THE EFFECTS OF TACRINE ON CATECHOLAMINE SECRETION AND MEMBRANE CURRENTS IN ADRENAL MEDULLARY CHROMAFFIN CELLS

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1. The mechanism of action of tacrine on cholinergic transmission was investigated using perfused adrenal glands and dispersed chromaffin cells of the guinea pig.
2. In perfused adrenal glands, continuous application of tacrine (10^{-4}M) inhibited catecholamine (CA) secretion induced by acetylcholine (ACh, 5×10^{-5}M), which was partially restored after the washout of tacrine. This inhibitory effect was also seen in the presence or absence of atropine (10^{-6}M) or hexamethonium (10^{-3}M).
3. When ACh and tacrine were simultaneously applied, ACh-evoked CA secretion was potentiated depending on the concentration of tacrine added within the range between 10^{-6} and 10^{-4}M, regardless of the presence or absence of atropine (10^{-6}M) or hexamethonium (10^{-3}M).
4. Catecholamine secretion evoked by nicotine (2×10^{-5}M) was inhibited by continuous application of tacrine in a dose-dependent manner ($10^{-6}-10^{-4}$M). Unlike the secretory response to ACh however, the response to nicotine was not enhanced by simultaneous application with tacrine.
5. Tacrine had no effect on KCl-evoked CA secretion.
6. In dispersed adrenal chromaffin cells, ACh-evoked CA secretion was inhibited by tacrine.
7. Under voltage-clamp in the whole-cell recording mode (holding potential, −70mV), ACh (10^{-4}M) induced an inward current. Tacrine (10^{-4}M) reversibly abolished this inward current.
8. Tacrine (10^{-4}M) reversibly inhibited tetrodotoxin (TTX, 10^{-6}M)-sensitive inward Na current and outward K current evoked by depolarizing pulse without changing their voltage-current relationships.
9. Tacrine did not affect sustained inward Ca current, which was evoked by a depolarizing pulse after treatment of TTX and replacement of intracellular KCl with CsCl.
10. These results show that tacrine has dual effects on the actions of ACh : inhibition upon continuous application and potentiation upon simultaneous application of tacrine with ACh. Potentiation may be a result of the cholinesterase inhibition by tacrine.