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Title	Effects of tacrine on catecholamine secretion from guinea-pig adrenal chromaffin cells : in comparison with the effects of a cholinesterase inhibitor, physostigmine
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by maximal doses of these three agents was 78%, 15% and 6%, respectively. When these three agents were applied onto the same cell, I_{Ca} was inhibited additively. Rises in $[Ca^{2+}]_i$ and catecholamine release in response to stimulation by high K^+ were inhibited to about 50% by either ω -CgTx (1 μ M) or nifedipine (10 μ M) but not by ω -AgTx (0.1 μ M). In addition, these responses were almost abolished by the combined application of ω -CgTx and nifedipine. A strong depolarizing pulse (a prepulse to +100 mV) applied prior to a test pulse caused about 20% increase of amplitude of I_{Ba} evoked by the test pulse (facilitation of I_{Ba}). The degree of the facilitation of I_{Ba} was increased with the increase in the voltage (in a range over +20 mV) and duration of the prepulses. Moreover the facilitation of I_{Ba} was decreased with increase in intervals between the prepulses and the test pulses. The application of 8-Bromo-cAMP (1 mM) or forskolin (10 μ M) decreased the amplitudes of I_{Ba} without affecting the degree of facilitation of I_{Ba} by the prepulses. In addition, an intracellular application of Rp-cAMPS, an inhibitor of PKA, did not have any effects on the amplitudes of I_{Ba} and the degree of

facilitation of I_{Ba} . The intracellular application of GTP γ S (100 μ M) decreased the amplitudes of I_{Ba} , but not affected those in the presence of prepulses. On the other hand, the application of GDP β S (100 μ M) caused a slight increase in the amplitudes of I_{Ba} but had no effects on the amplitudes of I_{Ba} in the presence of prepulses. GTP γ S-sensitive component of I_{Ba} was sensitive to ω -CgTx but not to nifedipine. The facilitation of I_{Ba} by the prepulses was abolished by ω -CgTx but not by either ω -AgTx or nifedipine.

Based on these results, it is clarified that porcine adrenal chromaffin cells possess ω -CgTx-sensitive N- and nifedipine-sensitive L- and ω -AgTx-sensitive P/Q-type Ca channels and that L- and N-type channels mainly contribute to the rise in $[Ca^{2+}]_i$ and catecholamine release by depolarizing the cells. N-type Ca channels are mainly involved in the depolarizing prepulse-induced facilitation of I_{Ba} . The facilitation seems to result from the prepulse-induced relief of tonic inhibition on Ca channels by G-protein but not from PKA-induced phosphorylation of channels during the prepulse.

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Effects of tacrine on catecholamine secretion from
guinea-pig adrenal chromaffin cells: in comparison with the
effects of a cholinesterase inhibitor, physostigmine

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1. Effects of tacrine and physostigmine (Phys) on catecholamine (CA) secretion induced by acetylcholine (ACh) and their mechanisms were stu-

died in perfused adrenal glands and dispersed adrenal chromaffin cells of the guinea-pig.

2. In perfused adrenal glands, tacrine and Phys

enhanced CA secretion induced by ACh (50 μ M) at lower concentrations (0.1–20 μ M), but decreased it at higher concentrations (100–200 μ M).

3. CA secretion induced by carbachol (50 μ M) was not enhanced by low concentrations, but was markedly decreased by high concentrations of tacrine and Phys.

4. Tacrine and Phys inhibited cholinesterase activities of adrenal homogenate in a dose-dependent manner, and the effects reached a maximum at 10 μ M and 20 μ M, respectively.

5. In perfused adrenal glands, CA secretion induced by nicotine (50 μ M) was inhibited by high concentrations of tacrine (100 μ M) and Phys (200 μ M). Nicotine-induced CA secretion from dispersed adrenal chromaffin cells was also inhibited dose-dependently by tacrine and Phys, and was almost abolished by 100 μ M tacrine and Phys.

6. In dispersed adrenal chromaffin cells, CA secretion induced by veratridine (20 μ M) was significantly decreased by tacrine (100 μ M) and Phys (1 mM).

7. Secretory response to high K^+ (46.2 mM) was

not affected by tacrine and Phys (1–100 μ M).

8. In voltage-clamped cells, tacrine and Phys dose-dependently inhibited membrane currents in a following order; inward currents induced by nicotine (50 μ M) > voltage-dependent sodium currents > voltage-dependent calcium currents.

9. Nicotinic currents were inhibited by both drugs with a similar potency, and were almost abolished by 100 μ M tacrine and 200 μ M Phys. On the other hand, voltage-dependent sodium and calcium currents were more sensitive to tacrine than Phys.

10. These results demonstrate that low concentrations of tacrine and Phys increase ACh-induced CA secretion by their anti-cholinesterase actions in guinea-pig adrenal chromaffin cells. On the other hand, high concentrations of both drugs inhibit nicotine- and veratridine-induced CA secretion by probably blockade of nicotinic receptor channels and sodium channels, respectively. Inhibitory effects of tacrine and Phys on nicotinic receptor channels appear to be one of the major mechanisms of inhibition of CA secretion induced by ACh in guinea-pig adrenal chromaffin cells.

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Efficiency and safety studies of a humanized antibody to human interleukin-6 receptor in primates

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A humanized antibody, hPM-1, was constructed by grafting the complementarity determining regions to human interleukin-6 receptor (IL-6R), raised in mouse, onto a human antibody backbone. hPM-1 is expected to be useful as a therapeutic agent for IL-6-related diseases such

as multiple myeloma and rheumatoid arthritis.

In order to investigate the efficacy and safety of hPM-1 preclinically, we first selected suitable species IL-6R of which cross-reacts with hPM-1. We examined the binding activity of hPM-1 to IL-6R with peripheral blood lympho-