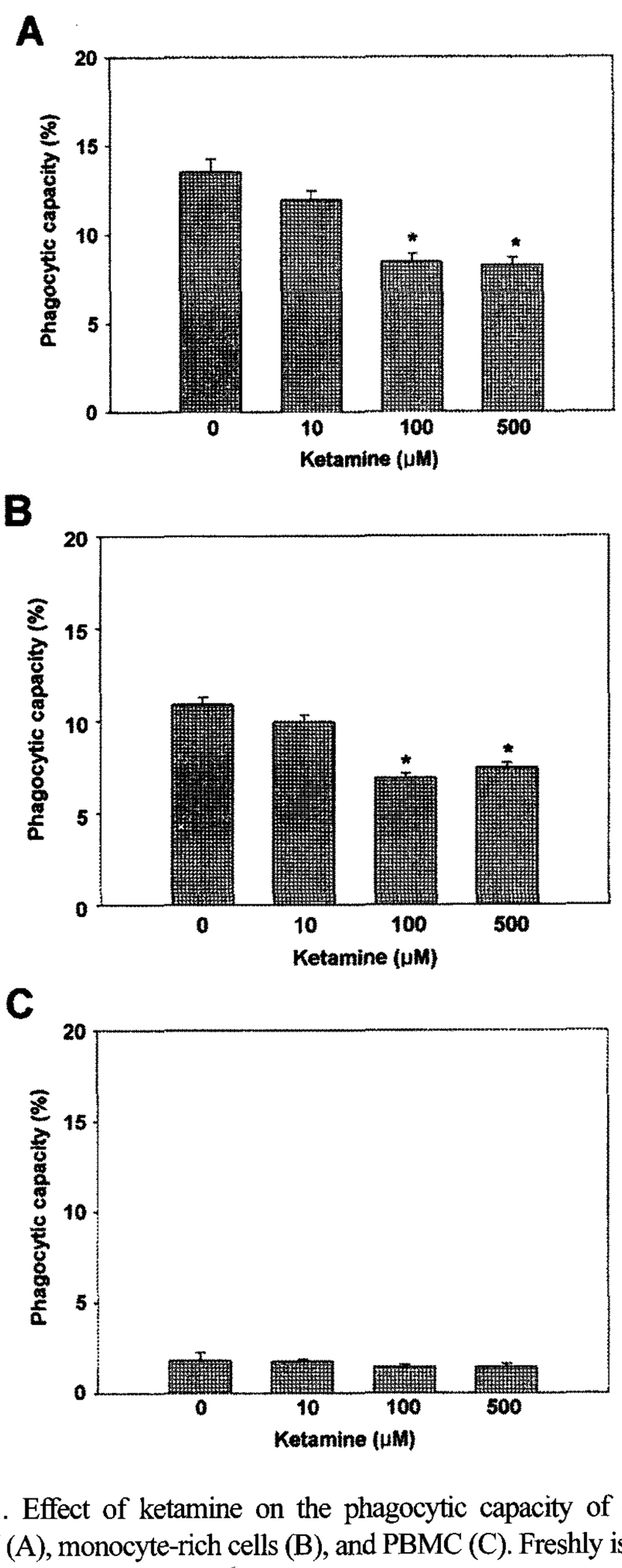

Fig 1. Effect of ketamine on the phagocytic capacity of canine PMN (A), monocyte-rich cells (B), and PBMC (C). Freshly isolated PMN or PBMC (1×10^6 cells/ml/well) were incubated for 12 h with ketamine at the indicated concentrations. FITC-latex beads were added to the cultures for the final 1 h, and the phagocytic capacity was measured by using a flow cytometry. One-way ANOVA was used to investigate differences between control (0 μM) and treatments, followed by post-hoc Dunnett's test. The values are means ± SE (n = 3). *$P<0.05$ *versus* 0 μM ketamine.

Results

Direct effect of ketamine on phagocytic capacity of canine peripheral blood leukocytes

To examine the direct effect of ketamine on phagocytic capacity of peripheral blood leukocytes, freshly isolated PMN or PBMC was cultured with ketamine at concentrations ranging from 10 to 500 μM for 12 h. The treatment with 10 μM ketamine had no effect on phagocytic capacity of leukocytes. However, when compared with 0 μM ketamine treatments, the treatments with 100 and 500 μM of ketamine significantly ($P < 0.05$) decreased the phagocytic capacity of the PMN (Fig 1A) and the monocyte-rich cell population of the PBMC (Fig 1B), which were identified by their typical location on the flow cytometric scattergram, although the total PBMC did not show this (Fig 1C).

Phagocytic capacity of peripheral blood phagocytes exposed to the culture supernatant of ketamine-treated leukocytes

To examine the effect of culture supernatant from PBMC or PMN treated with ketamine on the phagocytic capacity of phagocytes, PMN and PBMC were respectively incubated with culture supernatant fraction collected from cells treated

Table 1. Effect of ketamine-treated PBMC culture supernatant on the phagocytic capacity of canine PMN

Ketamine-treated PBMC culture supernatant (%)	Concentration (μM) of ketamine				P value
	0	10	100	500	
0	12.900 ± 0.721	12.633 ± 0.561	12.267 ± 0.418	12.167 ± 0.835	0.847
3.13	13.800 ± 0.755	13.300 ± 0.529	12.067 ± 0.203	13.033 ± 0.578	0.237
6.25	14.100 ± 0.666	13.700 ± 0.551	12.367 ± 0.348	13.033 ± 0.203	0.128
12.5	15.500 ± 0.361	14.700 ± 0.404	12.300 ± 0.529*	13.100 ± 0.361*	0.002
25.0	16.367 ± 0.384	15.867 ± 0.649	13.300 ± 0.379*	13.100 ± 0.513*	0.003
50.0	16.700 ± 0.814	16.567 ± 0.384	13.667 ± 0.578*	13.933 ± 0.524*	0.010

* $P < 0.05$ *versus* 0 μM ketamine, as determined by one-way analysis of variance (ANOVA) followed by a Dunnett post hoc test. Data presented as mean ± standard error (n = 3).

Table 2. Effect of ketamine-treated PBMC culture supernatant on the phagocytic capacity of canine monocyte-rich cells

Ketamine-treated PBMC culture supernatant (%)	Concentration (μM) of ketamine				P value
	0	10	100	500	
0	10.200 ± 0.436	9.933 ± 0.426	10.267 ± 0.260	10.067 ± 0.240	0.910
3.13	10.967 ± 0.418	10.967 ± 0.448	10.233 ± 0.318	10.033 ± 0.260	0.234
6.25	12.267 ± 0.318	12.333 ± 0.176	10.433 ± 0.491*	10.033 ± 0.176*	0.001
12.5	13.033 ± 0.233	13.033 ± 0.088	10.600 ± 0.379*	9.733 ± 0.291*	<0.001
25.0	14.033 ± 0.353	13.600 ± 0.321	10.567 ± 0.689*	9.600 ± 0.681*	<0.001
50.0	14.733 ± 0.233	14.400 ± 0.252	11.400 ± 0.416*	10.567 ± 0.504*	<0.001

* $P < 0.05$ *versus* 0 μM ketamine, as determined by one-way analysis of variance (ANOVA) followed by a Dunnett post hoc test. Data presented as mean ± standard error (n = 3).

Table 3. Effect of ketamine-treated PBMC culture supernatant on the phagocytic capacity of canine PBMC

Ketamine-treated PBMC culture supernatant (%)	Concentration (μM) of ketamine				P value
	0	10	100	500	
0	1.333 ± 0.318	1.533 ± 0.176	1.600 ± 0.306	1.533 ± 0.120	0.878
3.13	1.767 ± 0.145	1.233 ± 0.233	1.533 ± 0.145	1.300 ± 0.208	0.248
6.25	1.367 ± 0.318	1.600 ± 0.404	1.433 ± 0.176	1.700 ± 0.252	0.853
12.5	1.467 ± 0.348	1.667 ± 0.233	1.667 ± 0.167	1.533 ± 0.120	0.905
25.0	1.667 ± 0.120	1.433 ± 0.176	1.867 ± 0.176	1.700 ± 0.231	0.449
50.0	1.633 ± 0.203	1.567 ± 0.273	1.667 ± 0.318	1.233 ± 0.219	0.634

No significant differences between the four concentrations of ketamine treatment, as determined by one-way analysis of variance (ANOVA). Data presented as mean ± standard error (n = 3).

Table 4. Effect of ketamine-treated PMN culture supernatant on the phagocytic capacity of canine PMN

Ketamine-treated PBMC culture supernatant (%)	Concentration (μM) of ketamine				P value
	0	10	100	500	
0	12.700 ± 0.723	0.723 ± 0.635	12.667 ± 1.011	12.467 ± 0.754	0.996
3.13	13.367 ± 0.426	12.600 ± 0.520	12.067 ± 0.801	14.167 ± 0.338	0.110
6.25	12.467 ± 0.865	12.600 ± 0.462	12.500 ± 0.872	12.967 ± 0.906	0.968
12.5	13.800 ± 0.208	13.567 ± 0.384	12.667 ± 0.722	3.633 ± 0.555	0.434
25.0	12.600 ± 0.529	13.467 ± 0.448	12.667 ± 0.521	14.067 ± 0.296	0.151
50.0	12.333 ± 0.426	13.267 ± 0.754	13.100 ± 0.473	12.667 ± 0.536	0.652

No significant differences between the four concentrations of ketamine treatment, as determined by one-way analysis of variance (ANOVA). Data presented as mean ± standard error (n = 3).

Table 5. Effect of ketamine-treated PMN culture supernatant on the phagocytic capacity of canine monocyte-rich cells

Ketamine-treated PBMC culture supernatant (%)	Concentration (μM) of ketamine				P value
	0	10	100	500	
0	10.267 ± 0.775	10.033 ± 0.677	10.533 ± 0.348	9.833 ± 0.694	0.880
3.13	10.300 ± 0.351	10.833 ± 0.273	10.800 ± 0.723	10.667 ± 0.233	0.819
6.25	10.200 ± 0.361	10.167 ± 0.186	10.567 ± 0.120	10.367 ± 0.240	0.651
12.5	10.200 ± 0.379	10.367 ± 0.536	10.600 ± 0.208	10.533 ± 0.410	0.893
25.0	10.400 ± 0.416	10.700 ± 0.252	10.233 ± 0.328	10.400 ± 0.306	0.794
50.0	10.567 ± 0.433	10.000 ± 0.252	10.367 ± 0.285	10.400 ± 0.520	0.771

No significant differences between the four concentrations of ketamine treatment, as determined by one-way analysis of variance (ANOVA). Data presented as mean ± standard error (n = 3).

Table 6. Effect of ketamine-treated PMN culture supernatant on the phagocytic capacity of canine PBMC

Ketamine-treated PBMC culture supernatant (%)	Concentration (μM) of ketamine				P value
	0	10	100	500	
0	1.63 ± 0.524	1.400 ± 0.404	1.400 ± 0.462	1.800 ± 0.551	0.921
3.13	1.867 ± 0.393	1.067 ± 0.219	2.000 ± 0.351	1.467 ± 0.296	0.240
6.25	1.833 ± 0.273	1.500 ± 0.551	1.267 ± 0.260	1.967 ± 0.296	0.549
12.5	1.467 ± 0.376	1.267 ± 0.203	1.533 ± 0.481	1.633 ± 0.186	0.884
25.0	1.900 ± 0.208	0.933 ± 0.285	1.700 ± 0.473	1.500 ± 0.208	0.229
50.0	1.100 ± 0.252	1.733 ± 0.328	1.233 ± 0.546	1.700 ± 0.361	0.581

No significant differences between the four concentrations of ketamine treatment, as determined by one-way analysis of variance (ANOVA). Data presented as mean ± standard error (n = 3).

with ketamine. The culture supernatant from PBMC treated with 10 μM ketamine had no significant effect on the phagocytic capacities of phagocytes. However, the phagocytic capacities of PMN (Table 1) and monocyte-rich cells (Table 2) but not total PBMC (Table 3) were significantly ($P < 0.05$) inhibited by the culture supernatant from PBMC treated with 100 and 500 μM of ketamine when compared with those of 0 hibited by the culture s culture supernatant. On the other hand, the culture supernatant from PMN treated with ketamine had no significant effect on the phagocytic capacities of PMN (Table 4), monocyte-rich cells (Table 5), and PBMC (Table 6).

Discussion

A previous study reported that *in vitro* treatment with ketamine concentrations below 500 μM showed no cytotoxic effect and high cell viability, but a higher concentration of 1,000 μM exhibited a low viability of canine PMN and PBMC (12). Therefore, ketamine was used in the present study at concentrations below 500 μM. The treatment with ketamine directly suppressed the phagocytic capacity of both PMN and monocytes, and this reduction was begun from the 100 μM of ketamine concentration that is within the range of

clinical relevance (6,8). However, ketamine did not affect the phagocytic capacity of the canine total PBMC population. This probably reflects the fact that the monocytes in the PBMC comprise just 30% of all the cells, with the remainder being lymphocytes.

It has been known that the phagocytic responses were regulated by adenosine triphosphate (ATP) (7). Moreover, the amount of ATP produced by mitochondrial respiratory chain reaction is influenced by the membrane potential of mitochondrion in particular (16). After all, an increase of ATP synthesis induces the enhancement of phagocytic responses including chemotactic migration, phagocytic ingestion and the oxidative burst by either increasing intracellular calcium ions or the purinergic P2 receptor pathway (7). Conversely, if the ATP synthesis from mitochondria is suppressed, the phagocytic responses of phagocytes may be decreased (10,13). Recently, *in vitro* treatment with ketamine can decrease the mitochondrial membrane potential of mouse RAW 264.7 macrophages (5). Therefore, it was assumed that the inhibitory effects of ketamine on phagocytic capacity of canine PMN might be attributed to decreased ATP synthesis through the reduction of mitochondrial membrane potentials.

In the current study, we also observed that the phagocytic capacity of PMN or monocytes was inhibited by culture supernatant fraction from PBMC but not PMN treated with ketamine, similar to a previous study showing that the oxidative burst activity of canine PMN and monocyte-rich cells was inhibited by culture supernatant from ketamine-treated PBMC (12). This suggests one possibility that in ketamine-treated PBMC culture supernatant, there were the presences of the soluble factor(s) such as prostaglandin E_2 (PGE_2), which can disturb the phagocytic responses of PMN and monocytes (3). It has been perceived that PGE_2 has potent immunosuppressive effects including the inhibition of phagocytic capacity (3), chemotaxis (2), and reactive oxygen species production (14). TNF-α could increase neutrophil phagocytosis and superoxide generation and thus play a central role as mediators of the host response to infection and injury (15). Recently, it has been reported that ketamine inhibits the production of TNF-α in human whole blood (11) and in rat PBMC (21). Thus, the other possible explanation is that the inhibitory effect on phagocytic capacity by the culture supernatant fraction may be associated with the decreased spontaneous expression of TNF-α from PBMC.

In conclusion, our results appear that ketamine plays an inhibitory role on phagocytic capacity of canine peripheral blood phagocytes through not only a directly suppressive effect but also some soluble factor(s) driven from canine PBMC. Due to a pivotal role of neutrophils in immune system, the inhibitory effects of ketamine on phagocytosis may result in an increased possibility of infection. However, additional experiment will be also necessary to clarify a decrease of immune functions by the clinical application with ketamine.

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*In Vitro*에서 개 말초혈액 탐식세포의 탐식능에 대한 케타민의 효과

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요 약 : 케타민은 N-methyl-D-aspartate (NMDA) 수용체의 비경쟁적인 길항제로 인의와 수의학에서 전신 마취제로 사용하는 약물이다. 본 연구진은 이전에 케타민이 개 말초혈액 백혈구의 순간산소과소비현상(oxidative burst activity)을 손상시킨다고 보고하였다. 현재 연구에서는 개 말초혈액 탐식세포의 탐식능(phagocytic capacity)에 대한 케타민의 효과를 검토하였다. 탐식능은 유세포 분석기로 분석하였다. 말초혈액 다형핵백혈구(peripheral blood polymorphonuclear cells; PMN)와 단구(monocytes)의 탐식능은 케타민의 직접 처리에 의해 감소하였으나 단핵구세포(peripheral blood mononuclear cells; PBMC) 분획에서의 탐식능은 케타민의 직접 처리에 의해 변화가 없었다. 말초혈액 다형핵백혈구와 단구의 탐식능은 케타민을 처리한 단핵구세포 배양상층액에 의해서도 감소하였다. 이상의 결과로부터 케타민은 호중구와 단구와 같은 개 말초혈액 탐식세포의 탐식능에 있어 직접적인 억제효과를 나타내며, 또한 케타민 처리 단핵구세포로부터 생산되는 가용성인자에 의해서도 탐식세포의 탐식능이 억제되는 것으로 사료되었다.

주요어 : 개, 말초혈액탐식세포, 케타민, 탐식능