Proposed Biomolecular Theory of Fasting During Fevers Due to Infection

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Abstract
The folk admonition to "starve a fever" may have a scientific basis. Fevers due to infectious organisms that produce neuraminidase (sialidase) may contribute to the pathophysiology of autoimmune conditions. Neuraminidase unmasks host cellular lectins that interact with food lectins and can induce human leukocyte antigen type II (HLA II) expression. HLA II can then bind food lectins and serve as targets for antibody production. Some of these antibodies can then cross-react and attack healthy tissue, inducing disease. The example of insulin-dependent diabetes mellitus is discussed, helping to explain why infectious organisms and dairy product ingestion appear to be linked to some cases of this disease. Genetic variants and other factors may contribute to disease pathogenesis, so this model does not explain all instances of autoimmune disease. Fasting as a way to avoid the process by not introducing food lectins is briefly reviewed. Neuraminidase inhibitors might be useful in preventing genesis of autoimmunity during infection, although this possibility has not been formally tested.
(*Altern Med Rev* 2001;6(5):482-487)

Introduction

It is a long-held belief in folk and naturopathic medicine that people should fast if they have a fever. A well-known folk admonition is, "starve a fever, feed a cold." Any seriously held notion that this platitude has scientific merit is generally if not universally rejected by mainstream medicine in the 21st century. However, this article suggests a biomolecular rationale explaining how fasting during a fever may, in fact, actually be efficacious, thus validating naturopathic medical beliefs and lending support to adoption of this practice.

Fever is an essentially normal phenomenon.[1] During invasion by pathogenic microbes, a person's leukocytes and macrophages respond by producing large quantities of cytokines. The purpose of these cytokines is to mobilize other leukocytes to respond to and directly attack the invading pathogens. One consequence of the release of the cytokine interleukin-1 (IL-1) is the activation of a fever-generating response in the pre-optic nucleus of the hypothalamus. The hypothalamus subsequently produces prostaglandins, particularly PGE_2, which are the final mediators of temperature increase. If the infection is not handled by the initial immune response, including fever-induced increases in immune activity, the fever can continue to rise to

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the point of harm. Fever can be caused by phenomena that provoke cytokine release other than infection. This paper focuses only on fevers in response to infectious organisms that produce neuraminidase. There may be reasons to fast during other types of fevers, particularly in immunological diseases with accompanying intestinal hyperpermeability, but these will not be considered here.[2]

Sialic Acid and Neuraminidase

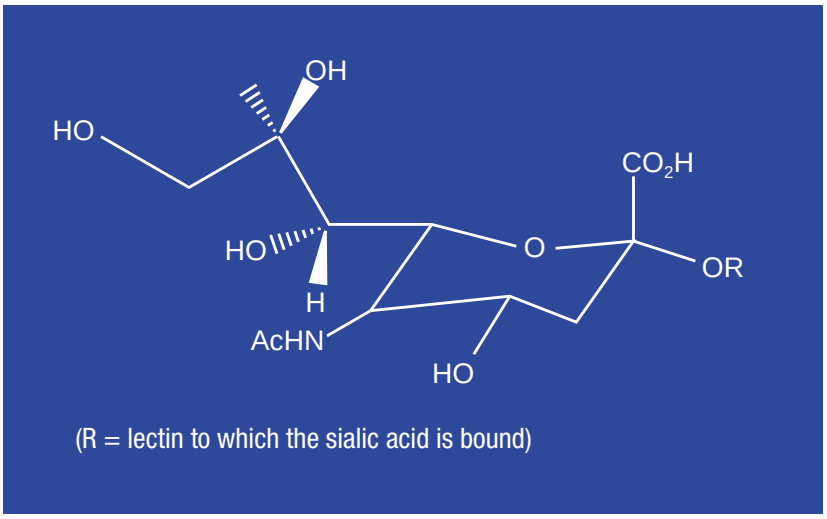
Many human pathogens (Table 1), including influenza viruses, possess neuraminidase enzymes (also known as sialidases).[3] These enzymes remove sialic acid molecules from the cell surface. Normally, sialic acid (Figure 1) acts as a physical barrier against invasion by microbes by decreasing access to cell membrane receptors. Influenza's hemagglutinin molecule actually binds to sialated lectins, as well as sialated glycolipids known as gangliosides. For influenza to migrate into the cell, the virus uses neuraminidase to cleave the sialic acids and release itself from the membrane. Influenza is an enveloped virus and its membrane is derived from the cells of its host. The viral envelope does not have attached sialic acid because this would interfere with the ability of the virus to enter new host cells. Therefore, its neuraminidase removes the sialic acid, in part to ensure the viral envelope will work properly.[4] Neuraminidase is essential for influenza's exit from infected cells.[5]

Removal of sialic acid enables a virus to enter a host cell to replicate as well as to exit the host cell.[6] Inadvertently, the removal of sialic acid also removes a shield that blocks lectins (carbohydrate-binding glycoproteins) on animal cells from T-lymphocyte and possibly other immune cells' surveillance.[7] For example, peanut lectin cannot normally bind to erythrocytes unless the glycocalyx first has its sialic acid residues removed by neuraminidase.[8] In persons genetically primed, these lectins may then bind to lectins found in foods. Thus, dietary lectins, after binding, induce HLA II antigens on cells that do not normally display them.[9] In turn, HLA II antigens bind dietary lectins, creating a potential target for autoantibody formation. This process has been shown in the interaction between N-acetyllactosamine on islet cells and its interaction with tomato, wheat, potato, and peanut lectins.[10] If autoantibodies are formed, they can damage a variety of host cells.

Table 1. Partial List of Microorganisms Producing Neuraminidase

Actinomyces viscosus
Arthrobacter ureafaciens
Aspergillus niger
Bacillus subtilis
Bacteroides fragilis
Clostridium septicum
Clostridium perfringens
Enterobacter aerogenes
Haemophilus parasuis
Influenza virus A and B
Mumps virus
Newcastle virus
Parainfluenza virus
Pasteurella multocida
Proteus vulgaris
Salmonella typhimurium
Streptococcus pneumoniae
Trypanosoma cruzi
Vibrio cholerae

Figure 1. Structure of Sialic Acid as an α-Sialoside



Induction of Autoimmunity

A pathogenic mechanism for autoimmunity (Figure 2), proposed by Freed,[11] may explain the epidemiological association between infectious organisms and particular foods and a variety of autoimmune diseases, particularly type 1 or insulin-dependent diabetes mellitus.[12] When a child is infected with a relatively benign organism like adenovirus, or a more serious one, like influenza, then suffers a bout of fever and diarrhea (although these symptoms are not required or universal), sialic acid molecules are removed and lectins are revealed on beta cells in the pancreas. If that child is eating during the fever and is genetically susceptible, food lectins may induce pancreatic beta cells to display HLA II antigens. In particular, consumption of dairy products seem to be associated with this phenomenon according to some epidemiological evidence,[13] perhaps because of the molecular similarity of cow milk proteins with proteins and lectins on beta cells.[14] Food lectins bind the HLA II antigens and autoantibodies are produced against HLA II antigen-food lectin complexes. Eventually enough beta cells are destroyed by the autoantibodies and the symptoms of type 1 diabetes occur.

If the child were to fast during the original infection, the process might be circumvented, because the de-sialated, exposed cell does not interact with dietary lectins. Food lectins other than those from dairy products may activate diabetogenic HLA II antigens, and it may vary from person to person based on genetic differences.[15] Thus, it is postulated that only total fasting (except for water) during a fever can be expected to reliably prevent induction of type 1 diabetes.

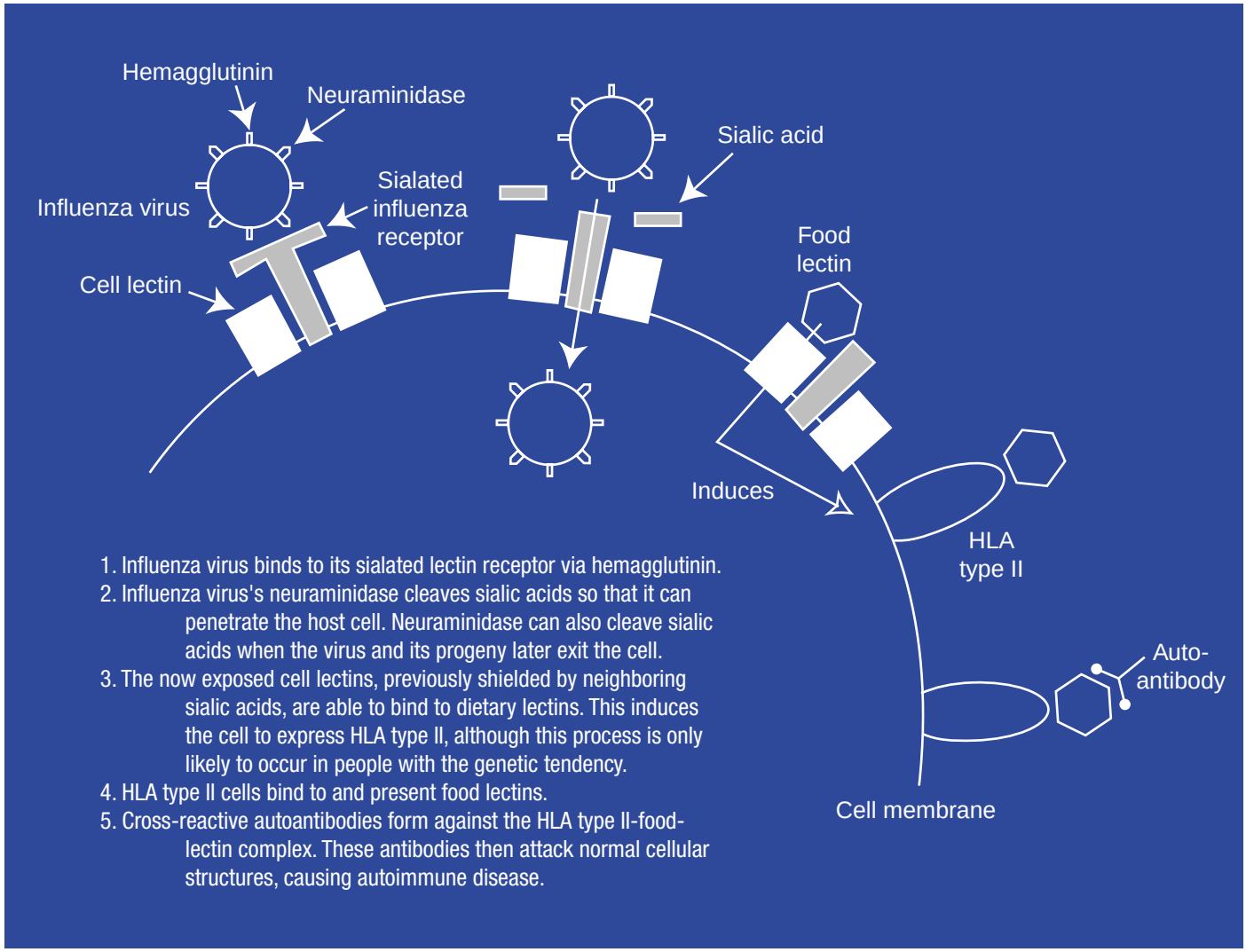
Not all studies looking at infant dairy product consumption and infections support the link to the development of type 1 diabetes.[16] Little work has been done to determine why some studies do show an association and others do not. The theory presented here suggests the two factors may have to be considered together, along with other dietary intakes and genetic susceptibility issues, as well as the role of fasting during fever, to truly understand the complex etiology of type 1 diabetes.

Genetic Factors

The role of genetic uniqueness in this theory is important. Not all infants and children will be affected by autoimmune disease if they eat during an infectious fever. There is mounting evidence that the HLA-DQB1*02 and *0302 alleles are associated with production of antibodies against bovine albumin, glutamate decarboxylase autoantibodies, and insulin autoantibodies.[17,18] It is possible that children with these alleles are most susceptible to the negative effects of eating while feverish or during any state of increased intestinal permeability.

Until these genetic associations are better established and ways to readily assess risk in the clinic are developed, the safest option may be to have all children fast during

Figure 2. Proposed Pathogenesis of Autoimmunity When Food is Consumed During an Influenza Infection



infectious fevers. Long-term water fasting is not reasonable for children, so caregivers may instead choose to restrict intake to hypoallergenic foods and/or human breast milk. This approach may still contain a degree of risk of triggering problems in unique individuals.

Neuraminidase Inhibitors

Another possible option to prevent the autoimmune-inducing effects of dietary lectins during fevers is the use of a class of drugs that block the neuraminidase of influenza such as zanamivir (Relenza®) and oseltamivir (Tamiflu®). These agents might be helpful in preventing autoimmune disease by preventing unmasking of cellular lectins and subsequent food-lectin binding and HLA II expression. This hypothesis has not been tested, however, and these drugs can cause adverse effects, including resistance after repeated use.[6] It is also unclear if these drugs would work against the neuraminidase enzymes of infectious organisms besides influenza. Therefore, fasting may

be a superior option, though these drugs and natural neuraminidase inhibitors warrant investigation as alternatives or adjuncts to fasting.

Safety of Fasting During Fevers

Fasting during a fever due to infectious disease raises concerns among patients, parents, caregivers, and health care professionals. A thorough review of therapeutic fasting and its clinical aspects has been published, although fasting in children has received far less discussion.[19] Therapeutic fasting means intake of nothing but water. Maintaining a high intake of water is essential, but consuming anything else may lead to the potential for induction of disease as described above. Micronutrient deficiencies rarely develop during short fasts in well-nourished people.[20] If diarrhea is a problem, electrolytes should be provided, either as isolated supplements or in the form of broths. Based on the theory presented here, these broths should be made from vegetables (preferably greens like spinach, collard, dandelion, and kale), should not contain any grain, potatoes, tomatoes, or nuts, and should be thoroughly cooked. These steps will greatly reduce the likelihood of the broths delivering problematic lectins, although this may not be entirely avoided if broths are used. In patients with a family history of type 1 diabetes or other autoimmune diseases, broths should probably be avoided and isolated electrolyte supplements used instead.

If an infant is being breast fed, this should be continued throughout the course of the infection and the mother should eat a hypoallergenic diet. If an infant is being partially breast fed, all other food (except water) should probably be avoided while the fever resolves. If an infant is being exclusively formula-fed, formulae based on soy or cow milk should be strictly avoided until the fever and infection have completely resolved. Infants are at greater risk of problems because their gut permeability is increased to allow absorption of protective proteins from breast milk. Avoiding ingestion of non-human milk proteins is of critical importance in children less than six months of age.

Resting as much as possible is recommended during the fast. Some people will develop symptoms of hypoglycemia during fasting, such as fatigue, hunger, or irritability, which exercise may exacerbate. Hypoglycemic symptoms usually pass fairly quickly. Adding small amounts of food, including vegetable juices, generally only exacerbates and prolongs hypoglycemic symptoms.[19]

The fast will usually be maintained only as long as the fever persists and usually no more than three days. In children, three days may be too long to maintain a water fast. Fasts longer than five days are not recommended in adults except under conditions where in-patient observation is possible.[19] Longer modified fasts may sometimes be therapeutic because the passing of a fever does not necessarily mean the infection and any related gut permeability increases have resolved. It is recommended that a fast be broken using green leafy vegetables and fish as opposed to sources of lectins more strongly linked to disease like grains, dairy products, or meat.

An alternate approach for situations in which caregivers are concerned about fasting is to water fast for the first day of the fever, then introduce foods with very little chance of inducing problems. Although no food can be guaranteed safe, the least problematic include foods the child has never eaten before, foods unusual in the diet of the family and racial/cultural/ethnic group the child belongs to (e.g., teff in people of European descent, quinoa in people of African or Asian descent), and foods so far not reported to be linked to any autoimmune or other condition.

Conclusion

Eating during an episode of fever due to infection by a neuraminidase-producing organism could potentially lead to autoimmune

and other chronic diseases. The oft-quoted platitude, "starve a fever," is supported by the theory presented in this paper, although much more work is needed to determine to what extent the theory is correct. Fasting during a fever due to infectious disease or a fever of unknown origin should be standard practice in this author's opinion until more information becomes available definitively refuting the theory presented here.

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