Batrachotoxin: activity-dependent prolongation of the cardiac action potential and positive inotropic effect

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Two steroid alkaloids, veratridine and batrachotoxin (BTX), are known to increase P_{Na} of excitable membranes. In the case of veratridine, this effect is thought to underlie its positive inotropic action; increased passive Na influx will increase $[Na]_i$, Na/Ca exchange and therefore net Ca influx (Honerjäger & Reiter, 1975). We have examined (i) whether BTX increases P_{Na} of guinea-pig myocardial cells and (ii) whether BTX has a positive inotropic effect analogous to that of veratridine. Our results confirm and extend some of the findings published recently by Shotzberger, Albuquerque & Daly (1976), but are at variance with their observations on the effect of BTX on the resting membrane potential of ventricular myocardium.

Six to ten minutes after addition of BTX (0.7 nM) to papillary muscles contracting at a rate of 1 Hz, the duration of the action potential starts to increase. Unlike veratridine, BTX prolongs the action potential at a progressively increasing rate. Quantitatively, this rate is proportional to the effect itself, suggesting that positive feedback is involved in the action of BTX. Twenty to forty minutes after addition of the alkaloid the prolonged repolarization phase gives rise to coupled extrasystoles. The effect on action potential duration is abolished by tetrodotoxin (10 μM) and largely reversed by washing with alkaloid-free solution (for 5 h) or by allowing the preparation to rest in the presence of BTX (for 2 h). The transient *hyper*polarization of the resting potential (Glitsch, 1973) which is observed after cessation of stimulation (1 Hz for $\geqslant$5 min) is increased from 1.55 ± 0.16 mV to 3.72 ± 0.36 mV by BTX ($P < 0.001$).

The first action potential elicited after exposing a resting muscle for 30 min to BTX is not prolonged, no matter whether the muscle has been kept under control conditions ($[K]_o = 5.9$ mM), has been accumulating Na ($[K]_o = 0$) or has been depolarized ($[K]_o = 145.9$ mM). The 'slow response' ($[K]_o = 24.0$ mM; 1 Hz) is not prolonged during 30 min of exposure to BTX, neither is the first action potential elicited after return to 5.9 mM $[K]_o$. In each case, however, the action potential is prolonged during subsequent stimulation at 1 Hz and 5.9 mM $[K]_o$.

Concomitantly with its effect on action potential duration (but in the absence of a marked change of resting potential) BTX produces a positive inotropic effect by increasing rate of force development and prolongs relaxation time. These effects persist in preparations from reserpine-pretreated animals, but are prevented in muscles pretreated with tetrodotoxin. If stimulation is interrupted, the positive inotropic effect decays much faster than the effect on action potential duration. The positive inotropic effect of BTX is significantly enhanced under conditions known to inhibit Na extrusion (dihydro-ouabain, 20 μM; $[K]_o$ reduced to 2.0 mM).

In conclusion, our results suggest: (i) BTX prolongs the cardiac action potential by keeping Na channels open. This increases passive Na influx, $[Na]_i$ and Na extrusion as suggested by increased electrogenic Na pumping. The BTX-membrane interaction appears to require conditions which are known to be associated with the repetitive activation of fast Na channels. (ii) The effect of BTX on sarcolemmal P_{Na} is responsible for its positive inotropic effect, but the relation is indirect. The probable link is increased $[Na]_i$ leading to increased Na/Ca exchange.

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