INVOLVEMENT OF SKELETAL MUSCLE K^+ CHANNELS IN GENETIC AND NON GENETIC DISEASES: FROM GENE EXPRESSION TO DRUG THERAPY

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K^+ channels are involved in genetic and acquired channelophaties of skeletal muscle including periodic paralysis(PP), paraneoplastic syndrome(PNS), in various conditions associated with muscle disuse. The recently characterized molecular composition of the muscle ATP-sensitive K^+(KATP) and Ca^{2+}-activated K^+(BK) channels leads us to investigate on drugs acting in those conditions associated with down-regulation of K^+ channels or with their upregulation(1, 2). BK and KATP channels are differently expressed in fast-twitch and slow-twitch muscles. The BK channel of fast-twitch muscle generates a reduced BK activity potentiated by acetazolamide, while the BK channel of slow-twitch muscle generates an high BK activity drug-resistant. Fast-twitch muscle also shows an high expression/activity of KATP channel SUR2A-B, SUR1/Kir6.2 subunits sensitive to ATP and drugs, while low expression/activity of SUR2A-B/Kir6.2 subunits with reduced ATP and drug sensitivity is observed in slow-twitch muscle. The observed phenotype-dependent activity of KATP and BK channels suggests that these are involved in the muscle plasticity and in disuse. In acquired and genetic forms of hypokalemic periodic paralysis(hypoPP), a reduced expression/activity of the SUR2A/Kir6.2 subunits has been found while the SUR1-2B subunits were not affected. Muscles from humans and animals affected by hypoPP are less sensitive to SUR2A/Kir6.2 agonists while are responsive to acetazolamide that activates the BK channel which is normally expressed in muscles humans and animals affected by hypoPP. Acetazolamide is also effective in the Andersen's syndrome, a PP associated with loss-of-function mutations of the cardiac Kir2.1 channel also expressed in skeletal muscle. Loss of function of Kv1.1/Kv1.2 channels due to an enhanced turnover/degradation of the proteins is the basis of Neuromyotonia, a PNS due to an autoimmune response against channel-antigens. In addition, the involvement of the muscle K^+ channels in diseases not primarly affecting skeletal muscle is emerging. A form of diabetes type-2 and a dilated cardiomyopathy with compromised muscle performance associated with mutations of pancreatic and cardiac KATP channel subunits also expressed in skeletal muscle have been discovered. Drugs targeting muscle K^+ channels are new challenge for genetic and not genetic diseases. Supported by Telethon Grant GGP04140.

1) Tricarico D, Mele A. and Conte Camerino D. (2005) Neurobiol. of Dis. 20:296-302.
2) Tricarico D., Mele A., Lundquist A.L., Desai R.R., George A.L. Jr. and Conte Camerino D. (2006) PNAS 103:1118-1123.