Visions & Reflections

The clinical potential of sphingolipid-based therapeutics

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Received 11 November 2005; received after revision 19 January 2006; accepted 30 January 2006
Online First 29 March 2006

Abstract. The era of sphingolipid-based therapeutics is upon us. A large body of work has been accumulating that demonstrates the distinct biological roles of sphingolipids in maintaining a homeostatic environment and in responding to environmental stimuli to regulate cellular processes. It is thus necessary to further investigate alterations in sphingolipid-metabolism in pathological conditions and, in turn, try to exploit altered sphingolipid-metabolizing enzymes and their metabolites as therapeutic targets. This review will examine how advances in the fields of drug delivery, drug discovery, synthetic chemistry, enzyme replacement therapy, immunobiology, infectious disease and nanotechnology have delivered the potential and promise of utilizing and/or targeting sphingolipid metabolites as therapies for diverse diseases.

Keywords. Sphingolipids, ceramide, therapeutics, inflammation, infectivity, immunity.

Introduction

Sphingolipids have routinely been implicated as mediators of cellular apoptosis, growth and differentiation [1, 2]. A compelling case can now be made for the emerging role of sphingolipids to regulate inflammation, immune response and infectivity. These additional roles for sphingolipids may be a function of both the biochemical and biophysical properties of these lipids. As an example, the pro-apoptotic sphingolipid ceramide exerts its effects via biochemical (second messenger and target proteins) [3, 4] as well as through biophysical (lipid microdomains, negative membrane curvature) properties [5–7]. Critical components linking these biochemical and biophysical mechanisms include the flux between sequential sphingolipid metabolites as well as the subcellular localization and compartmentalization of these sphingolipid metabolites [8].
ceramide kinase, glycoceramide synthases, or sphingomyelin synthase and enhanced via ceramide synthase or sphingomyelinases. In a similar scenario, activation of Sph1P lyase or Sph1P phosphatase could reduce endogenous Sph1P content and therefore increase the ratio of ceramide to prosurvival sphingolipids. Pharmacological or molecular manipulations of any of these enzymes have the potential to reset the critical balance between sphingolipid metabolites. Thus, understanding altered sphingolipid flux may identify new therapeutic targets for various diseases. With the National Institute of Health (NIGMS) funding of the Lipid MAPS Consortium to effectively utilize lipidomics to measure imbalances in lipid metabolism, this goal is now becoming a reality (http://www.lipidmaps.org).

Emerging roles of ceramide and ceramide metabolites in diseases

For over a decade now, enzyme replacement therapy (ERT) had been in use for lysosomal storage diseases, caused by accumulation of ceramide metabolites [10, 11]. Cerezyme and its predecessor, Ceredase (recombinant glucosylceramidase), has been the standard of care for Gaucher’s disease. More recently, recombinant forms of agalsidase, Replagal and/or Fabrazyme have been approved for patients with Fabry’s disease. Additionally, ERT for Niemann-Pick B disease (defective acid sphingomyelinase) shows promise as a future therapeutic [12]. Unfortunately, these drugs are only efficacious for visceral forms of these diseases, and are less effective against the neuropathic forms due to their inability to cross the blood-brain barrier. As an alternative strategy, substrate reduction therapy (SRT) with N-butyldeoxynojirimycin (NB-DNJ; Zavesca), an inhibitor of glucosylceramide synthase, can also be effective in patients with Gaucher’s disease by restoring the balance between glucosylceramide synthase and glucosylceramidase. While this drug crosses the blood-brain barrier, there are still many side effects. These ERT and SRT adverse effects may be a reflection of less than optimal pharmacokinetic parameters, lack of drug specificity (SRT) and/or the lack of targeted drug delivery.

SRT is not just effective for diseases of accumulation of higher-order glycosphingolipids. Several recent studies demonstrate that the inhibition of de novo ceramide production itself is therapeutic for multiple diseases. First, inhibition of serine palmitoyltransferase, the first committed step of de novo synthesis, via the use of myriocin, was highly efficacious in an apolipoprotein E (apoE)-deficient mouse model of atherosclerosis. Inhibition of ceramide synthesis with myriocin decreased atherosclerotic plaque formation [13]. Inhibition of ceramide de novo synthesis is also therapeutic in an animal model of emphysema. Ceramide levels are increased in this emphysema model, which is created by treating with a vascular endothelial growth factor receptor inhibitor. Upon inhibition of the de novo pathway with either myriocin or fumonisin B1 (ceramide synthase inhibitor), emphysema was inhibited [14]. Inhibiting the de novo pathway may also be a strategy for treating oral mucositis, which is a potential side effect of ionizing radiation used as treatment for head and neck cancer. Irradiated mice treated with fumonisin B1 exhibited a less severe course of oral mucositis [15]. On the other hand, promising phase I oncological clinical trial results have been reported with agents that increase de novo synthesis of ceramide (farnesitide) combined with agents that inhibit ceramide metabolism (B13, safingol) [16–18].

Reduction of sphingolipid de novo flux may not be the only pharmacological methodologies to impact the actions of ceramide and ceramide metabolites. In fact, exogenous applications of pro-mitogenic sphingolipid mimetics have shown unusual applications in immunology. FTY720, a substrate for SphK, has shown tremendous promise as an immunosuppressant as evidenced by a recent phase 2A trial in renal transplant patients, in combination with cyclosporine A [19]. In addition, this therapeutic approach was also therapeutic in a model of emphysema [14] and limited the development of experimental autoimmune encephalomyelitis, a model of human multiple sclerosis [20–22]. Further utility for this Sph1P mimetic may also be in diabetes where FTY720 has been demonstrated to be effective in preventing both diabetes and islet allograft rejection in rodents and non-human primate models [23–25]. KR70000 (α-galactosylceramide) has also been shown to be a potent in vivo modulator of host-graft interactions [26] and in a model of pulmonary fibrosis [27]. This expands the potential utility of KR70000 from its originally described antitu-