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Adaptive thermogenesis enhances the life-threatening response to heat in mice with an Ryr1 mutation

Hui J Wang [1 2], Chang Seok Lee [1], Rachel Sue Zhen Yee [1], Linda Groom [3], Inbar Friedman [4], Lyle Babcock [1], Dimitra K Georgiou [1], Jin Hong [1], Amy D Hanna [1], Joseph Recio [1], Jong Min Choi [5], Ting Chang [1], Nadia H Agha [1], Jonathan Romero [1], Poonam Sarkar [6], Nicol Voermans [7], M Waleed Gaber [1 6], Sung Yun Jung [5], Matthew L Baker [5], Robia G Pautler [1], Robert T Dirksen [3], Sheila Riazi [4], Susan L Hamilton [8]

Affiliations

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Free article

Abstract

Mutations in the skeletal muscle Ca^{2+} release channel, the type 1 ryanodine receptor (RYR1), cause malignant hyperthermia susceptibility (MHS) and a life-threatening sensitivity to heat, which is most severe in children. Mice with an MHS-associated mutation in Ryr1 (Y524S, YS) display lethal muscle contractures in response to heat. Here we show that the heat response in the YS mice is exacerbated by brown fat adaptive thermogenesis. In addition, the YS mice have more brown adipose tissue thermogenic capacity than their littermate controls. Blood lactate levels are elevated in both heat-sensitive MHS patients with RYR1 mutations and YS mice due to Ca^{2+} driven increases in muscle metabolism. Lactate increases brown adipogenesis in both mouse and human brown preadipocytes. This study suggests that simple lifestyle modifications such as avoiding extreme temperatures and maintaining thermoneutrality could decrease the risk of life-threatening responses to heat and exercise in individuals with RYR1 pathogenic variants.

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