British Journal of Pharmacology 2011 vol.163 N4, pages 732-744

Different sensitivities of rat skeletal muscles and brain to novel anti-cholinesterase agents, alkylammonium derivatives of 6-methyluracil (ADEMS)

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Abstract

BACKGROUND AND PURPOSE The rat respiratory muscle diaphragm has markedly lower sensitivity than the locomotor muscle extensor digitorum longus (EDL) to the new acetylcholinesterase (AChE) inhibitors, alkylammonium derivatives of 6-methyluracil (ADEMS). This study evaluated several possible reasons for differing sensitivity between the diaphragm and limb muscles and between the muscles and the brain. EXPERIMENTAL APPROACH Increased amplitude and prolonged decay time of miniature endplate currents were used to assess anti-cholinesterase activity in muscles. In hippocampal slices, induction of synchronous network activity was used to follow cholinesterase inhibition. The inhibitor sensitivities of purified AChE from the EDL and brain were also estimated. KEY RESULTS The intermuscular difference in sensitivity to ADEMS is partly explained caused by a higher level of mRNA and activity of 1,3-bis[5(diethyl-o-nitrobenzylammonium)pentyl]-6-methyluracildibromide (C-547)-resistant BuChE in the diaphragm. Moreover, diaphragm AChE was more than 20 times less sensitive to C-547 than that from the EDL. Sensitivity of the EDL to C-547 dramatically decreased after treadmill exercises that increased the amount of PRiMA AChE(G4), but not ColQ AChE(A12) molecular forms. The A12 form present in muscles appeared more sensitive to C-547. The main form of AChE in brain, PRiMA AChE(G4), was apparently less sensitive because brain cholinesterase activity was almost three orders of magnitude more resistant to C-547 than that of the EDL. CONCLUSIONS AND IMPLICATIONS Our findings suggest that ADEMS compounds could be used for the selective inhibition of AChEs and as potential therapeutic tools. © 2011 The British Pharmacological Society.

http://dx.doi.org/10.1111/j.1476-5381.2011.01211.x

Keywords

acetylcholine, acetylcholinesterase, alkylammonium anti-cholinesterases, brain, diaphragm, locomotor muscle