Research Advances on the Role and Mechanism of Vitamin A in Enhancing Animal Antiviral Capacity: Postprint

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Abstract

Vitamin A enhances antiviral capacity in animals, with its metabolite all-trans retinoic acid serving as the principal active form mediating this effect. Vitamin A exerts antiviral activity through multiple pathways: enhancement of innate antiviral capacity via upregulation of retinoic acid-inducible gene I receptor-mediated interferon-I expression; augmentation of adaptive antiviral capacity through increased immunoglobulin A production by B lymphocytes; and modulation of intestinal microbiota to enrich Lactobacillus populations with antiviral properties. This article provides a concise review of the effects of vitamin A on antiviral capacity in animals and its underlying mechanisms.

Full Text

Enhancing Effect of Vitamin A on Antiviral Ability of Animals and Its Mechanism: A Review

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Abstract: Vitamin A enhances antiviral capacity in animals, with its metabolite all-trans retinoic acid (ATRA) serving as the primary active form. Vitamin A exerts antiviral effects through multiple pathways: enhancing innate antiviral immunity by increasing retinoic acid-induced gene I (RIG-I) receptor-mediated type I interferon (IFN-I) expression, boosting adaptive antiviral immunity by elevating immunoglobulin A (IgA) production from B lymphocytes, and modulating gut microbiota to increase populations of antiviral Lactobacillus species.

This review summarizes the current research progress on vitamin A' s antiviral effects in animals and their underlying mechanisms.

Keywords: vitamin A; antiviral ability; retinoic acid-induced gene I; immunoglobulin A; Lactobacillus

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Viruses are obligate intracellular parasites that disrupt normal cellular activities and cause diseases, posing severe threats to human and animal health as well as livestock production. Nutrients form the material basis of all life activities, influencing not only animal production potential and efficiency but also determining health status. Recent studies have demonstrated that antiviral capacity in both humans and animals is closely associated with nutritional status. Therefore, enhancing viral resistance through nutritional strategies holds significant theoretical and practical importance. Vitamin A, also known as retinol (ROH), is an essential nutrient for all vertebrates. Beyond its role in maintaining normal growth and development, vitamin A possesses anti-infective properties and has been termed the "anti-infective vitamin." Research has shown that vitamin A can enhance animal resistance to viral infections.

Liver-stored retinyl esters (REs) are continuously hydrolyzed to produce ROH, which is released into circulation for tissue uptake and utilization. Within cells, ROH is first oxidized to retinaldehyde by retinol dehydrogenase, then irreversibly converted to retinoic acid (RA) by retinaldehyde dehydrogenase. RA exists in multiple isoforms, including ATRA, 13-cis-RA (13cRA), and 9-cis-RA (9cRA), with ATRA considered the primary active form mediating most vitamin A physiological functions. Retinoic acid receptors (RARs) belong to the nuclear receptor superfamily and typically form heterodimers with retinoid X receptors (RXRs) to regulate gene transcription by binding to retinoic acid response elements (RARE) in target gene promoters.

As the natural ligand for RARs, ATRA exerts its classical effects by binding to the ligand-binding domain of RARs, thereby enhancing the induced expression of functional genes. Cho et al. found that vitamin A's antiviral effects are closely related to its metabolism into ATRA. Multiple studies have confirmed ATRA' s ability to enhance antiviral capacity, which is associated with its regulation of antiviral molecule expression. Research indicates that ATRA enhances antiviral effects in a RARs-dependent manner. Thus, vitamin A primarily exerts its antiviral effects by converting to ATRA and acting through RAR-dependent pathways.

2 Effects of Vitamin A on Animal Antiviral Capacity

Vitamin A plays a crucial role in resisting single-stranded (ss)RNA viruses, double-stranded (ds)RNA viruses, and DNA viruses (Table 1). ssRNA viruses are divided into non-segmented (Paramyxoviridae, Filoviridae, Rhabdoviridae, and Bornaviridae) and segmented (Orthomyxoviridae, Bunyaviridae, and Are-

naviridae) groups. Current research on vitamin A against (-)ssRNA viruses has focused on Paramyxoviridae, which includes measles virus, mumps virus, canine distemper virus, and Newcastle disease virus. Measles and mumps viruses primarily infect humans, causing measles and mumps, respectively. Clinical studies show that vitamin A supplementation reduces morbidity and mortality from measles virus infection, leading the World Health Organization to recommend vitamin A for treating acute measles in children. Trottier et al. demonstrated that physiological concentrations of ROH significantly inhibit measles virus replication in peripheral blood mononuclear cells and various cell lines, confirming vitamin A' s anti-measles activity. Soye et al. found that ROH dose-dependently inhibits mumps virus replication, indicating vitamin A' s anti-mumps virus effects.

Newcastle disease virus primarily infects poultry, causing highly contagious and lethal disease in chickens. Okpe et al. supplemented broiler diets with an additional 600 IU vitamin A per kg and found that this supplementation delayed the onset of clinical signs after Newcastle disease virus challenge, significantly reduced tissue damage and disease symptoms, and decreased mortality by 36% compared to unsupplemented controls, demonstrating that vitamin A can enhance antiviral capacity against Newcastle disease virus in chickens. Canine distemper virus severely threatens canid and felid health. Rodeheffer et al. reported that ferrets with adequate vitamin A status showed no obvious infection symptoms when administered 30 mg vitamin A intramuscularly on the day of and one day after intranasal canine distemper virus inoculation, while unsupplemented ferrets developed clear infection signs. These findings indicate vitamin A enhances antiviral capacity against canine distemper virus. Since existing studies have focused on Paramyxoviridae members among (-)ssRNA viruses, whether vitamin A enhances resistance to other (-)ssRNA viruses requires further investigation.

Positive-sense (+)ssRNA viruses include norovirus, enterovirus 71, and hepatitis C virus. Studies show that ATRA reduces the number of infected cells and apoptosis in U937 cells challenged with enterovirus 71, while also inhibiting virus replication. In Huh7 cells, ATRA inhibits hepatitis C virus replication. For dsRNA viruses (such as rotavirus), vitamin A supplementation reduces diarrhea and viral antigen levels. In DNA viruses (such as adenovirus), ATRA reduces hepatic inflammation and damage. These findings demonstrate that vitamin A exerts antiviral effects against various viruses through its metabolite ATRA.

3.1 Enhancing Innate Antiviral Immunity by Increasing RIG-I Receptor-Mediated IFN-I Expression

Innate antiviral immune responses are essential for limiting early viral dissemination. Vitamin A can upregulate RIG-I expression in a retinoic acid receptor (RAR)-dependent manner, enhancing RIG-I-mediated signaling cascades and promoting IFN-I induction to strengthen innate antiviral immunity. Cellular detection of viral invasion depends on pattern recognition receptors that specif-

ically recognize pathogen-associated molecular patterns expressed by viruses, including Toll-like receptors (TLRs) and RIG-I-like receptors (RLRs). RIG-I is a core RLR member, and studies show that ATRA upregulates RIG-I expression in a RAR -dependent manner during responses to (-)ssRNA viruses (measles and mumps) and (+)ssRNA viruses (enterovirus 71).

ATRA' s antiviral effects against measles and mumps viruses require RIG-I participation. Interferon regulatory factor-1 (IRF-1) is a transcription factor that binds to the RIG-I gene promoter, which is crucial for RIG-I induction. Research demonstrates that ATRA upregulates IRF1 expression in a RAR-dependent manner, increases its nuclear localization, and recruits IRF-1 to the RIG-I promoter. Therefore, ATRA can enhance viral recognition capacity by upregulating RIG-I expression through the IRF-1 signaling pathway. Upon recognizing viral RNA, RIG-I triggers downstream signaling cascades that activate transcription factors including IRF-3, IRF-7, and nuclear factor- B (NF- B), thereby inducing expression of antiviral genes such as IFN-I. Type I interferons, including IFN- and multiple IFN- subtypes, are key immune molecules that interrupt viral replication and prevent viral spread during early infection. Studies show that ATRA inhibits measles virus, mumps virus, and enterovirus 71 infection by upregulating IFN-I expression through the RIG-I signaling pathway. In summary, ATRA likely upregulates RIG-I expression via the IRF-1 pathway, enhancing viral recognition and promoting RIG-I-mediated IFN-I expression to strengthen IFN-I-dependent innate antiviral immunity (Figure 1 [Figure 1: see original paper]).

[Figure 1: see original paper]

3.2 Enhancing Adaptive Antiviral Immunity by Increasing Mucosal Virus-Specific IgA Secretion

Viruses are effective antigens that induce adaptive immune responses. B lymphocytes proliferate and differentiate into plasma cells that produce immunoglobulins, mediating humoral immunity to suppress viral infection. IgA is the predominant immunoglobulin in mucosal secretions, distributed on mucosal surfaces of the respiratory and gastrointestinal tracts, forming the first line of defense against viral and microbial infections. Studies demonstrate that vitamin A plays an important role in regulating mucosal IgA responses to viruses and vaccines in the respiratory tract. Mice fed diets with different vitamin A levels showed significantly higher virus-specific antibody titers in saliva after intranasal inoculation with influenza A virus H3N2 in the high vitamin A group compared to the low-level group.

Vitamin A deficiency significantly reduces virus-specific IgA antibody titers in nasal-associated lymphoid tissue after Sendai virus inoculation in mice. However, intranasal supplementation with retinyl palmitate (0.6, 6.0, 60.0, and 600.0 IU) to vitamin A-deficient mice at the time of virus inoculation dose-dependently increased virus-specific antibody titers, with significant differences observed at

60.0 IU. Vitamin A deficiency also reduces influenza vaccine (FluMist)-induced virus-specific IgA titers in nasal-associated lymphoid tissue, but supplementation with 300 g RA or 600 IU vitamin A palmitate via gavage on the day of vaccination and days 3 and 7 post-vaccination increased these titers in vitamin A-deficient mice. Increasing IgA antibody-forming cell numbers can enhance IgA production. Vitamin A deficiency significantly reduces virus-specific IgA antibody-forming cell numbers in nasal-associated lymphoid tissue after Sendai virus inoculation, but intranasal retinyl palmitate supplementation (0.6, 6.0, 60.0, and 600.0 IU) dose-dependently increases these cell numbers, with significant differences at 6.0 IU. Similarly, vitamin A deficiency reduces FluMist vaccine-induced IgA antibody-forming cells, but supplementation with 300 g RA or 600 IU vitamin A palmitate significantly increases these cells. These results indicate that appropriate vitamin A and RA levels can increase virus- and vaccine-induced specific IgA antibody-forming cell numbers and enhance virus-specific IgA secretion, thereby strengthening mucosal IgA-mediated adaptive antiviral capacity.

3.3 Antiviral Effects Through Increasing Antiviral Lactobacillus Populations in the Gut

The gut microbiota plays a crucial role in pathogen infection and mucosal immune responses through interactions with the mucosal immune system. Lactobacillus, as an important component of gut microbiota, includes members with antiviral activity. Four Lactobacillus strains (L. ruminis SPM 1308, L. fermentum KCTC 3112, L. rhamnosus KCTC 18427P, and L. reuteri KCTC 18428P) significantly inhibit norovirus replication in RAW264.7 cells while upregulating IFN- mRNA abundance, indicating these strains suppress norovirus replication by enhancing IFN- expression.

Diet composition significantly influences gut microbiota structure. Mice fed vitamin A-deficient diets showed increased total bacterial loads in the jejunum, ileum, and cecum compared to vitamin A-sufficient diets (containing 3,000 IU/kg), but Lactobacillus relative abundance decreased by 62%, 82%, and 86%, respectively. These findings demonstrate that adequate vitamin A increases gut Lactobacillus populations. Therefore, vitamin A may indirectly enhance antiviral capacity by modulating gut microbiota composition to increase antiviral Lactobacillus populations, though the specific mechanisms require further investigation.

4 Summary

In summary, vitamin A enhances animal antiviral capacity through mechanisms involving upregulation of RIG-I-mediated IFN-I expression to strengthen innate antiviral immunity, increased virus-specific IgA secretion to enhance adaptive antiviral immunity, and modulation of gut microbiota to increase antiviral Lactobacillus populations. In livestock production, adequate dietary vitamin A not

only enhances antiviral resistance but also improves vaccine efficacy. However, the specific mechanisms underlying vitamin A' s antiviral effects require further investigation.

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