The health of our muscles is maintained by physical activity. Under conditions of prolonged inactivity, such as during immobilization or loss of neural input, muscle health deteriorates. Muscle cells shrink (i.e. atrophy) and lose both strength and energy. The reduced energy is a result of mitochondrial dysfunction, evident by lower ATP production. Poorly functioning mitochondria need to be removed from the cell because they also produce damaging reactive oxygen species that can enhance muscle atrophy. This disposal of mitochondria is achieved via the pathway termed mitophagy, in which damaged mitochondria are packaged and delivered to lysosomes, the organelles responsible for the degradation of cellular debris. In this study we modelled muscle inactivity by the surgical removal of the nerve innervating the hindlimb muscles of both male and female mice, and we assessed the degree of atrophy, the amount of mitophagy and the quantity of lysosomes in muscle. Our main results showed that female mice are more able to mobilize damaged mitochondria to the lysosome for degradation, in part because of a greater content of lysosomes compared to males. In addition, females were better able to maintain muscle mass during the loss of innervation. Some of these benefits were reliant on the presence of a regulatory protein termed TFE3, indicating that it is partly responsible for maintaining the different responses between males and females in response to chronic muscle inactivity.