THE EFFECTS OF MONENSIN AND NIGERICIN, MONOVALENT CATION IONOPHORES, ON ATRIAL AND VENTRICULAR MYOCARDIA

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SUMMARY

The monocarboxylic acid ionophores, monensin and nigericin, which are capable of transporting Na^+, K^+ and H^+ ions across biological membranes, were found to produce several qualitatively similar, concentration-dependent (1.0 -45.0 μM) effects on tension development by isolated guinea pig left atria (paced at 2 Hz). An initial positive inotropic effect was observed, which was attenuated (-70%) by beta-receptor blockade with d,l-propranolol (1.75 μM) or catecholamine-depletion induced by pretreatment of the animals with 6-hydroxydopamine (50 mg/kg, 24 hr prior to use). Monensin was more potent than nigericin in producing the positive response. A secondary negative inotropic effect occurred which was accompanied by the development of contracture. Apparent conduction blockade frequently occurred following the contracture. These effects were partially antagonized by propranolol administration, but not by 6-hydroxydopamine pretreatment. A transient occurrence of aftercontractions was produced by monensin (30 μM), both in the presence and absence of d,l-propranolol.

Exposure of cat papillary muscles (paced at 0.2 Hz) to monensin also resulted in positive inotropic responses which were diminished, but not abolished by the presence of alpha-, beta- and histamine (H_2) receptor blockade (phentolamine, 2 μM; l-propranolol, 2 μM; metiamide, 5 μM) or catecholamine-depletion by pretreatment of the animals with reserpine (3 mg/kg, 18-24 hr prior to use). Papillary muscles from reserpinized animals did not respond to tyramine (100 μM) and did not contain

measurable levels of norepinephrine. Contracture was not observed in papillary muscles, but did occur in Langendorff-perfused cat ventricles paced at 2 Hz. In perfused guinea pig ventricles, frozen when resting tension had increased by 10% during monensin-induced contractures, the levels of ATP and creatine phosphate were reduced by 10 and 25% (the latter value being significant, $p \leq 0.05$), respectively, below those of control hearts. Even though similar reductions in the tissue levels of ATP and creatine phosphate were induced by isoproterenol (10 μM), contracture did not result. In canine Purkinje fibers (paced at 2 Hz) the ionophores resulted in a reduction in action potential duration, which was accompanied by only a modest reduction in resting potential.

The positive inotropic effects of monensin and nigericin are due in part to the indirect effect of catecholamine release. In addition, part of the positive response as well as the negative inotropic response and contracture are likely due to ionophore-induced alteration of the ionic state in both atrial and ventricular myocardia. The inotropic pattern produced in cat papillary muscles by monensin is consistent with an increased intracellular level of Na^+.