Vitamin e blocks connexin hemichannels and prevents deleterious effects of glucocorticoid treatment on skeletal muscles

Balboa E.

Saavedra F.

Cea L.A.

Ramírez V.

Escamilla R.

Vargas A.A.

Regueira T.

Sáez J.C.

Glucocorticoids are frequently used as anti-inflammatory and immunosuppressive agents. However, high doses and/or prolonged use induce undesired secondary effects such as muscular atrophy. Recently, de novo expression of connexin43 and connexin45 hemichannels (Cx43 HCs and Cx45 HCs, respectively) has been proposed to play a critical role in the mechanism underlying myofiber atrophy induced by dexamethasone (Dex: a synthetic glucocorticoid), but their involvement in specific muscle changes promoted by Dex remains poorly understood. Moreover, treatments that could prevent the undesired effects of glucocorticoids on skeletal muscles remain unknown. In the present work, a 7-day Dex treatment in adult mice was found to induce weight loss and skeletal muscle changes including expression of functional Cx43/Cx45 HCs, elevated atrogin immunoreactivity, atrophy, oxidative stress and mitochondrial dysfunction. All these undesired effects were absent in muscles of mice simultaneously treated with Dex and vitamin E (VitE). Moreover, VitE was found to rapidly inhibit the activity of Cx HCs in freshly isolated myofibers of Dex treated mice. Exposure to alkaline pH induced free radical generation only in HeLa cells expressing Cx43 or Cx45 where Ca2+ was present in the extracellular milieu, response that was prevented by VitE. Besides, VitE and two other anti-oxidant compounds, Tempol and Resveratrol, were found to inhibit Cx43 HCs in HeLa cells transfectants. Thus, we propose that in addition to their intrinsic

anti-oxidant potency, some antioxidants could be used to reduce expression and/or opening of Cx HCs and consequently reduce the undesired effect of glucocorticoids on skeletal muscles.

Connexons

Dexamethasone

Mitochondrial dysfunction

Muscle atrophy

Oxidative stress

alpha tocopherol

antioxidant

atrogin 1

connexin 43

dexamethasone

gap junction protein

glucocorticoid

adult

animal cell

animal experiment

animal model

Article

body weight loss

cell culture

cell isolation

controlled study

HeLa cell line

histology

immunofluorescence test

immunoreactivity

mitochondrial membrane potential

mouse

muscle atrophy

nonhuman

oxidative stress

oxygen consumption

protein degradation

protein expression

skeletal muscle

tibialis anterior muscle