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Effects of Glibenclamide on Na^+-K^+ Pump and L-type Ca^{2+} Channel in Guinea-pig Ventricular Myocytes

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Glibenclamide, a sulfonylurea derivative, has been used in the treatment of type II diabetes mellitus. Recent studies provided evidence that glibenclamide, in addition to blocking ATP-sensitive K^+ channels, also affected Na^+-K^+ pumps and L-type Ca^{2+} channels in noncardiac cells. The effect of glibenclamide on the cardiac muscle is not clearly known. In the present study, the effects of glibenclamide on intracellular Na^+ concentration ($[Na^+]_i$), twitch tension, Ca^{2+} transient, and membrane potential were investigated in isolated guinea-pig ventricular myocytes. Glibenclamide at concentration of 200 μM increased $[Na^+]_i$ by 3.9 ± 0.4 mM (mean ± SE, n=12), decreased twitch tension by 36.1 ± 4.0% (mean ± SE, n=8), reduced Ca^{2+} transient by 24.4±5.1% (mean ± SE, n=3), slightly depolarized diastolic membrane potential, and did not change action potential duration. To determine whether inhibitions of Na^+-K^+ pumps and L-type Ca^{2+} channels are responsible for the increase of $[Na^+]_i$ and the decrease of twitch tension, we tested effects of glibenclamide on Na^+-K^+ pump current and L-type Ca^{2+} current. Glibenclamide decreased Na^+-K^+ pump current and L-type Ca^{2+} current in a concentration-dependent manner. These results indicate that glibenclamide increases $[Na^+]_i$ by inhibition of the Na^+-K^+ pump and decreases twitch tension and Ca^{2+} transient by blocking the L-type Ca^{2+} channel. The threshold concentration for the effect of glibenclamide on $[Na^+]_i$, twitch tension, Ca^{2+} transient , Na^+-K^+ pump current, and L-type Ca^{2+} current was between 1 μM and 10 μM. Therefore, it is suggested that studies attributing the beneficial or deleterious effects of glibenclamide in the heart only to block up ATP-sensitive K^+ channels should use submicromolar concentrations to minimize possible secondary interactions with cardiac Na^+-K^+ pumps, L-type Ca^{2+} channels.