INHIBITORY EFFECTS OF CAFFEINE ON CATECHOLAMINE SECRETION AND MEMBRANE CURRENTS IN ADRENAL MEDULLARY CHROMAFFIN CELLS OF THE GUINEA-PIG

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The mechanisms of the inhibitory action of caffeine on catecholamine secretion were investigated using perfused adrenal glands and dispersed chromaffin cells of the guinea-pig.

1. In perfused adrenal glands, continuous application of caffeine (10mM) inhibited catecholamine (CA) secretion induced by acetylcholine (ACh, 5×10^{-5}M), 56mM KCl, and veratridine (10^{-4}M), which were partially restored after washout of caffeine.
2. Caffeine (1–40mM) caused a dose-dependent inhibition of CA secretion evoked by 10^{-4}M ACh, veratridine, nicotine or pilocarpine in dispersed cells.
3. Theophylline and purine (5mM) also caused an inhibition of ACh (10^{-4}M)-induced CA secretion equal to that of caffeine (5mM). The inhibitory effect was markedly increased, when the concentration of theophylline and caffeine, but not purine, were increased to 10mM.
4. In perfused adrenal glands, continuous application of forskolin (3×10^{-5}M) did not affect CA secretion induced by ACh (10^{-4}M) and 56mM KCl.
5. In dispersed adrenal chromaffin cells, CA secretion evoked by 10^{-4}M ACh or veratridine was not inhibited by forskolin (3×10^{-5}M), dibutyryl cAMP (1mM) and 8–bromo cAMP (1mM).
6. In the voltage-clamp used for the whole-cell recording mode (holding potential, −60mV), ACh (10^{-4}M) induced an inward current, which was reversibly inhibited by caffeine (20mM).
7. Caffeine (20mM) reversibly inhibited tetrodotoxin-sensitive inward Na^+ current, inward Ca^{2+} current and outward K^+ current evoked by depolarizing pulses (from −70mV to 0mV).
8. Caffeine (20mM) reversibily inhibited a transient rise in the cytosolic Ca^{2+} level induced by ACh (10^{-4}M).
9. In β-escin-permeabilized adrenal chromaffin cells, caffeine (20mM) caused a significant inhibition of Ca^{2+} (10 μM)-evoked CA secretion.
10. These results suggest that caffeine indirectly inhibits agonist-induced CA secretion from adrenal chromaffin cells of the guinea-pig by preventing nicotinic channel currents and Ca^{2+} influx through voltage-dependent Ca^{2+} channels, and directly by decreasing the sensitivity to Ca^{2+} of the secretory mechanism.