

A22

3,5-Di-*t*-butyl catechol (DTCAT) as an activator of the human skeletal muscle ryanodine receptor Ca²⁺ channel and its evaluation as a test substance for the assessment of susceptibility to malignant hyperthermia

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Introduction

3,5-Di-*t*-butyl catechol (DTCAT) has been shown to release Ca²⁺ from rat skeletal muscle sarcoplasmic reticulum (SR) vesicles, which makes it a possible candidate for use as a substitute for halothane or caffeine in the *in vitro* contracture test (IVCT) for the assessment of susceptibility to malignant hyperthermia (MHS).

Methods

To characterize the effect of DTCAT at the cellular level, Ca²⁺ release experiments were performed on cultured, human skeletal muscle cells using the fluorescent Ca²⁺ indicator fura2-AM. DTCAT was also used for the first time in the IVCT to induce contractures in human skeletal muscle bundles obtained from individuals diagnosed susceptible (MHS), normal (MHN) or equivocal (MHE); these effects were compared to those elicited by the standard test substances caffeine and halothane.

Results

In single cultured skeletal muscle cells, DTCAT released Ca²⁺ from intracellular stores with a higher potency when compared to caffeine. This effect, however, was unspecific, since the release of Ca²⁺ from stores other than the SR was evident, as well as a Ca²⁺ influx, possibly triggered by depletion of intracellular Ca²⁺ stores. DTCAT induced contractures in skeletal muscle bundles in a concentration-dependent manner with an EC₅₀ value of 160 ± 91 μM. However, the reaction to DTCAT in muscles from MHS individuals was similar to reactions to DTCAT in MHE or MHN muscles.

Conclusions

Due to its low specificity in inducing the release of Ca²⁺ from SR stores and the additional activation of Ca²⁺ influx, DTCAT is not an appropriate test substance for the diagnosis of MH.