Regulation of creatine kinase in rat skeletal muscle during development

Kloosterboer, Helenius Jan

Summary.

Some of the factors which regulate creatine kinase in rat skeletal muscle during postnatal development are described in this thesis.

In chapter I a short introduction is given on the aim of the study. Many studies have yielded evidence that the development of enzymes in the liver is under multiple hormonal control. Such studies have never been made for the development of enzymes in muscle. It seemed therefore worthwhile to investigate whether or not the principles which are operative for the development of enzymes in liver can be applied to the development of enzymes in muscle.

A short review of the literature on creatine kinase is given in chapter II. The recent opinions about myogenesis in vitro are discussed. Furthermore attention is paid to the factors which may influence muscle development in vivo.

In chapter III the development of various biological parameters is reported. The creatine kinase activity increases 15-fold and this increase occurs in a stepwise manner during development. Three isoenzymes of creatine kinase occur in the sarcoplasm: MM, MB and BB. The increase of creatine kinase activity is mainly due to an activation of the M-gene. The first two increases of creatine kinase run parallel to transient increases in the DNA content. The requirement of cell division for the synthesis of creatine kinase is discussed.

In chapter IV experiments are described which provide strong evidence that hormones play indeed an important part in muscle development. Both thyroxine and glucocorticoids can be considered as natural stimuli for the synthesis of creatine kinase. Testosterone is necessary for body growth. The effects of these hormones on creatine kinase synthesis and/or body growth are age-dependent. The maximum increase of creatine kinase activity (25%) occurs between 5 and 7 days after birth. Thyroxine administration has virtually no effect during this period. When a pretreatment with thyroxine was given cortisone acetate increased creatine kinase activity to about 155%. These effects are also discussed in chapter IV.

In chapter V the results of experiments with hormones whose action is mediated via c-AMP are described. Db-c-AMP shows some small effects on the creatine kinase activity and the isoenzyme ratio after the transient increases of the DNA content. However, neither insulin nor adrenalin show any effect

on creatine kinase development during the same period. Innervation is very important for normal muscle growth and creatine kinase development. Muscle weight decreased less if db-c-GMP was administered after denervation. Together with the increases of the BB isoenzyme after db-c-GMP or succinylcholine administration in the denervated muscle suggests an effect of these agents on the proliferation of satellite cells. Growth hormone stimulates creatine kinase synthesis immediately after birth until about the increase in the plasma thyroxine level.

The existence of binding proteins for glucocorticoids and testosterone in the sarcoplasm of the muscle suggests that the muscle is a target tissue for these hormones. The significance of these measurements as well as the developmental changes of these binding proteins are discussed in chapter VI.

Chapter VII reports that thyroxine as well as glucocorticoid administration results in an increase of the content of mitochondria in muscle. Both these hormones also have an effect on myofibrillogenesis.

A general discussion of the experimental results is presented in chapter VIII. It is shown that thyroxine has an important function in creatine kinase and muscle development. A model, based on Holtzers hypothesis on myogenesis *in vitro* is presented which may explain the observed isoenzyme ratios during development and after the various hormonal and surgical treatments.