Molecular Mechanisms Responsible for the Change of ClC-1 Chloride Channel Conductance in Skeletal Muscle from Rats Chronically Treated with Statin and Fibrate

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In skeletal muscle ClC-1 chloride channel is responsible for a large resting chloride conductance (gCl) and plays an important role in membrane repolarisation following muscle contraction. Indeed, a reduction of gCl can be observed during myotonia, a disease characterised by muscle hyperexcitability or during pathological states due to the administration of certain drugs. A calcium-dependent Protein Kinase C (PKC) is responsible for the regulation of ClC-1 as well as of resting gCl, since the activation of this protein closes the channel and decreases gCl (\textsuperscript{1}). An abnormal reduction of membrane gCl together with increased excitability has been found in rats chronically treated with lipophilic statins, such as simvastatin, fluvastatin and atorvastatin as well as with fenofibrate (\textsuperscript{2}). At the aim to elucidate the mechanism that mediates the statin or fibrate-induced skeletal muscle damage we investigate on the causes responsible for the reduction of gCl by using several experimental approaches such as 2-intracellular microelectrodes technique, patch clamp, RT-PCR. The \textit{in vitro} application of the PKC inhibitor, chelerythrine, on muscle dissected from rats treated with fluvastatin at 5 mg/kg/day and 20 mg/kg/day, partially restored gCl toward the control value (11\% and 14\% increase, respectively), suggesting the involvement of this enzyme in statin action. Chelerythrine almost completely restored the reduction of gCl induced by 10 mg/kg/day atorvastatin chronic treatment. In contrast the reduction of gCl found in 60 mg/kg/day fenofibrate treated rats was not antagonised by chelerythrine. Accordingly to these results, preliminary data showed that the reduction of gCl paralleled a not significant decrease in ClC-1 mRNA expression in both fluvastatin and fenofibrate treated rats. Fenofibric acid but not fluvastatin, applied \textit{in vitro}, reduced chloride current recorded from human ClC-1 channel heterologously expressed in Xenopus oocytes. We demonstrate that statins are able to modulate PKC mediated regulatory pathway finally affecting gCl, while fenofibrate is responsible for a direct inhibition of the ClC-1 channel. On the basis of these conclusions pharmacological interventions may be planned to prevent skeletal muscle side effects that may arise during hypolipidemic drug therapy (Supported by FIRB-RBAU015E9T).