FLUVASTATIN MAY INDUCE A CHRONIC REDUCTION OF THE STORE OPERATED CALCIUM ENTRY IN STRIATED FIBRES: AN OTHER BRICK IN THE WALL OF THE HYPOLIPEDEMIC DRUGS' MYOTOXICITY ?

Rolland Jean-francois, Liantonio Antonella, Conte Camerino Diana.

Department Pharmaco-Biology, Faculty of Pharmacy, University of Bari

Muscle toxicity is one of the first major adverse drug reactions associated with statin therapy. We previously identified the muscle chloride conductance and the calcium homeostasis as early targets of the HMGCoA-reductase inhibitors that may contribute to milder symptoms of myotoxicity whereas the increase of myoglobinemia may be a later phenomenon (1). In particular, we showed evidence that a 2-months *in vivo* chronic treatment of rats with fluvastatin (FS) caused a significant increase in resting cytosolic Ca^{2+} level in fast-twitch EDL muscle fibres, while the K^+ depolarization and the caffeine responsiveness were reduced (2).
We describe here for the first time the electrophysiological evidence of the presence of a voltage-insensitive permeable Ca^{2+} current in rat skeletal muscle cells. Patch-clamp experiments using the cell-attached configuration show that this current is dose dependently inhibited *in vitro* by FS. On another hand, experiments using the manganese quenching method, show that an *in vitro* application of FS counteract the reduction of fluorescence resulting form the ingress of Mn^{3+} in resting conditions. This reduction is more drastic when the intracellular pools of Ca^{2+} were emptied (caffeine and thapsigargine pre-treatment) so that the phenomenon of the Store Operated Ca^{2+} Entry (SOCE) is activated.
From a recent work (3), it emerges that the SOCE is essential for the maintenance of Ca^{2+} homeostasis in skeletal muscle. Because calcium transients elicited by K^+ depolarization and caffeine are drastically reduced in muscle from FS treated rats and *in vitro* application of FS reduce both the activity of the voltage-insensitive Ca^{2+} permeable current and the SOCE phenomenon; it is plausible to postulate that these latter are strictly correlated, since a reduction in SOCE would lead to a chronic depletion of intracellular Ca^{2+} stores. Thus, we can hypothesize that the reduction of the voltage-insensitive permeable Ca^{2+} current induced by FS may be relevant to the myotoxicity of this HMGCoA-reductase inhibitor.

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