EVALUATION OF THE EFFECTS OF A COMBINED CHRONIC TREATMENT WITH ATORVASTATIN AND FENOFIBRATE ON RAT SKELETAL MUSCLE: AN *EX VIVO* ELECTROPHYSIOLOGICAL AND CYTOFLUORIMETRIC STUDY

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Statins and fibrates, widely used to treat lipid disorders, can cause myopathy as a rare event, but combined therapy with these drugs can enhance this risk. We previously showed that lipophilic statins (atorvastatin, fluvastatin) and fenofibrate at doses higher than therapeutics affect skeletal muscle function by reducing resting chloride conductance (gCl) and by altering the mechanical threshold for contraction (MT), a calcium-sensitive parameter (1). Here we have evaluated the effects of a two-month chronic treatments with atorvastatin (5 mg kg^{-1} day^{-1}), fenofibrate (30 mg kg^{-1} day^{-1}) or with the association of these two drugs at the doses used in monotherapy. At the end of treatments we measured gCl and MT in extensor digitorum longus (EDL) muscle by means of two intracellular microelectrodes technique and we determined the cytosolic calcium level ($[Ca^{2+}]_i$) in intact EDL muscle fibres by using FURA-2 cytofluorimetric technique. The manganese quenching technique was used to estimate the sarcolemmal permeability to divalent cation. Atorvastatin treated rats showed a 9% reduction of gCl with respect to controls, while fenofibrate reduced resting gCl by 17%. A marked decrease of gCl was observed in rats treated with the combined therapy, which showed a 25% reduction of this parameter. Atorvastatin and the combined therapy caused a shift of the MT toward more negative potentials with respect to controls, while fenofibrate alone did not modify this parameter, suggesting that only atorvastatin can impair the calcium handling structures. In parallel, we observed that atorvastatin, but not fenofibrate, was able to increase by 20% the $[Ca^{2+}]_i$ with respect to the control. Interestingly, the combined treatment caused the same $[Ca^{2+}]_i$ increase observed with atorvastatin, confirming that only the statin, not the fibrate, can alter the calcium homeostasis of the muscle. No modification of cation sarcolemmal permeability was found in all treated animals, suggesting that atorvastatin-induced $[Ca^{2+}]_i$ increase was dependent on an internal calcium store depletion. We hypothesize that the increase of $[Ca^{2+}]_i$ due to atorvastatin and combined treatment may contribute to the modification of gCl, since this parameter can be modulated by calcium-dependent protein kinase C. In contrast, fenofibrate may alter gCl in a calcium-independent manner.

(1) Pierno S., Didonna M.P., Cippone V., De Luca A., Pisoni M., Frigeri A., Nicchia G.P., Svelto M., Chiesa G., Sirtori C., Scanziani E., Rizzo C., De Vito D. and Conte Camerino D. (2006) Br J Pharmacol. 149(7):909-19.