Summary

Skeletal muscles are an essential part of human everyday life. They account for approximately 40-50% of body mass, allowing humans to eat, talk, move, breathe etc. Skeletal muscle is able to modify its structural and metabolic properties as different stimuli cause metabolic or contractile adaptations. The phenotypic shift can cause a change in myosin heavy chain (MHC) isoform distribution, enzyme content and the number of mitochondria. The creatine kinase system (CKs) is an energy transfer system, which is composed of two main elements, creatine (Cr) and creatine kinase (CK). Cr is synthesized by two enzymes: L-Arginine: Glycine amidinotransferase (AGAT) and Guanidinoacetate N-methyltransferase (GAMT). For the purpose of learning how Cr and CK deficiency could affect mammals, AGAT and GAMT knock-out (KO) mouse models have been generated. Cr depletion in AGAT KO mice muscles results in reduced grip strength, loss of bodyweight, phenotypic shift, changes in metabolism and muscle atrophy, which seem to be muscle-specific. An AMP-activated kinase (AMPK) is a cellular energy sensor, which could possibly be involved with the phenotypic shift of muscle fiber in AGAT KO mice, by activating different signaling pathways.

This thesis aimed to describe how creatine deficiency affects different types of muscle and their MHC isoforms in a muscle-dependent manner. Also, whether AMPK activation would be upregulated in AGAT and GAMT KO mice in a muscle-specific manner. To this end, muscle cross-section area (CSA), the number of fibers, fiber size, MHC isoforms expressions and AMPK activation was assessed.

Our results showed muscle atrophy resulted from lowering of the fiber size in AGAT KO mice, which seemed to be muscle-dependent and affects glycolytic muscles. We also showed a muscle-specific phenotypic change in AGAT KO mice, which was also observed in glycolytic muscles towards a more oxidative phenotype. We suggested that AMPK could be responsible for the phenotypic change in AGAT KO mice muscle. Our results showed increased AMPK activation in AGAT KO mice glycolytic muscles, which could support our suggestions. However, further research must be conducted to unravel the role of AMPK in the phenotypic shift. We also showed that similar changes did not occur in GAMT KO, which could be explained by GAMT KO mice ability to phosphorylate GAA and use it instead of PCr, therefore avoiding a severe energy crisis. This thesis showed how the loss of Cr affects mice's skeletal muscles and leads to atrophy and shift in MHC isoforms in a muscle-dependent manner. Further studies should be conducted in order to confirm our suggestion about AMPK role in AGAT KO mice glycolytic muscle phenotypic change, and understand what role AMPK has in oxidative muscles.