Papers of the Week

Not All Gains Are Healthy

See referenced article, J. Biol. Chem. 2010, 285, 11178–11187

Hereditary Sensory Neuropathy Type 1 Is Caused by the Accumulation of Two Neurotoxic Sphingolipids

Hereditary sensory and autonomic neuropathy type 1 (HSAN1) is an inherited disorder characterized by a loss of pain and temperature sensation in the feet and hands, often accompanied by atrophy and weakness of distal limb muscles. HSAN1 is brought on by a variety of missense mutations in the SPTLC1 subunit of serine palmitoyltransferase (SPT), the enzyme that catalyzes the first step of de novo sphingolipid synthesis. However, despite these mutants being identified several years ago, the etiology of HSAN1 remains unclear. Now, in this Paper of the Week, Anke Penno and colleagues show that the HSAN1 mutations alter the substrate specificity of SPT, leading to the formation of two atypical deoxysphingoid bases (DSBs) that lack the C1 hydroxyl group of sphinganine. These metabolites can neither be converted to complex sphingolipids nor degraded, and thus they accumulate in cells; Penno and colleagues confirmed the presence of elevated DSB levels in the plasma of HSAN1 patients with different SPTLC1 mutations. They also demonstrated that the DSBs induced pronounced toxic effects on neurite formation and neurofilament structure in cultured cells, indicating that HSAN1 disease pathology likely occurs through a toxic gain of function as opposed to a loss of function.

DOI 10.1074/jbc.P109.092973

Effects of sphinganine (SA), deoxysphinganine (m18:0), and deoxymethylsphinganine (m17:0) on cultured dorsal root ganglia neurons. The addition of SA had no effect on neurite number and length compared to controls, but the presence of m18:0 and, to a lesser extent, m17:0 resulted in a greatly reduced neurite number.