Interactions of benzocaine with Na channels in myelinated nerve

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Local anesthetics inhibit nervous transmission by blocking Na channels in the nerve membrane. To study details of the blocking effect we have investigated the actions of the neutral local anesthetic benzocaine on single myelinated nerve fibres of the frog Rana esculenta under voltage clamp.

1) Analysis of Na-current fluctuations

At the end of various depolarizations (V) the steady-state Na current (I) and the variance (var) of Na-current fluctuations were measured without and with 0.1 mM benzocaine in the external solution. In addition 7 µM Anemonia Toxin II were always applied externally to increase I. From I and var a lower limit of the current i through a single Na channel was estimated by $i > var/I$. Benzocaine reduced I and var by one order of magnitude, but the ratio var/I remained unchanged (0.8 pA at V = 40 mV). Thus a small fraction of normally conducting Na channels persists after benzocaine application whereas most of the channels are fully closed. This implies that the blocking of Na channels by benzocaine is an "all-or-none" process.

2) Analysis of asymmetry currents

If Na and K channels in the nerve membrane are blocked, the sum of the current responses elicited by equal positive and negative voltage steps reveals a small asymmetry current. The corresponding asymmetrical charge displacement is thought to arise from the movement of gating subunits in Na channels. Application of 1 mM external benzocaine does not affect the kinetics of asymmetry currents but reduces the amount of charge displacement during the pulse. For depolarizations V between 20 and 120 mV the charge is decreased to 64 % of the control value independent of voltage.

Without benzocaine the fast charge displacement Q_{off} after a pulse V of duration Δt declines exponentially from the charge value Q_{on} during the pulse:

$$|Q_{off}/Q_{on}| = (1-c)\exp(-\Delta t/\tau) + c.$$

τ is approximately equal to the time constant of Na inactivation and $c = 0.42$ and 0.25 at V = 40 and 100 mV, respectively. After treatment with 1 mM benzocaine the charge Q^*_{off} after a pulse V is given by $|Q^*_{off}/Q_{on}| \approx c$ even after short pulse durations Δt. It is concluded that immobilization of mobile charges can be caused either by Na inactivation or by benzocaine, but that these two effects are not additiv.

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