Gender-dependent involvement of potassium channel in sarcopenia evaluated by ultrasonographyc measurements

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Sarcopenia, the progressive atrophy of the skeletal muscle that occurs with aging, has been associated to loss of muscle mass, strength and function. Several mechanisms contribute to this phenomenon among these apoptosis, activation of catabolic pathways, denervation and altered metabolism. At the cellular level, alterations in the metabolic state of the muscle affect the redox potential of the cells that in turn induce an increase of the activity of the oxygen free radicals. These notable changes alter the expression and function of the ion channels proteins. A reduced activity of the ATP-dependent K+(KATP) channel contributing to the muscle weakness as well as an increase of the big calcium-activated K+(BK) channel has been observed in the aged rat fibers. The age-related changes of muscle function are gender-dependent. Here, we performed an age-gender characterization of KATP and BK channels by performing patch-clamp experiments on native skeletal muscle fiber (ongoing) in parallel to gene expression of the channel subunits. The atrophy of the skeletal muscle has been determined by in vivo evaluation of flexor digitorum longus(FDL) muscle volume, pennation angle(PA) and fiber length(Fl) by ultrasonographyc measurement (Vevo 2100; Visualsonics, Canada). The female rats of 24-26 months old showed a lean phenotype and a better clinical condition vs that of the aged male rats. A significant reduction of -48.6% and -31.7% for the FDL volume has been observed in old male and female rat vs the young counterpart, respectively. The FDL atrophy match with the significant reduction of -59.4% for PA and of -63.4% for the Fl in old male rat vs young. A significant reduction of -27.5% for PA has been observed in old female rat vs young without any significant change in Fl value. The muscle EDL dry weight/rat body weight ratio was significantly reduced by -19.4% and -50.1 %, respectively, in the female and male rats. The muscle SOL dry weight /rat body weight was significantly reduced by -33.9% and -35.6%, respectively, in the female and male rats. RT-PCR expression analysis showed that Atrogin-1 mRNA level was significantly enhanced by 2.1 and 2.4 folds in male aged rat vs adult male in either EDL and SOL muscles, respectively, while it was not affected in female rats. Murf-1 was not affected. The mRNA level of the mitochondrial Pgc1alpha gene was enhanced by 2.5 and 2 folds, respectively, in SOL muscle in either aged female and male rats. The authophagic Bnip3 gene was not affected. Linear correlation analysis showed that the changes of the expression levels of the Atrogin-1 gene were correlated with the changes of the muscle SOL dry weight /rat body weight and muscle EDL dry weight /rat body weight, respectively, showing a coefficient of correlation R=0.72 and R= 0.47 in male rats. The mRNA levels of the KcnJ11 gene encoding for the kir6.2 subunit of the KATP channel was not affected during aging in either gender and muscle phenotypes. While, the Abcc8 gene encoding for the SUR1 subunit was significantly down-regulated by 1.6 and 1.51 in female and male aged rat vs adult rats in SOL muscle. The mRNA levels of the splicing variants C1-e17, C2-87, C4-Slo0, C4-Slo27 of the Slo1 subunit were upregulated in the SOL muscle of aged female rats; the Slo27, Slo0 and Slo87 were

upregulated in the EDL muscle. In aged male rats, the C4-Slo0 and C4-Slo27 were the only upregulated variants. The full length of the Slo1 subunit was however significantly down-regulated in either gender in the EDL muscles with aging. In sum, the age-related atrophy is associated with a primary loss of fast-twitching FDL and EDL muscles in male rats with a marked contribution of the slow-twitching SOL muscle Atrogin-1 dependent. SOL muscle is less responsive to atrophy being protected by the mitochondrial Pgc1alpha gene in either gender. A gender-dependent cytoprotective role of the splicing variants of the slo1 subunit in SOL muscle of female rats is emerging.