The time course of noradrenaline release caused by high potassium-low sodium solution. Effects of methacholine or decrease of the calcium ion concentration.

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Muscarinic drugs including methacholine (MCh) have previously been shown to inhibit calcium-dependent release of noradrenaline by various stimuli (Muscholl, 1973). The present report deals with two phases of noradrenaline release caused by high K^+-low Na^+ solution (equivalent substitution of 132.3 mmol/l NaCl of Tyrode solution by KCl) and the selective effects of MCh or calcium deprivation on the first phase.

Hearts were removed from rabbits (1.6-2.1 kg) and perfused at constant flow of 20 ml/min according to the Langendorff method with Tyrode solution at 36.5°C. After 20 min the perfusion with high K^+-low Na^+ was started. Noradrenaline in the perfusates was determined fluorimetrically and the rate of output plotted on semi-log paper.

The noradrenaline output of the hearts during perfusion with high K^+-low Na^+ declined exponentially in two phases with half-times of 1.59 and 16.9 min (Table 1). The initial rates of release differed by a factor of 10. The first phase did not extend beyond the 10th minute. The total noradrenaline output from 0-10 min was 3 times that from 10-30 min, the latter comprising only phase two.

MCh was perfused 0.5-15 min before and during high K^+-low Na^+. Independent of the *duration* of pre-perfusion, but depending on the *concentration*, MCh decreased the initial rate of noradrenaline release and its total output from 0-10 minutes. However, the second phase of noradrenaline release remained unaffected by MCh. Atropine (1.44 μmol/l) did not alter the above parameters but completely antagonized the effects of MCh (320 μmol/l). When the calcium ion concentration of high K^+-low Na^+ solution was reduced from 1.8-0.113 mmol/l the semi-log plot of outputs could not be resolved into two phases. The output 0-10 min depended on the length of pre-perfusion of low calcium solution. After 1, 3, 30 and 60 min the outputs were 1085 ± 153; 839 ± 180; 537 ± 114 and 393 ± 63 ng, respectively (each n = 3). In contrast, the outputs from 10-30 min were not significantly different from that observed in normal calcium solution.

Table 1 Effect of MCh on the rate of noradrenaline output evoked by high K^+-low Na^+

MCh μmol/l	n	First phase		Second phase		Total noradrenaline released	
		Initial rate (ng/min)	$T_{½}$ (min)	Initial rate (ng/min)	$T_{½}$ (min)	0-10 min (ng)	10-30 min (ng)
0	8	1240 ± 115	1.59 ± 0.18	124 ± 10.9	16.9 ± 2.2	3254 ± 315	1038 ± 43
40	6	373** ± 110	2.11 ± 0.55	144 ± 21	16.4 ± 1.4	1741* ± 284	1050 ± 187
320	12	228** ± 32	2.88** ± 0.25	122 ± 10.4	17.5 ± 1.0	1457** ± 122	1119 ± 113

Given are means ± s.e. of *n* observations. Level of significance (*t*-test) from values of first line, * $P < 0.05$; ** $P < 0.005$.

The findings confirm the suggestion that excitation of muscarinic receptors decreases the availability of calcium for noradrenaline release.

References

MUSCHOLL, E. (1973). Muscarinic inhibition of the norepinephrine release from peripheral sympathetic fibres. *Proc. 5th Int. Congr. Pharmacology*, **4**, 440-457.