Medical Hypotheses (2008) **70,** 826–830

ELSEVIER

medical hypotheses

http://intl.elsevierhealth.com/journals/mehy

Hypothesized role of galactocerebroside and NKT cells in the etiology of multiple sclerosis

Megan M. Blewett *

Harvard College, 1129 Harvard Yard Mail Center, Cambridge, United States

Received 31 July 2007; accepted 31 July 2007

Summary According to the molecular mimicry theory, multiple sclerosis (MS) develops when the immune system mistakenly attacks a component of the myelin sheath that is structurally similar to a foreign epitope. The glycolipid galactocerebroside (GalC) is a major component of myelin. As lipids comprise between 70% and 85% of myelin, glycolipids should be investigated as candidate autoantigens in MS. GalC displays broad structural similarities to the *Borrelia burgdorferi* glycolipid antigen BbGL-2 and to the *Sphingomonas* antigen GalAGSL. In principle, therefore, these bacteria may induce an autoimmune attack on the myelin sheath. GalC is also structurally similar to natural killer T (NKT) cell ligand α-galactosylceramide (α-GalCer). Further studies must be performed to clarify the role of GalC in the activation of NKT cells and the development of MS.
© 2007 Elsevier Ltd. All rights reserved.

Introduction

The glycolipid galactocerebroside (GalC) is a major component of central nervous system myelin [1] and appears to regulate myelin formation [2–5], Here, I argue that GalC should be investigated as a candidate autoantigen in multiple sclerosis (MS). In addition, further studies should determine whether and to what extent GalC activates natural killer T (NKT) cells.

Background: molecular mimicry theory

A large body of evidence shows that the etiology of MS is linked to the environment [6,7]. However, no causative environmental agent has been definitively and consistently identified, despite many attempts [8,9]. Other reports suggest that MS is an autoimmune disease [10–12], in which the immune system attacks an autoantigen of the myelin sheath. Recently, the molecular mimicry theory has provided a compromise between these two bodies of evidence. According to the molecular mimicry theory, MS results when the immune system mistakenly attacks a component of the myelin sheath that is similar to an antigen of a pathogenic agent [13].

With the advent of the molecular mimicry etiological hypothesis, researchers have been searching for homologies between foreign antigens and self-components of the myelin sheath. Though the myelin sheath is <30% protein [1], it is myelin proteins which have been most heavily investigated as candidate autoantigens. The most widely

* Tel.: +1 973 377 6117.
E-mail address: mblewett@fas.harvard.edu

0306-9877/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.mehy.2007.07.037

studied protein candidate autoantigens include myelin basic protein (MBP), myelin oligodendrocyte protein (MOG), and proteolipid protein (PLP) [14–17]. However, several factors complicate these proteins' autoantigen statuses: antibodies against myelin proteins are also found in healthy controls and do not appear to be specific to MS patients [18], neither anti-MBP nor anti-MOG antibody levels are associated with the progression of MS [19], and MBP autoantibodies in MS are characterized by low-affinity interactions [20]. Despite the number of reports, researchers have been unable to definitively label MBP or PLP as autoantigens in MS [18].

Meanwhile, a growing body of evidence has revealed that self glycolipids can be the targets of autoreactive T cells [21–23]. Several reports have linked self-glycolipid autoantigens specifically to MS [24,25]. Furthermore, such anti-self-glycosphingolipid autoreactivity can be induced by bacterial infection [26,27].

Several bacteria have been implicated in the etiology of MS, including *Chlamydia pneumoniae* [28–30], *Mycoplasma pneumoniae* [31], and *Borrelia burgdorferi* [9,32–35].

In extreme cases, the symptoms of *B. burgdorferi* infection are similar to the symptoms of MS, potentially leading to demyelination [36,37], partial paralysis [38], fatigue and arthritis [39]. *B. burgdorferi* infection can eventually develop into an autoimmune disease [40,41], the geographic distribution of MS parallels the distribution of tick-borne diseases [42], and both MS and *B. burgdorferi* infection have been associated with autoimmune thyroid conditions [43,44]. Ticks are the common carriers of *B. burgdorferi*. In addition, penicillin use has been associated with lower risk of acquiring MS, while no link was found between antibiotics against C. pneumoniae and development of MS [45]. Finally, *B. burgdorferi* cysts have been identified in the cerebrospinal fluid of relapse-remitting MS patients [34]. However, other studies have found mixed results [46,47] The molecular mimicry theory would explain the difficulty in replicating *B. burgdorferi* findings. Thus, *B. burgdorferi* may be involved in the etiology of MS.

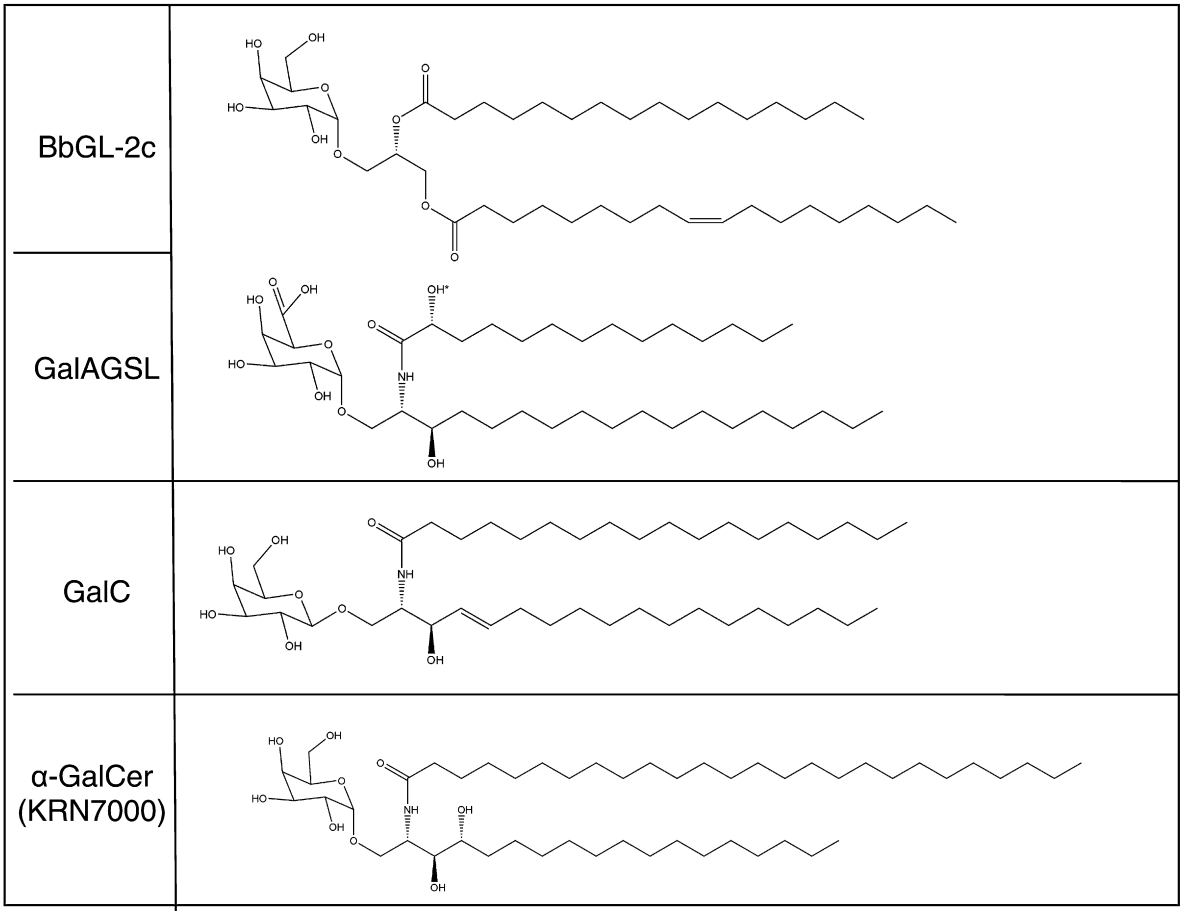

Figure 1 The *Borrelia burgdorferi* antigen BbGL-2 and *Sphingomonas* antigen GalAGSL show broad structural similarities to the glycolipid GalC, a major component of myelin. α-GalCer is a powerful NKT cell activator. *Indicates that GalAGSL does not always contain the marked hydroxyl group.

Download English Version:

https://daneshyari.com/en/article/2491278

Download Persian Version:

https://daneshyari.com/article/2491278

Daneshyari.com