



Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: <http://www.elsevier.com/locate/jic>

Review article

Lactoferrin for prevention of common viral infections

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ARTICLE INFO

Article history:

Received 30 July 2014

Received in revised form

4 August 2014

Accepted 4 August 2014

Available online xxx

Keywords:

Lactoferrin

Virus

Norovirus

Gastroenteritis

Interferon

NK

ABSTRACT

Although lactoferrin has many biological functions, the host-protective effects against pathogenic microorganisms including bacteria, fungi, and viruses are regarded as one of the most important. Here, we review research on the protective role of lactoferrin administration against common viral infections. Many studies have shown the *in vitro* antiviral activity of lactoferrin against viral pathogens that cause common infections such as the common cold, influenza, gastroenteritis, summer cold, and herpes, where lactoferrin inhibits mainly viral attachment to the target cells. Recently, studies indicating the *in vivo* protective effects of lactoferrin by oral administration against common viral infections have been increasing. For instance, norovirus is an extremely important emerging human pathogen that causes a majority of gastroenteritis outbreaks worldwide that may be a target candidate for lactoferrin. Lactoferrin consumption reduced the incidence of noroviral gastroenteritis in children and a similar effect was observed in a wide range of ages in a preliminary survey. A recent *in vitro* study reported that lactoferrin inhibits both cellular attachment of the murine norovirus, a virus closely-related to the human norovirus, and viral replication in the cells by inducing antiviral cytokines interferon (IFN)- α/β . Lactoferrin administration also enhances NK cell activity and Th1 cytokine responses, which lead to protection against viral infections. In conclusion, lactoferrin consumption may protect the host from viral infections through inhibiting the attachment of a virus to the cells, replication of the virus in the cells, and enhancement of systemic immune functions.

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1. Introduction

Lactoferrin, an 80-kDa iron-binding glycoprotein of the transferrin family, is a component of exocrine secretions such as milk and saliva, and is present in neutrophil granules [1]. Lactoferrin is thought to play a role in host defense and exhibits a diverse range of biological activities, including antimicrobial activities, antiviral activities, antioxidant activities, immunomodulation, modulation of cell growth, and binding of several bioactive compounds [2–4]. The first report on the antiviral effect of lactoferrin was in the studies conducted by Broxmeyer's group in the 1980s. They showed that lactoferrin affects the myelopoiesis of mice inoculated with a friend virus complex [5]. Then, they found that ip-injected lactoferrin improved the survival rate of mice infected with a friend virus complex [6]. In the 1990s, the target viruses for which lactoferrin

was shown to exhibit antiviral activity were propagated to cytomegalovirus (CMV), herpes simplex virus (HSV), human immunodeficiency virus (HIV), hepatitis C virus (HCV), rotavirus, poliovirus (PV), respiratory syncytial virus (RSV) [7]. The author of this review article described that the antiviral effect of lactoferrin lies in the early phase of infection, preventing the entry of a virus into the host cells, either by blocking cellular receptors, or by direct binding to the virus particles [7]. In a recent review article by Berlutti, the hepatitis B virus (HBV), parainfluenza virus (PIV), alphavirus, hantavirus, human papillomavirus (HPV), feline calicivirus (FCV), adenovirus, enterovirus 71 (EV71), echovirus 6, influenza A virus, Japanese encephalitis virus, and tomato yellow leaf curl virus (TYLCV) were added as newly identified viruses which are inhibited by lactoferrin [8]. In this review, the authors described that lactoferrin may exert its antiviral effect not only in the early phase of surface interaction between virus and cell, but also intracellularly because the nuclear localization of lactoferrin in different epithelial human cells has been observed.

Recently investigations to study the effects of orally administered lactoferrin against virus infections in animals and humans have been performed. These studies suggested that lactoferrin

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consumption exerts some protective effect against common viral infections. Here, we review the studies regarding common viral infections including the common cold, influenza, viral gastroenteritis, summer cold, and herpes, both in vitro and in vivo effect by oral administration, and discuss the prophylactic potential of lactoferrin as a food component.

2. Common cold and influenza

The common cold and influenza are the most common viral infections and they occur in the respiratory tract. The in vitro effects of lactoferrin against viruses causing common infections are summarized in Table 1. Many viruses cause the common cold. Among common cold viruses, the antiviral activity of lactoferrin is reported against the respiratory syncytial (RS) virus [9–11] and parainfluenza virus [12]. The anti-influenza virus activity of lactoferrin is also reported against the influenza A virus H1N1, H3N2, and H5N1 (avian) [13–16].

Effects of orally administered lactoferrin on common viral infections are summarized in Table 2. A questionnaire survey of adult women revealed that consumption of lactoferrin-containing tablets decreases the incidence of common cold-like symptoms and gastroenteritis symptoms [17]. Another study reported that lactoferrin administration with milk immunoglobulin reduces the incidence of the common cold in humans [18]. On the other hand, lactoferrin did not show a favorable effect in an RS virus infection model of mice [19]. In a mouse influenza virus-infection model, lactoferrin feeding lowered lung inflammatory markers [20]. There is no report regarding the effects of lactoferrin on influenza in humans yet. NK cells recognize and destroy target cells infected by influenza or the parainfluenza virus [21] and the relationship between the frequency of the common cold and the activity of NK cells has been reported [22]. It has been shown that lactoferrin feeding enhances NK cell activity in patients with adenomatous colorectal polyps [23] and the NK cell number in mice [24]. Therefore, increased NK cell activity or number by lactoferrin may mediate at least partly the host protection against the common cold and influenza.

3. Viral gastroenteritis

Gastroenteritis caused by rotavirus and norovirus is a major illness prevalent in winter. Rotavirus causes gastroenteritis only in children. Norovirus is an extremely important emerging human pathogen that causes a majority of gastroenteritis outbreaks worldwide. The in vitro anti-rotavirus effects of lactoferrin have been reported [25,26] (Table 1). The human norovirus remains difficult to study, because there is a lack of cell cultures and animal models. Instead, feline calicivirus and murine norovirus, which can be cultured and share a number of biochemical properties, similar genomic organization and primary RNA sequences with human norovirus, have been used as a virus surrogate to study human norovirus. A study using feline calicivirus showed that bovine lactoferrin inhibits the viral infection of Crandell-Reese feline kidney cells by binding to the cells and lactoferrin B inhibits the infection by binding to the virus [27]. Bovine lactoferrin also decreased murine norovirus infection to murine macrophage cell line Raw264.7 through inhibition of the initial murine norovirus attachment to cells and the subsequent interference with murine norovirus replication [28]. The induction of antiviral cytokine interferon (IFN)- α/β expression by lactoferrin was involved in inhibition of viral replication in the infected cells. This is the first report that shows the inhibition of viral replication in the cells and the involvement of IFN- α/β in the antiviral effect of lactoferrin. It has already been reported that oral administration of lactoferrin

induces IFN- α/β in the small intestine of mice [24,29]. From these findings, IFN- α/β may be a key mediator in the antiviral effects of orally administered lactoferrin and the deduced antiviral mechanism of lactoferrin was illustrated in Fig. 1.

The effects of the oral administration of lactoferrin against viral gastroenteritis, where rotavirus or norovirus was identified as a pathogen, have been reported (Table 2). In a study of rotaviral gastroenteritis in children, daily intake of bovine lactoferrin-containing products ameliorated the severity of the disease, although there was no significant benefit in reducing infection incidence [30]. The addition of recombinant human lactoferrin and lysozyme to a rice-based oral rehydration solution had beneficial effects on children with acute diarrhea in whom rotavirus was identified as a pathogen in 18–19% of stool samples [31]. The daily administration of lactoferrin tablets to children reduced the incidence of noroviral gastroenteritis [32]. Lactoferrin administration exhibited no decrease in diarrhea incidence, but decreased longitudinal prevalence and severity in children, where norovirus was isolated as a pathogen in 35% of diarrheal samples [33]. Recently, we performed a survey on norovirus-like gastroenteritis incidence in subjects consuming 100 mg lactoferrin-containing products including yogurt, yogurt drinks, and milk-type drinks [34]. The results indicated a lower incidence of norovirus-like gastroenteritis in groups who frequently consumed lactoferrin products compared with groups who consumed them at a lower frequency (Fig. 2). Because there is no prophylactic or therapeutic treatment for noroviral gastroenteritis, lactoferrin is a promising candidate to prevent infection and further studies are warranted to establish more reliable evidence.

4. Summer colds

Summer colds, also called summer minor illnesses, are caused by adenoviruses and a family of viruses called enteroviruses. These have a preference for warmer weather. Adenovirus mainly causes upper and lower respiratory tract infections, but also causes diseases of the intestine, eyes, liver, urinary tract and lymphoid tissue. Adenovirus is known to cause pharyngoconjunctival fever, also called pool fever. Runny nose, nasal congestion and postnasal drainage are complaints associated with both summer and winter colds. However, enteroviruses may cause more complicated illnesses, which include fever, sore throat, hacking cough, diarrhea, and skin rash. Enteroviruses, enterovirus 71 and coxsackievirus A16, are known as common causative viral agents for hand, foot, and mouth diseases in humans.

Lactoferrin inhibits the cytopathic effect of adenovirus in HEP-2 cells [35–37], where the effect of bovine lactoferrin is more potent than that of human lactoferrin (Table 1). On the other hand, another investigation reported that human lactoferrin promotes the binding of adenovirus to human corneal epithelial cells and also infection of the cells by adenovirus [38]. In this experimental system, there was no data on bovine lactoferrin. The anti-enteroviral activities of lactoferrin are indicated in poliovirus, enterovirus 71, coxsackievirus A16, echovirus 5, and echovirus 6 [39–44]. Remarkably, bovine lactoferrin induced IFN- α expression of human neuroblastoma cells (SK-N-SH) and inhibited enterovirus 71-induced interleukin (IL)-6 production [41]. The antiviral activity of bovine lactoferrin was not obvious in echovirus 9 [40].

Following enterovirus 71 infection, neonatal pups ingesting transgenic milk expressed recombinant porcine lactoferrin showed significantly higher survival rate and heavier body weight compared to wild-type mice [45] (Table 2). On the other hand, oral supplementation of bovine lactoferrin at a dose of 70 mg/day did not show beneficial effects in the prevention of enterovirus 71 or rotavirus infection in children [46].

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