Title: THE EFFECT OF PANCURONIUM ON THE RELEASE OF ACETYLCHOLINE FROM THE RIGHT ATRIUM OF THE GUINEA-PIG

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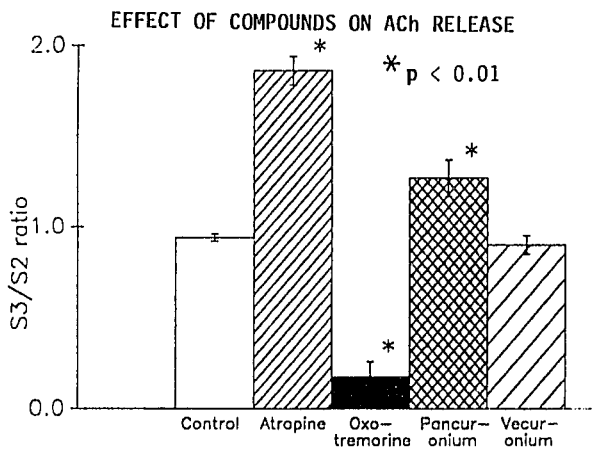
Introduction. The elevation of the heart rate (HR) by pancuronium or gallamine has been attributed to pre- and postsynaptic inhibition of the cardiac vagus and facilitation of the release of norepinephrine (NE) [for references see (1)]. Stimulation of muscarinic receptors of the sympathetic and parasympathetic nerve endings of the g.p. atrium by acetylcholine (ACh) or oxotremorine (OXT) inhibits and their inhibition by atropine facilitates evoked release of ACh or NE, respectively (2). NE release was also facilitated by pancuronium or gallamine which antagonized the inhibitory effect of ACh. To obtain further information on the mechanism of the pancuronium induced elevation of HR we measured its effect on the evoked release of ACh from the right atrium of the g.p.

Methods. The excised right atria of g.p. were incubated for 40 min at 37°C in Kreb's solution, containing 5 μc/ml ^{3}H-choline, bubbled with 95% O_2-5% CO_2. To facilitate ^{3}H-choline uptake preparations were stimulated with supramaximal impulses of 1 ms duration at 1 Hz for 60 min. After incubation preparations were suspended in 1.5 ml organ baths. To wash out excess ^{3}H-choline and prevent readsorption of ^{3}H-choline, liberated by the hydrolysis of the synthetized ^{3}H-ACh, the preparations were superfused at the rate of 1 ml/min with Krebs' solution containing 50 μM hemicholinium-C for 90 min. Subsequently 3 min (3 ml) fractions of the perfusate were collected for 60 min. During this time the preparations were stimulated 3 times (S_1, S_2, S_3) for 2 min with 1 ms impulses administered at 2 Hz, at the 9th, 27th and 45th min. Radioactivity was measured with liquid scintillation spectrometry in each fraction. Stimulation increases the release of ^{3}H-ACh, but not that of ^{3}H-choline (3). Therefore, the stimulation induced increase of radioactivity can be attributed to release of ^{3}H-ACh. Evoked release was calculated by subtracting from the total amount of radioactivity (Bq/g) released by electrical stimulation the mean resting release measured immediately before and after S_1, S_2 or S_3. The amount of radioactivity was variable in different preparations. In contrast, the ratios of radioactivity, released during subsequent stimulation periods, i.e. S_2/S_1 or S_3/S_2 were relatively constant. Therefore, the effects of drugs, added between S_2 and S_3, on the evoked release of ^{3}H-ACh could be calculated by comparing the S_3/S_2 measured after the addition of drugs with control S_2/S_3 ratios. Increase of this ratio indicates facilitation, its decrease inhibition of evoked release. Results were analyzed by ANOVA followed by Tuckey's test (4) ($p < 0.05$ was accepted as significant).

Results. There was no difference in the S_2/S_1 ratios (0.73±0.10 to 0.85±0.05; Mean ± SEM; n = 4). None of the compounds had any effect on resting release of radioactivity. After the addition of atropine or pancuronium the S_3/S_2 ratios were significantly higher, after that of OXT significantly lower than that of control (see figure). Vecuronium had no effect on $S_3/_2$ ratios.

Discussion. Elevation of the HR by pancuronium has been attributed to: a. Increased release of NE the sympathetic innervation of the cardiac pacemaker; b. inhibition of the reabsorption of the released NE; and c. inhibition of the parasympathetic innervation of the cardiac pacemaker (1). It has been demonstrated by direct measurement of the evoked release of NE that pancuronium does increase evoked release of NE from the cardiac sympathetics, but it does not inhibit its reabsorption. Theoretically the parasympathetic effect on HR could be cuased by inhibition of the evoked release of ACh from the cardiac vagus or to inhibition of the adsorption of ACh to post ganglionic muscarinic recepters on the cardiac pacemaker. The findings presented indicate that the first of these 2 hypothetical mechanisms can be excluded, because pancuronium instead of inhibiting increased the evoked release of ACh (see fig). In other words, two of the 4 possibilities, namely inhibition of the reabsorption of NE (2) and inhibition of the evoked release of ACh, have been excluded by direct measurement of the respective chemical mediators. Therefore, it may be assumed that pancuronium increases HR by increasing the release of NE and perhaps also by inhibiting adsorption of ACh to postganglionic muscarinic receptors.



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