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Gambierol action on K⁺ currents and catecholamine release in cultured single chromaffin cells from fetal rat adrenal medulla

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Gambierol, characterized by a transfused octacyclic polyether core, was first isolated and chemically typified from cultured *Gambierdiscus toxicus* dinoflagellates collected in French Polynesia. Subsequently, distinct groups in Japan and the USA, using various strategies, achieved its total chemical synthesis. This allowed detailed studies on its mode of action. Gambierol inhibits voltage-gated K⁺ (K_V) channels in various excitable and non-excitable cells, as well as in motor nerve terminals of the skeletal neuromuscular junction. In the present study, we have investigated first, the effects of nanomolar concentrations of gambierol on K⁺ current of cultured chromaffin cells from fetal rat adrenal medulla using perforated patch-clamp current-recordings. Our results show that gambierol only blocked a small component of the total K⁺ current, and affected neither calcium-activated K⁺ (K_{Ca}) nor ATP-sensitive K⁺ (K_{ATP}) channels, as revealed using apamin and iberiotoxin (selective K_{Ca} channel blockers) and glibenclamid (K_{ATP} channel blocker). After inhibiting K_{ATP} and K_{Ca} channel activation, the gambierol concentration blocking 50% the K⁺ current-component (IC₅₀) was 7.6 ± 1.1 nM. The repolarizing phase of all-or-none elicited action potentials, recorded under current-clamp conditions (triggered by 1-ms depolarizing pulses), was sensitive to the action of gambierol but insensitive to the action of apamin and iberiotoxin, indicating that K_{Ca} channels do not participate in the modulation of action potential duration triggered by short depolarizing pulses. The use of simultaneous patch-clamp and single-cell amperometry allowed controlling the membrane potential and detecting exocytosis events (with a carbon electrode polarized to +650 mV to allow the oxidation of released catecholamines). Such recordings revealed that gambierol did not modify the membrane potential following 14-second depolarizing current-steps, and did not increase significantly the number of exocytotic catecholamine release events with respect to controls. The addition of K_{Ca} channel blockers (in the continuous presence of gambierol) enhanced the membrane depolarization by about 15 mV (during the 14-second current step), and at the same time increased significantly the number of exocytotic events related to catecholamine secretion. Such enhanced depolarization induced by the K_{Ca} channel blockers probably brings the membrane potential above the activation threshold of high-voltage activated Ca_v channels triggering both Ca²⁺ influx and subsequent catecholamine secretion. These results emphasize the diversity of K_V channels in chromaffin cells from fetal rat adrenal medulla and highlight the modulatory role played by K_{Ca} channels in the control of exocytosis in the absence of splanchnic innervation.

Keywords: catecholamine release, cultured chromaffin cell, fetal rat adrenal medulla, gambierol, potassium current.
