Diabetes, obesity, and the metabolic syndrome can have serious consequences on organ systems containing smooth muscle tissue. For example, atherosclerosis and bladder dysfunction can both result from the high lipid levels that occur with obesity and diabetes and can cause cell dysfunction and death, termed lipotoxicity, in various cell types. However, lipotoxicity has not been shown in smooth muscle. The goal of this dissertation was to determine if lipotoxicity does occur in vascular smooth muscle and to determine how to modulate this lipotoxicity. We found that vascular smooth muscle takes up fatty acid and does not store it adequately, thus rendering it free to cause lipotoxicity in the cell. This lipotoxicity did not seem to be due to an increase in reactive oxygen species (ROS) production the unsaturated fatty acid oleate protected against palmitate-induced apoptosis. Bladder smooth muscle may also be susceptible to lipotoxicity. We found that there were significant differences in the levels of certain peroxisome proliferator-activated receptors (PPARs) between Yucatan and Ossabaw male swine and between male and female Ossabaw swine, suggesting genetic and gender differences in PPARs. These results may explain the differences in prevalence of bladder dysfunctions between males and females and within the sexes. To modulate lipotoxicity in smooth muscle, we overexpressed caveolin-1 (Cav-1), a protein found in caveolae. Cav-1 increased CD36 expression and redistribution inside the cell and increased apoptosis. These studies may have implications for atherosclerosis and bladder dysfunctions that result from obesity, diabetes, and the metabolic syndrome.