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Effects of dietary nucleotides and cationic peptides on vaccination response in cats

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Abstract: Modulation of the immune system through nutrition is the aim of many studies. As the induction of a rapid onset of immunity in cats is often critical, the objective of this study was to evaluate the effects of orally administered dietary nucleotides and cationic peptides, on the vaccination response in cats. The cats were allocated to two groups: Group A (n = 8) was fed a diet with dietary nucleotides and cationic peptides for ninety-two days, and Group C (n = 8) was fed a diet without the nucleotides and cationic peptides. The cats were vaccinated against feline herpesvirus 1 (FHV-1), feline calicivirus (FCV) and feline panleukopenia virus (FPV). The proliferation activity of lymphocytes and antibody response after vaccination were evaluated using ELISA kits. Comparing the two groups, a significant increase in the proliferation activity of the lymphocytes ($P < 0.01$) was observed in Group A, as well as a significant increase in the antibody titres after vaccination against feline herpesvirus ($P < 0.05$; $P < 0.001$), feline calicivirus ($P < 0.01$; $P < 0.001$) and feline panleukopenia virus ($P < 0.01$; $P < 0.001$). Protective levels of the antibodies were reached significantly earlier in Group A than in Group C. In conclusion, dietary nucleotides and cationic peptides have a positive effect on the lymphocyte proliferation and antibody production after vaccination against FHV-1, FCV and FPV in cats. Therefore, we assume that they can be used as a suitable immunostimulatory substance in feline practice.

Keywords: feline calicivirus; feline herpesvirus; feline panleukopenia virus; fed supplementation; immunity

Dietary nucleotides are low molecular weight intracellular compounds, playing key roles in nearly all biochemical processes and they are naturally present in all foods of animal and vegetable origin as free nucleotides and nucleic acids (Gil 2002). Cationic peptides are a part of the immediate, effective and nonspecific defence against infections in all organisms, from plants and animals to humans (Ntwasa 2012). They are generally 12–50 amino acids in length with an excess of basic lysine and arginine residues over acidic residues (Hancock 2001). Dietary nucleotides and cationic peptides are characterised as substances able to improve the immune status in various animal species as well as in humans (Straus and Hancock 2006; Wei et al. 2015; Karimzadeh et al. 2020). Their immunomodulatory activities include the modulation of the innate immune response (Yang et al. 2004; Hemsheker et al. 2016), chemotaxis stimulation, cytokine production, modulation of cellular differentiation pathways, modulation of dendritic cell activation and differentiation (Yeung et al. 2011).

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In addition, dietary nucleotides influence the lymphocyte maturation, activation and proliferation (Nagafuchi et al. 1997; Gil 2002), an increase in the production of immunoglobulins, an improved response to vaccines, a reduction in morbidity (Maldonado et al. 2001) and can modulate type 1 and type 2 T-helper (Th) cell responses by promoting a shift in the Th1/Th2 balance toward a Th1-dominant immunity (Jyonouchi et al. 2001).

The dietary supplementation of these substances has already been used in animals and humans with proven health benefits. Jiao and Kim (2018) noticed positive effects on improving the health of the immune system as well as reducing foot-and-mouth disease vaccine stress in growing pigs. Romano et al. (2007) found the positive effects of dietary nucleotides (higher unspecific immunoglobulin levels and better CRP and haematocrit results) in puppies at weaning. The modulation of antibody-forming cells by dietary nucleotides in mice was studied by Navarro et al. (1996). Furthermore, a higher antibody response to different vaccines was observed in children fed on a nucleotide-supplemented diet (Pickering et al. 1998; Schaller et al. 2004).

Because feline herpesvirus (FHV-1), feline calicivirus (FCV) and feline panleukopenia virus (FPV) are common, highly prevalent and easily transmitted causes of infections, the vaccination of all cats is recommended by the Advisory Board on Cat Diseases (Horzinek et al. 2013). Since cats often fail to respond to these vaccinations or only develop low levels of antibodies (Jas et al. 2009; Sykes 2014), the aim of our study was to evaluate the effects of orally administered dietary nucleotides and cationic peptides on the immune response after these vaccinations in cats.

MATERIAL AND METHODS

Animals

Sixteen clinically healthy, six week-old kittens were used in our study. The kittens of mixed breeds were obtained from two mothers, divided by sex and randomly allocated to Groups A and C using the Graphpad Quick Calcs system. Group A (n = 8; 4 males, 4 females): healthy cats, fed with a pelleted feed (Royal Canine Indoor) supplemented with a cationic peptide and dietary nucleotide based preparation for ninety-two days. The control Group C (n = 8; 4 males, 4 females): healthy cats, fed with a pelleted feed without the cationic peptides and dietary nucleotides. All the cats in the trial came from private owners and were only kept indoors. The clinical study was approved by the Ethical Committee of the University of Veterinary Medicine and Pharmacy in Košice, Slovakia.

Immunomodulation, vaccination and sampling

For the immunomodulation, a cationic peptide and dietary nucleotide based preparation was used (Aminex; Uniregen, Náchod, Czech Republic). The content of the preparation per 100 g was 11.667 mg of protein (cationic peptides) and 3 mg of nucleotides dissolved in distilled water. The manufacturer's recommended dose was 0.5 ml/kg once a day. The design of the trial is shown in Table 1. The cats were vaccinated against FHV-1, FCV and FPV (Felocell CVR; Elanco Animal Health, Vienna, Austria).

Lymphocyte proliferation test

The lymphocyte activity was determined using a Cell Proliferation ELISA Kit, BrdU colorimetric (Roche, Mannheim, Germany). Briefly, the density of the cell suspension was adjusted to 10^6 cells/ml of an RPMI 1640 medium (Sigma, St. Louis, MO, USA) supplemented with a 10% heat inactivated foetal bovine serum, 100 000 IU/ml of penicillin and 0.2 ml of streptomycin. The cells were transferred into a 96-well micro-titre plate and incubated at 37 °C in a 5%

Table 1. Design of the trial

Day of trial	Age of cats (weeks)	Vaccination	Sampling and evaluation (serological analysis and SI)
1	6	–	+
22	9	V1	+
43	12	V2	+
64	15	–	+
92	19	–	+

SI = stimulation index of the lymphocytes; V1 = vaccination against feline herpesvirus (FHV-1), feline calicivirus (FCV) and feline panleukopenia virus (FPV); V2 = revaccination against FHV-1, FCV and FPV at 12 weeks of age

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CO_2 atmosphere for 3 days. For lymphocyte stimulation, phytohaemagglutinin (PHA; Sigma-Aldrich, St. Louis, MO, USA) at a concentration of 25 µg/ml was used. The incorporation of BrdU was performed according to the manufacturer's protocol. The results were expressed as the stimulation index (SI), calculated as the ratio of the optical density (OD) values of the stimulated cells and non-stimulated controls.

Serological analysis

A Feline Herpesvirus Antibttttty ELISA test, Feline Calicivirus Antibody ELISA test and Feline Panleukopenia Virus Antibody ELISA test (B.V. European Veterinary Laboratory EVL, Woerden, The Netherlands) were used for the serological analysis. The levels of the antibodies are expressed as the optical density (OD). The protective levels of the antibodies were determined according to the manufacturer as follows: OD ≥ 1.0 (titre ≥270) for FHV-1; OD ≥ 0.25 (titre ≥270) for FCV and OD ≥ 0.25 (titre ≥1 350) for FPV.

Statistical analysis

The data were expressed as the mean (±) standard deviation (SD). The statistical evaluation was performed using the Mann-Whitney test. The analyses were performed using the software GraphPad Prism v5.0 (GraphPad Software, Inc., San Diego, USA).

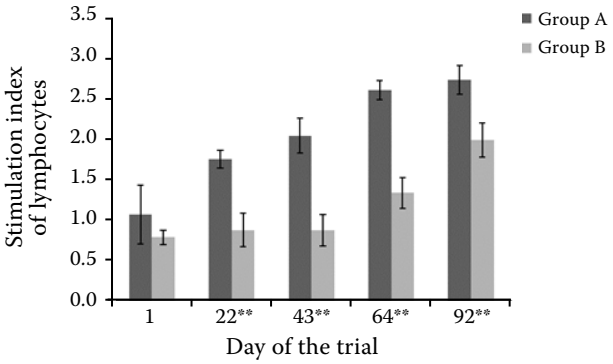

Figure 1. Comparison of the stimulation index of the lymphocytes in Group A (n = 8; cats with the dietary supplementation) and Group C (n = 8; cats without the dietary supplementation)

The data were analysed using the Mann-Whitney test (**P < 0.01). All the values are presented as the mean (±) standard deviation

RESULTS

Comparing Group A and C, the stimulation index (SI) of the lymphocytes was significantly increased (P < 0.01) on days 22, 43, 64 and 92 among the cats in Group A (Figure 1).

The antibody response after vaccination against FHV-1 in Groups A and C is shown in Figure 2A.

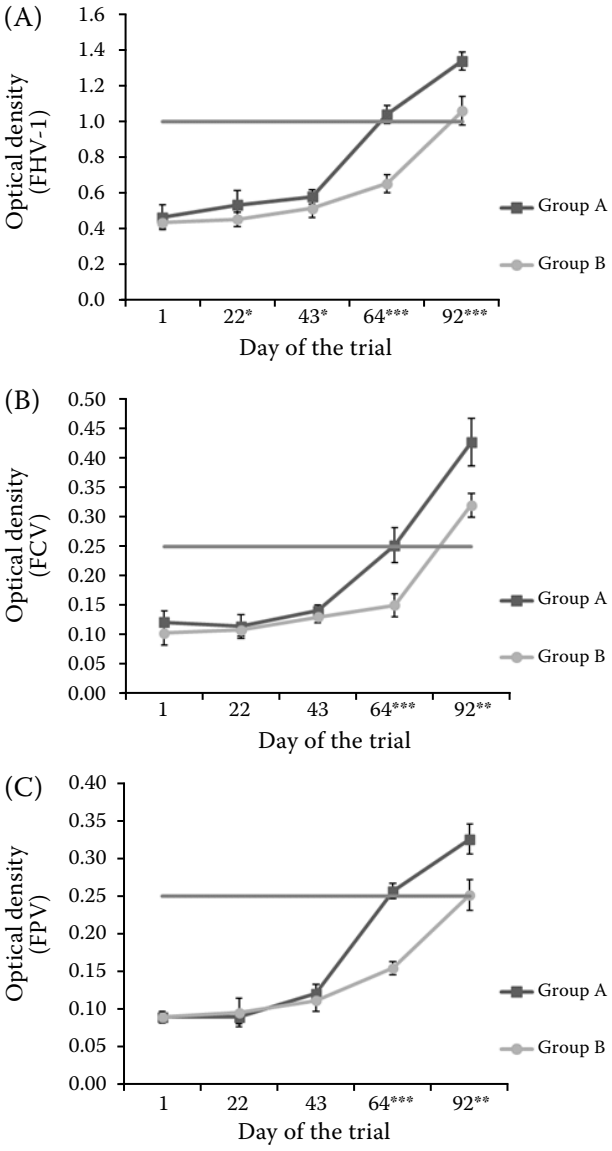

Figure 2. Production of the specific antibodies against the feline herpesvirus (A), feline calicivirus (B) and feline panleukopenia virus (C) in Group A (n = 8; cats with the dietary supplementation) and Group C (n = 8; cats without the dietary supplementation)

The levels of the antibodies are expressed as the optical density (OD). The data were analysed using the Mann-Whitney test (*P < 0.05; **P < 0.01; ***P < 0.001). All the values are presented as the mean (±) standard deviation

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Comparing the two groups, a significant increase in the antibody titres was recorded on days 22, 43 ($P < 0.05$), 64 and 92 ($P < 0.001$) in Group A. The protective antibody concentrations in Group A were detected on the 64th day (OD ≥ 1.04 ± 0.091) and on the 92nd day (OD ≥ 1.06 ± 0.08) in Group C.

The antibody response after vaccination against FCV in Groups A and C is shown in Figure 2B. Comparing the two groups, a significant increase in the antibody titres was recorded on days 64 ($P < 0.001$) and 92 ($P < 0.01$) in Group A. The protective antibody concentrations in Group A were detected on the 64th day (OD ≥ 0.252 ± 0.036) and on the 92nd day (OD ≥ 0.32 ± 0.023) in Group C.

The antibody response after vaccination against FPV in Groups A and C is shown in Figure 2C. Comparing the two groups, a significant increase in the antibody titres was recorded on days 64 ($P < 0.001$) and 92 ($P < 0.01$) in Group A. The protective antibody l concentrations in Group A were detected on the 64th day (OD ≥ 0.257 ± 0.017) and on the 92nd day (OD ≥ 0.252 ± 0.021) in Group C.

DISCUSSION

The effects of the oral administration of different dietary supplements to infectious diseases and the vaccination response against them are still being studied (Filho et al. 2019; Mayer et al. 2019; Mohamed et al. 2019). Dietary nucleotides have been reported to be beneficial since they positively influence the lipid metabolism, immunity, and tissue growth, development and repair (Gil 2001; Guo et al. 2019). Similarly, cationic peptides exhibit a wide range of biological activities from the direct killing of invading microbes to the modulation of the innate immune response and other biological responses of the host (Yang et al. 2004).

In our study, the effects of dietary nucleotides and cationic peptides on the lymphocyte proliferation were evaluated. We noticed a significant increase in the proliferation activity of the lymphocytes stimulated by PHA in cats with the dietary nucleotide and cationic peptide supplemented diet. These differences were largely found due to the fact that the control group values were below normal values. This could be explained by the fact that the feline immune system reaches maturity after eight weeks of life phenotypically as well as functionally and, furthermore, the blood lymphocyte levels increase over a ninety-day postnatal period (Sellon et al. 1996; Bortnick et al. 1999; Day 2007). The stimulation index in Group C was significantly lower in comparison to Group A. We assume that this is related to the fact that the cell proliferation and cytokine production after the mitogen stimulation is much lower in kittens below ten weeks of age (Levy and Tompkins 1998). The increase in the stimulation index in Groups A and C on days 64 and 92 can be a result of the effect of the dietary nucleotide and cationic peptide supplementation as well as the proliferative effect of the vaccines on the lymphocytes (Scherk et al. 2013; Stone et al. 2020).

Van Buren et al. (1985) suggested that dietary nucleotides exert effects on the immune responsiveness by acting on the T helper/inducer population, with the predominant effect on the initial phase of the antigen processing and lymphocyte proliferation. The exogenous nucleotides increased the proliferative response to the T-cell dependent mitogens (phytohaemagglutinin – PHA, concanavalin – ConA, pokeweed mitogen – PWM) (Gil 2002). Kulkarni et al. (1992) demonstrated a reduced proliferative response of the lymphocytes to the T-cell mitogens, PHA and ConA in mice fed a nucleotide-free diet. A similar study with mice fed with nucleotide-free diets showed a significant suppression of some T-cell responses in comparison with those that received the same diet supplemented with RNA as a source of the exogenous nucleotide (Rudolph at el. 1990). Romano et al. (2007) performed a study with dogs fed a diet supplemented with nucleotides. Their results showed an increased lymphocyte response after stimulation in dogs with a supplemented diet. Russo et al. (2018) indicated that nucleotides could be included in pet food processing. Also, Segara et al. (2018) noticed that the oral administration of nucleotides led to significant reduction in the anti-*Leishmania* antibodies and a lower disease progression rate in dogs. Similarly, Rutherfurd-Marwick et al. (2013) monitored the proliferative response to T-cell mitogens in forty-three cats. Although, in cats fed with dietary nucleotides, no significant effects on the proliferative response to ConA were found, though a significant effect on proliferative response to the PHA was noticed. Yeung et al. (2011) described that the immunomodulatory function of cationic peptides is the induction of chemokines for the neutrophils, monocytes, macrophages and T lymphocytes response.

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Our study also focused on the evaluation of the effects of the dietary nucleotides and cationic peptides on the antibody response after vaccination against FHV-1, FCV and FPV.

Our results showed a significant increase in the antibody titres and an earlier onset in the protective levels of the specific antibodies in the group of cats with the dietary nucleotide and cationic peptide supplemented diet. On the other hand, we noticed a later onset in the protective levels of the antibodies in Group C. The serologic response to the vaccination of kittens varies based on the vaccination type and maternal antibodies level, as they may persist for up to 16 weeks and interfere with the vaccination (Poulet 2007; DiGangi et al. 2012) and seroconversion may occur 7–14 days after vaccination (Jas et al. 2009; Lappin 2012).

Similarly, a higher antibody titre against parvovirus and unspecific immunoglobulin concentrations after vaccination were observed in dietary nucleotide supplemented groups of dogs by Romano et al. (2007). In vaccinated cats, the detection of FHV-1, FCV, and FPV-specific antibodies is predictive of whether cats are susceptible to disease (Lappin et al. 2006). FPV antibodies are useful in the assessment of the immunity, correlate strongly with the protection and the results can be used to decide whether to vaccinate or not (Lappin et al. 2002; DiGangi et al. 2012). In contrast, the concentrations of antibodies correlate to the protection against acute diseases caused by FCV and FHV, but cats can also be protected in the absence of antibodies (Poulet et al. 2005). Therefore, antibody testing for FHV and FCV is not reliable for an assessment of immunity, as an effective immunity against these viruses requires both an antibody and cell mediated immune response (Scherk et al. 2013; Stone et al. 2020).

As described by Yeung et al. (2011), cationic peptides have the potential for use in vaccine adjuvants, wound healing, anti-endotoxemia and anticancer drugs. Furthermore, an increased resistance to bacterial infections was observed in rodent models. Similarly, Nijnik et al. (2010) reported that host defence peptides can act in the direct killing of pathogens or clear an infection by stimulating an appropriate immune response.

In addition, the induction of a better immune response in cats is also of great importance in relation to human health as cats may act as vectors of many diseases including zoonoses (Dabritz and Conrad 2010; Jankowiak et al. 2020; Li et al. 2020; Taggart et al. 2020).

In conclusion, our results indicate that fed a supplementation with dietary nucleotide and cationic peptides could enhance the lymphocyte proliferation as well as humoral immune response after vaccination in cats. Therefore, we suggest that a diet supplementation with dietary nucleotides and cationic peptides has a beneficial effect on the vaccination response against a feline herpesvirus, feline calicivirus and feline panleukopenia virus in cats. Although further studies are necessary, we recommend these preparations as a suitable dietary supplement in an attempt to increase the feline immunocompetence.

Conflict of interest

The authors declare no conflict of interest.

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