Stabilizing-Labilizing Effects of Reserpine, Chlorpromazine, Tetracaine, and Quinidine on Frog Skeletal Muscle Fibers

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Summary. In order to characterize the interaction of reserpine, chlorpromazine, tetracaine, and quinidine with membrane phenomena, electrophysiological studies were performed on frog skeletal muscle fibers under various ionic environments. In addition the influence of these drugs on the contractility of the frog skeletal muscle was investigated.

1. Measurements of intracellular membrane potentials of the sartorius muscle fibers revealed that tetracaine, quinidine, chlorpromazine, and reserpine diminished the depolarizing action of high [K+]o; while the resting potential in normal Ringer's solution fell from −90 mV to −9.3 mV when 100 mM NaCl was replaced by the same amount of KCl, a time and dose-dependent increase of the membrane potential depolarized by potassium was observed after addition of these drugs. The order of the polarizing potency was reserpine > chlorpromazine > tetracaine > quinidine.

2. Maximal stabilizing effects (i.e. increase of the membrane potential in 100 mM KCl Ringer's solution to more negative values) were observed with the following drug concentrations (20 min incubation time): reserpine < 10^-4 M (13 mV increase); chlorpromazine 3 × 10^-4 M (21 mV increase); quinidine 3 × 10^-3 M (15 mV increase); tetracaine 10^-2 M (28 mV increase). At higher concentrations, reversion of the polarizing effects occurred as a consequence of labilization of the muscle membrane.

3. Evidence for such a biphasic effect, i.e. stabilizing-labilizing effect of the drugs came also from measurements of the relative membrane resistance Rr. In 100 mM KCl Ringer's solution tetracaine in concentrations up to 10^-3 M caused an absolute increase. Higher concentrations produced again a subsequent fall of Rr. Quinidine, chlorpromazine and reserpine inhibited only the time-dependent decrease of Rr normally found in control preparations.

4. In chloride-deficient 112 mM KCH3SO3 Ringer's solution, tetracaine produced a several fold higher increase of Rr. Under these experimental conditions also quinidine and chlorpromazine caused an absolute enhancement of Rr, but not reserpine. These findings indicate that chiefly the potassium conductance gK of the muscle fiber membrane was affected by tetracaine, chlorpromazine, and quinidine.

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5. Tetracaine, quinidine, chlorpromazine, and reserpine inhibited the KCl-induced contractions of the sartorius muscle as well as the acetylcholine-induced mechanical activity of the frog rectus abdominis muscle.

6. From the results it is concluded that the different drugs used in this investigation may exert their effects by a rather common mechanism, i.e. via membrane stabilization; this is indicated by the observed impairment of the membrane permeability for cations.

Key-Words: Membrane Stabilization — Frog Skeletal Muscle — Potassium Conductance — Depolarizibility.

Previous investigations (Balzer and Hellenbrecht, 1969) had shown that reserpine and chlorpromazine diminished the contraction amplitude of the electrically stimulated frog sartorius muscle. With reserpine this decline was preceded by a slight enhancement of the concentration amplitude. Additionally, the acetylcholine-induced contractions of the frog rectus muscle were suppressed after incubation with reserpine and chlorpromazine. It was concluded that, beside an inhibition of the sarcoplasmic calcium pump, permeability for calcium is reduced by these drugs also at the membrane of the muscle fiber. It was therefore of interest to see whether other ion permeabilities were also affected. Electrophysiological investigations seemed suitable to throw light on this point, and therefore the resting potential and the membrane resistance together with water uptake were studied under different ionic environments under the influence of reserpine and chlorpromazine. Tetracaine as a local anesthetic, and quinidine as an antiarrhythmic agent, were investigated for the sake of comparison because much information about their action can be obtained from the literature (for rev. see Shanes, 1958), while electrophysiological studies of the effects of reserpine and chlorpromazine have not been reported for the frog sartorius muscle fiber membrane.

1. Methods

1.1. Isolated frog sartorius and, for acetylcholine contractions, rectus muscles of Rana temporaria were used in all experiments. The muscles were dissected and immediately incubated in normal O₂-aerated Ringer’s solution for a period of 1/4 to 2 h. For the electrophysiological studies each muscle was mounted with its inside surface facing uppermost on a raised platform in a perspex chamber, with 20 ml of incubation medium. The rectangular chamber was divided into two compartments by a diaphragm which contained several perforations. By aerating the solutions with oxygen in the large compartment (about 4/5 of the whole volume), a steady stream was sustained through the diaphragm into the small muscle compartment; this avoided violent agitation of the microelectrodes.

Chemical agents were always added to the large compartment by a syringe in small volumes of 0.2—0.66 ml. The lag period required for mixing of the drug was estimated to be shorter than 30 sec.