Naunyn-Schmiedeberg's Archives of Pharmacology 2009 vol.380 N6, pages 551-560

Mechanisms of the inhibition of endplate acetylcholine receptors by antiseptic chlorhexidine (experiments and models)

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Abstract

Mechanisms of the inhibition of evoked multiquantal endplate currents (EPC) by chlorhexidine (CHX) were studied in electrophysiological experiments and by mathematical modeling to discriminate between possible channel, receptor, and non-receptor effects of this common antiseptic drug. Experiments were carried out on the isolated neuromuscular preparation of the cut m. sartorius of the frog Rana ridibunda. The nerve-stimulation-evoked endplate currents were measured by standard double microelectrode technique. For the mathematical simulation, a method based on the solution of a system of ordinary differential equations was used. CHX in milimolar concentrations suppressed the amplitude and shortened the evoked EPC. Recovery of the EPC amplitude was very slow, and EPC shortening persisted during 30-40 min washout of the drug. There is no indication that CHX competes for acetylcholine or carbachol binding site(s). A comparison of the experimental data with mathematical simulation made it possible to construct a reliable kinetic scheme, which describes the action of CHX. CHX induces a combined slow blockade of the open ionic channel and long-lasting allosteric inhibition of the nicotinic acetylcholine receptor. The very slow washout of the drug in terms of EPC amplitude and virtually no recovery of the shortened EPC time course might substantiate certain caution to avoid unintentional high-dose application during its antibacterial application. © 2009 Springer-Verlag.

http://dx.doi.org/10.1007/s00210-009-0458-0

Keywords

Acetylcholine, Allosteric modulation, Endplate currents, Mathematical modeling, NAChR