New Enzyme Inhibitors

Adamantanyl GlcCer
Avanti Number 860459

Adamantanyl GalCer
Avanti Number 860479

Mammalian glycosphingolipid (GSL) precursor mono-hexosylceramides are either glucosyl- or galactosylceramide (GlcCer or GalCer). Most GSLs derive from GlcCer. Substitution of the GSL fatty acid with adamantane generates amphipathic mimics of increased water solubility, retaining receptor function. We have synthesized adamantyl GlcCer (adaGlcCer) and adamantyl GalCer (adaGalCer). AdaGlcCer and adaGalCer partition into cells to alter GSL metabolism. At low dose, adaGlcCer increased cellular GSLs by inhibition of glucocerebrosidase (GCC). Recombinant GCC was inhibited at pH 7 but not pH 5. In contrast, adaGalCer stimulated GCC at pH 5 but not pH 7 and, like adaGlcCer, corrected N370S mutant GCC traffic from the endoplasmic reticulum to lysosomes. AdaGalCer reduced GlcCer levels in normal and lysosomal storage disease (LSD) cells. At 40 μM adaGlcCer, lactosylceramide (LacCer) synthase inhibition depleted LacCer (and more complex GSLs), such that only GlcCer remained. In Vero cell microsomes, 40 μM adaGlcCer was converted to adaLacCer, and LacCer synthesis was inhibited. AdaGlcCer is the first cell LacCer synthase inhibitor. At 40 μM adaGalCer, cell synthesis of only Gb(3) and Gb(4) was significantly reduced, and a novel product, adamantyl digalactosylceramide (adaGb(2)), was generated, indicating substrate competition for Gb(3) synthase. AdaGalCer also inhibited cell sulfatide synthesis. Microsomal Gb(3) synthesis was inhibited by adaGalCer. Metabolic labeling of Gb(3) in Fabry LSD cells was selectively reduced by adaGalCer, and adaGb(2) was produced. AdaGb(2) in cells was 10-fold more effectively shed into the medium than the more polar Gb(3), providing an easily eliminated “safety valve” alternative to Gb(3) accumulation. Adamantyl monohexosyl ceramides thus provide new tools to selectively manipulate normal cellular GSL metabolism and reduce GSL accumulation in cells from LSD patients.