Abstract: Recent data estimate that roughly 2.1 billion individuals are overweight or obese. Central obesity, which is accompanied by a low-grade metabolic inflammation in visceral adipose tissue, is also recognized as both a component and a driver of the metabolic syndrome (MetS). MetS is defined by the presence of multiple comorbidities, including dyslipidemia, insulin resistance, hyperinsulinemia, hyperglycemia, and hypertension. Though the central (CNS) and peripheral (PNS) nervous systems are quite distinct in form and function, both are susceptible to obesity-driven dysfunction and injury associated with the MetS, suggesting that common mechanisms contributing to disease progression are secondary to visceral adiposity. Meta-analyses show a strong association between obesity and dementia and Alzheimer’s disease (AD). Studies indicate that obesity doubles the risk of AD when compared to individuals of normal weight and also confers increased risk of mild cognitive impairment. Obesity and the MetS are also drivers of PNS injury, specifically peripheral neuropathy. Preclinical experimental studies reveal that hypothalamic injury occurs early in obesity secondary to unresolved inflammation, and contributes to a lack of satiety. Excess caloric intake in combination with changes in free fatty acids, triglycerides, and insulin resistance, lead to a feed-forward cycle of injury that eventually affects brain regions, most importantly the hippocampus, and in the PNS, both the axons and Schwann cells. Our research focuses on the mechanisms underlying obesity-mediated CNS and PNS injury; we have discovered that obesity-mediated increases in free fatty acids and long chain fatty acids (LCFAs) alter normal lipid metabolism in the CNS and PNS. Products of LCFA metabolism, LC-acylcarnitines, accumulate in both man and experimental animal models and cause nervous system injury, both by disrupting mitochondrial function as well as being directly toxic to the CNS and PNS. Changes in mitochondrial β-oxidation secondary to obesity also promotes loss of normal energy production in both neurons and supporting glia. These changes in mitochondrial biology secondary to excess caloric intake are compounded by our discovery that neurons and glia, both in the PNS and CNS, like fat and muscle cells, develop insulin resistance, and lose the ability to respond to essential neurotrophic factors. Gene expression patterns of both hippocampal neurons and peripheral nerves from obese animal models reveal dysfunction in pathways associated with lipid metabolism, inflammation and neurotrophism. As the obesity epidemic continues, the burden of associated neurological disorders is also increasing at an alarming pace. Continued research is needed to understand how to break the vicious cycle of obesity and associated disorders of the PNS and CNS.