Short communication

Batrachotoxin Decreases the Sensitivity of Sodium Channels to the Blocking Action of Phenobarbital

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In earlier experiments on frog myelinated nerves it was found that the steroidal alkaloid batrachotoxin (BTX) considerably decreases the affinity of Na channel binding sites to various amine blockers (local anesthetics, antiarrythmics, strychnine, yohimbine) (for review see Khodorov 1978; 1981) as well to oenanthotoxin (Dubois and Khodorov 1982) however, the blocking action of neutral benzocaine (Zaborovskaya and Khodorov 1982) and butanol (Dubois and Khodorov 1982) was not appreciably affected.

The aim of the present work was to examine the effect of BTX on Na channel blockage by phenobarbital (PB): the latter drug lacks amine groups and presents both neutral and anionic forms when dissolved. Experiments were carried out on frog (*Rana ridibunda*) myelinated nerves under voltage clamp conditions.

Fig. 1*A* illustrates a typical experiment with the administration of 2.5 and 5 mmol/l PB to the node of Ranvier pretreated with 10^{-5} mol/l BTX. The first "hump" of the current-voltage curve reflects the voltage dependence of stationary Na currents, I_{Na}, in BTX- modified channels. The second "hump" corresponds to peak I_{Na} in Na channels escaping modification by BTX ("normal" channels). Net conductances, g_{Na}, were calculated from these curves and plotted against membrane potential, E (Fig. *1B,C*).

It can be seen that BTX protected Na channels from the blocking action of PB: it decreased the maximum g_{Na} (G_{Na}) in population of "normal" channels, leaving G_{Na} of modified channels unaffected. By contrast, another effect of PB, the concentration-dependent shift of g_{Na}-E curve to more positive E values, was principally similar in both the "normal" and modified channels. A similar shift of the g_{Na}—E relation under the action of PB could be observed in normal (nontreated) fibres (Bolotina et al. 1982).

It is tempting to suppose that a decrease in g_{Na} would result from an interaction of PB (apparently in neutral form) with the Na channel binding site, while the positive shift in g_{Na} curve is due to an effect of the anionic form of PB, present in the axoplasm, on the inner surface potential of the nodal membrane. Note that neither amine local anestetics nor benzocaine, butanol or oenanthotoxin induce such a shift in the g_{Na}—E relation.

The similarity in the protective action of BTX on Na channels treated with

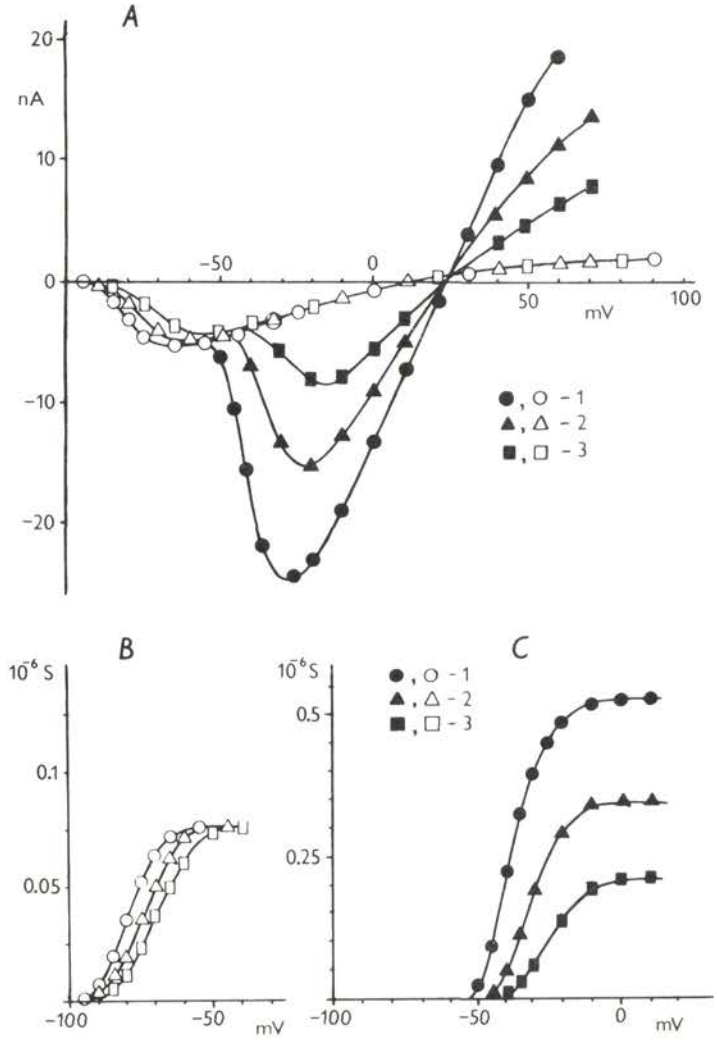

Fig. 1. Effect of phenobarbital (PB) on ionic currents (*A*) and sodium conductance g_{Na} (*B* and *C*) of the node of Ranvier pretreated with BTX. Open symbols: ionic currents (*A*) and g_{Na}(*B*) of BTX-modified Na channels. Full symbols: sodium currents, I_{Na}(*A*) and g_{Na}(*C*) of non-modified channels. (1)-control solution (in mmol/l): NaCl 112; KCl 2.5; $CaCl_2$ 2.0; Tris 5; $NaHCO_3$ 2.0; pH 7.3. The internodes were cut in 114 mmol CsF solution. Temperature 10 °C. (2)-effect of 2.5 mmol/l PB. (3)-effect of 5 mmol/l PB. Holding potential −100 mV; duration of test pulses: 40 ms. Na channels were modified by a 3 min treatment of the node by 10^{-5} mol/l BTX combined with repetitive membrane pulsing. After the end of the treatment, the node was superfused with control and subsequently with control + PB (2.5 and 5 mmol/l) solutions. Fibre 26.01.81.

amine local anesthetics, oenanthotoxine or PB, suggests that all these agents have a common target, likely the gating structures of Na channel.

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