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Calcium, strontium and barium elicit different patterns of exocytosis in chromaffin cells

We have studied three divalent cations (Ca^{2+}, Sr^{2+}, Ba^{2+}) capable of eliciting secretion in adrenal chromaffin and other secretory cells. These cations enter the cells through voltage-sensitive Ca^{2+} channels, yet Ba^{2+} and Sr^{2+} are poorly cleared from the intracellular space. In addition, Ba^{2+} blocks Ca^{2+}-activated K^{+} channels, promoting cell depolarization and action potentials.

The amount of catecholamines released by intact depolarized cells depends on the cation applied extracellulary following order: $Ba^{2+} > Sr^{2+} \geq Ca^{2+}$. Conversely, amperometric recordings on permeabilized cells (Fig. 1) show that Ca^{2+} promotes the longest lasting secretion, as Ba^{2+} only provokes secretion while present and Sr^{2+} induces intermediate-lasting secretion. Intracellular Ba^{2+} dialysis provokes exocytosis at concentrations 100-fold higher than those of Ca^{2+}, whereas Sr^{2+} exhibits an intermediate sensitivity.

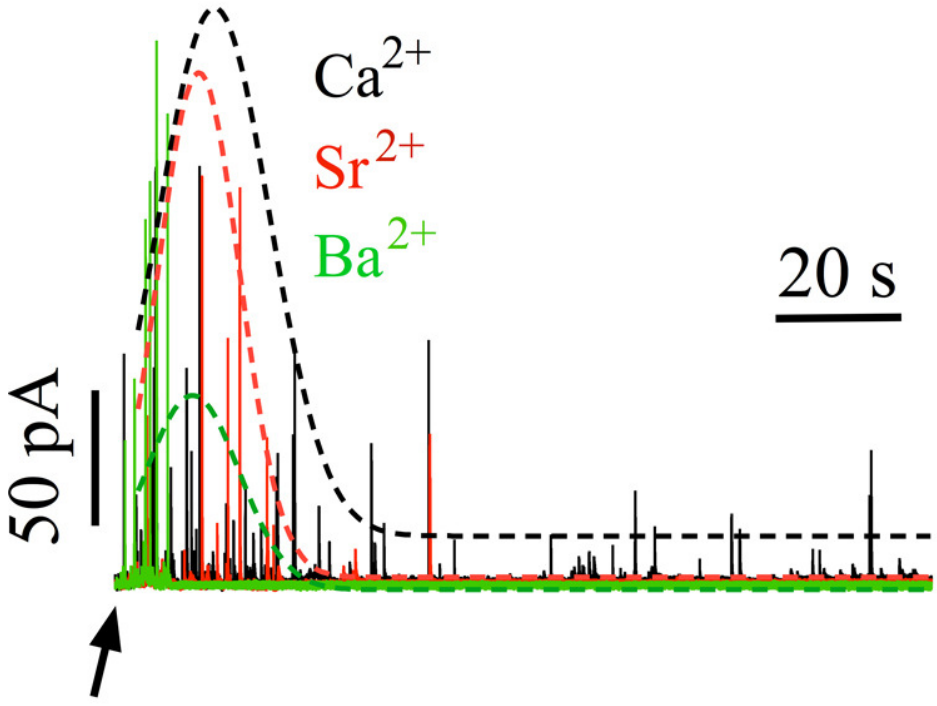

Fig. 1. Secretory responses induced by divalent cations in permeabilized chromaffin cells studied with single-cell amperometry. Superimposed, representative amperometric recordings obtained with 10 s application (arrow) of Ca^{2+}, Sr^{2+} or Ba^{2+} at the estimated concentrations (22.5, 44.5 and 41.5 µM of free Ca^{2+}, Sr^{2+} and Ca^{2+}, respectively). Barium effect (green trace) lasts only during the cation application whereas Ca^{2+} lasts for minutes (black trace) and Sr^{2+} (red trace) exhibits an intermediate duration. Superimposed dashed traces show the temporal distribution of spike firing. Calibration bar on the left (in pA) for oxidation currents of secretory spike, on the right for the frequency of secretory events (expressed in Hz) are. Temporal calibration is shown in seconds.

Using Fura-2 on intact chromaffin cells, the extracellular application of Ba^{2+} increases cytosolic Ca^{2+} concentrations also inducing long-lasting catecholamine release. When secretion is triggered by pressure application of 5 mM $BaCl_2$, the substitution of Ca^{2+} by Sr^{2+} largely affects the kinetics of exocytosis elicited by Ba^{2+}, whereas the replacement of Ca^{2+} by Mg^{2+} does not cause effects on secretory spikes (Fig. 2).

We also carried out an electrophysiological study under current-clamp configuration. This study shows that extracellular Sr^{2+} and Ba^{2+} cause membrane depolarization and action potentials, which are not blocked by Cd^{2+} but that can be mimicked by tetra-ethyl-ammonium. When applied intracellularly, only Ba^{2+} provokes action potentials. In addition, voltage-clamp monitoring of Ca^{2+}-activated K^+ channels (K_{Ca}) shows that Ba^{2+} reduces outward currents, which are enhanced by Sr^{2+}.

Our results are compatible with the following sequence of events: Ba^{2+} blocks K_{Ca} channels from both the outside and inside of the cell, causing membrane depolarization that, in turn, opens voltage-sensitive Ca^{2+} channels and favours the entry of Ca^{2+} and Ba^{2+}. Although Ca^{2+} is less permeable through its own channels, it is more efficient on triggering exocytosis. Strontium possesses both an intermediate permeability and an intermediate ability to induce secretion.

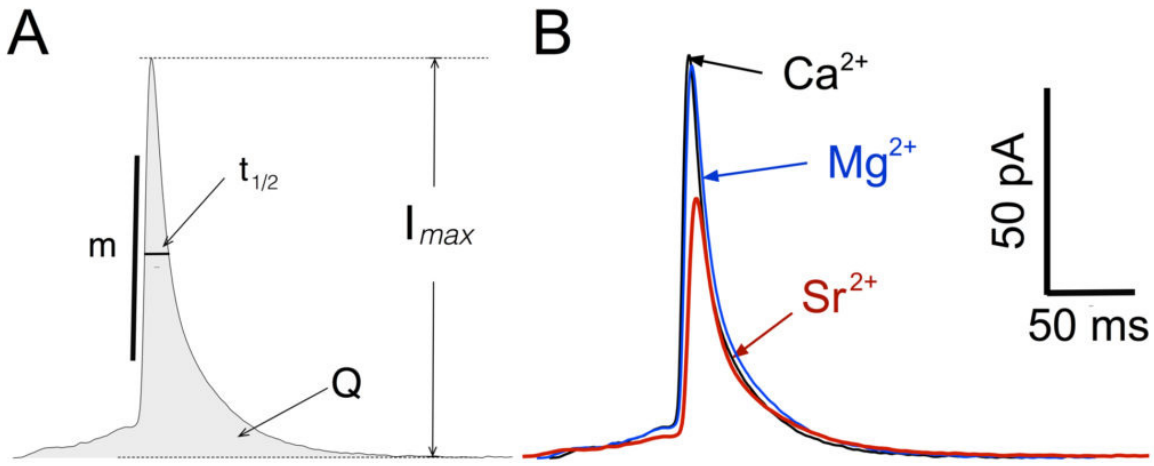

Fig. 2. The substitution of Ca^{2+} by Sr^{2+} largely affects the kinetics of exocytosis elicited by Ba^{2+} whereas the replacement of Ca^{2+} by Mg^{2+} does not cause effects on secretory spikes. Experiments are conducted using single cell amperometry. Secretion is triggered by pressure application of 5 mM BaCl2 during 5 s. A, kinetics parameters obtained from secretory vesicles I_{max}, maximal current caused by the catecholamines reaching the electrode; $t_{1/2}$, spike width at its half height; Q, the integrated area under the spike trace that indicates the total quantal catecholamines released during the exocytotic event; m, the ascending slope was linearized between the 25% and 75% of the I_{max}. B, Average spikes are built using real values.

We have provided further details of the mechanisms underlying the sustained, yet slower secretory effects of Ba^{2+} in chromaffin cells, and described some novel actions of the lesser studied cation Sr^{2+} on BK channel currents and cell excitability that contribute to increase its secretagogue capability in comparison with Ba^{2+} and Ca^{2+}.

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