INVOLVEMENT OF TYPE 1 AND 3 RYANODINE RECEPTOR IN MOUSE MUSCARINIC ANTINOCICEPTION

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Galeotti et al. (1) described the involvement of Ryanodine Receptors (RyRs) in muscarinic antinociception by preventing the increase of pain threshold induced by physostigmine by pretreatment with the RyR antagonist ryanodine. The aim of the present study was to investigate the role of type 1, 2 and 3 RyRs in the intracellular mechanism of muscarinic analgesia at a supraspinal level. To this purpose the expression of each RyRs was selectively inhibited by using antisense oligonucleotides (aODN). Knockdown of type 1, 2 and 3 RyRs was obtained by means of an antisense strategy to investigate the role of supraspinal endoplasmic RyRs in muscarinic analgesia in a condition of acute thermal nociception (hot-plate test). A statistically significant gene-specific RyR protein level reduction induced by aODN administration was demonstrated in all three cases by western blotting experiments in the brain areas investigated (cerebellum, cortex, striatum, hippocampus). I.c.v. pretreatment (0.5-5 nmol per mouse i.c.v.) with an aODN complementary to the sequence of the type 1 RyR and with an aODN against type 3 RyR dose-dependently prevented physostigmine antinociception. A shift to the right of the physostigmine dose-response curve was obtained after anti-RyR1 and anti-RyR3 treatments. This antagonistic effect on physostigmine antinociception was reduced 48h after the last i.c.v. injection and disappeared totally 7 days after the end of the aODN administration. dODN-pretreatment did not modify the mouse pain threshold in comparison with DOTAP- and saline-treated animals and with naïve. Conversely, pretreatment with an aODN complementary to the sequence of the type 2 RyR did not alter the analgesia induced by physostigmine. Pretreatment with an aODN against RyR1 and RyR3 at a dose of 5 nmol per mouse per i.c.v. did not produce any modification of the mouse pain threshold in comparison with dODN-treated animals.
Mice undergoing treatment with aODNs did not show any alteration of animals' gross behavior. Furthermore, any impairment of the locomotor activity, spontaneous motility and exploratory activity was revealed by the rota-rod and hole board tests. Seen as a whole, our data evidenced that the selective activation of type 1 and 3 RyRs is required in the induction of cholinergic supraspinal analgesia in mice in a condition of acute thermal nociception. Adding that, the lack of a prominent role of the type 2 RyR in the increase of pain threshold induced by physostigmine has also been observed.

1. Galeotti N., A. Bartolini A. and Ghelardini C. (2005) Behav. Brain Res. 164: 165-17.