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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,  $5 \times 10^{-5}$ 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 ( $3 \times 10^{-5}$ 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 ( $3 \times 10^{-5}$ M), dibutyryl cAMP (1mM) and 8-bromo cAMP (1mM).
6. In the voltage-clamp used for the whole-cell recording mode (holding potential,  $-60$ mV), ACh ( $10^{-4}$ M) induced an inward current, which was reversibly inhibited by caffeine (20mM).
7. Caffeine (20mM) reversibly inhibited tetrodotoxin-sensitive inward  $\text{Na}^+$  current, inward  $\text{Ca}^{2+}$  current and outward  $\text{K}^+$  current evoked by depolarizing pulses (from  $-70$ mV to 0mV).
8. Caffeine (20mM) reversibly inhibited a transient rise in the cytosolic  $\text{Ca}^{2+}$  level induced by ACh ( $10^{-4}$ M).
9. In  $\beta$ -escin-permeabilized adrenal chromaffin cells, caffeine (20mM) caused a significant inhibition of  $\text{Ca}^{2+}$  ( $10 \mu\text{M}$ )-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  $\text{Ca}^{2+}$  influx through voltage-dependent  $\text{Ca}^{2+}$  channels, and directly by decreasing the sensitivity to  $\text{Ca}^{2+}$  of the secretory mechanism.