# Functional Properties of the Sarcopenic Muscle and Pharmacological Approaches

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The sarcopenia is characterized by impaired muscle strength and mobility, increased fatigue and a greater risk of falls during aging. Comorbity conditions are neurodegenerative disorders, diabetes type II / obesity (Sakuma et al., 2013; Cetrone et al., 2014). Sarcopenia is characterized by specific type II fiber atrophy and necrosis, fiber transition from fast type II to slow type I. Muscle ecographic evaluation from our labs in female and male aged rats revealed a significant reduction of the mass of fast-twitching muscles and an elevated gender-dependent echogenicity. Dysfunction of the cytokines, insulin/IGF1, caspases and mitochondria signaling lead to the loss of protein (Fanzani et al., 2012).

Age-related changes of activity of the sarcolemma ion channels have been reported. These were associated to abnormality in the $Ca^{2+}$ ions homeostasis, oxidative stress, and dysregulation by intracellular signaling such as the protein kinase C (PKC) and genes down-regulation. A down-regulation of the expression of muscle ClC-1 chloride channel gene as well as a dysregulation of ClC-1 by PKC are the basis for the abnormally reduced resting chloride conductance (gCl) observed during aging (De Luca et al., 1994; Pierno et al., 1998). The observed reduced current density of $Na^{+}$ channels (Nav) explains the reduced excitability of the aged rat fibers (Desaphy et al., 1998). The activity of the metabolically regulated ATP-sensitive $K^{+}$ channels (KATP) and $Ca^{2+}$ activated $K^{+}$ channels (BK) were respectively reduced and enhanced in fast-twitching rat fibers (Tricarico et al., 1994, 1997). Sulfhydryl antioxidants restored channel functions suggesting the involvement of the oxidative stress molecules targeting SH- groups of subunits. The aged rat fibers also show an impairment of the mechanical threshold for contraction associated with elevated intracellular $Ca^{2+}$transient released from the $Ca^{2+}$store indicating abnormalities in the excitation-contraction coupling (Fraisse et al., 2006). GH/GH releasing drugs were partly effective in restoring the electrophysiological and functions of the fibers in aged rats (Desaphy et al., 1998; Pierno et al., 1999).

The KATP and BK channels show fibers phenotype molecular and pharmacological properties in adult rat fibers (Tricarico et al., 2006; Dinardo et al., 2012). Emerging evidences indicate that these channels regulate cell viability suggesting an involvement in phenotype-related diseases associated with cell survivals. The down-regulation of the KATP channel subunits or the block by sulfonylureas induces apoptosis and atrophy and these effects are prevented by the KATP channel opener diazoxide (Cetrone et al., 2014). Diazoxide is capable to prevent the atrophy induced by staurosporine in fast-twitching fibers (Mele et al., 2014). Kv/BK channel blockers including polyphenols were effective in enhancing neuronal viability (Curci et al., 2014). Polyphenols treatment were effective in restoring gCl, KATP and BK conductance and muscles weight in aged rats and their effects can be related with their antioxidant properties and to their direct actions on ion channels (Pierno et al., 2013). Therefore, drugs targeting the ion channel subunits expressed in fast-twitching fibers can be useful in sarcopenia.

De Luca et al. (1994) *Pflugers Arch* 427, 80–85.
Tricarico et al. (1994) *Mol Pharmacol*. 46(4), 754-61.
Tricarico et al. (1997) *Pflugers Arch.* 434(6), 822-9.
Pierno et al. (1999) *FEBS Lett* 449, 12–16.
Desaphy et al. (1998) *Pharmacol Res* 61:553–563.
Pierno et al. (2003) *Br J Pharmacol* 139, 575–584.
Fraisse et al. (2006) *Neurobiol Dis.* 21(2), 372-80.
Tricarico et al.(2006) *Proc Natl Acad Sci U S A.* 103(4), 1118-23.
Dinardo et al. (2012) *PLoS One* 7(7), e40235.
Sakuma et al. (2013) *Int J of Endo.* Article ID 204164, 1-12.
Pierno et al. (2014) *Age (Dordr)*. 36(1):73-88.
Cetrone et al. (2014) *Curr Diabetes Rev.* 10(4), 231-7
Mele et al. (2014) *Biochem Pharmacol* 91(2), 266-75.
Curci et al. (2014) *Front Physiol.* 5 , 476, 1-9.