Variations in noradrenaline output with respect to stimulus frequency, train length and origin of the transmitter

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The release of labelled noradrenaline (NA) has been studied in the superfused rabbit portal vein. The vein was preincubated with ^{3}H-NA (2·5 μCi/ml, 20 ng/ml) for 2 h and then with ^{14}C-L-tyrosine (2·5 μCi/ml, 2·58 μg/ml) for 1 h. The tissue was set up for superfusion with Krebs solution at 37°C ; and was suspended between two platinum electrodes to allow electrical stimulation of the intramural sympathetic nerves (Hughes & Roth, 1971). The vein was stimulated at 5 or 20 Hz for 60 s after a 30 min equilibration period and the superfusate was collected for consecutive 20 s periods. Labelled NA and its methylated metabolites were isolated on Dowex-50W columns.

The efflux patterns of ^{3}H-NA and ^{14}C-NA showed a marked difference during electrical stimulation. ^{14}C-NA, which was newly synthesized from ^{14}C-tyrosine, appeared more rapidly in the superfusate than ^{3}H-NA and reached a peak outflow within 40 s, whereas the ^{3}H-NA reached a peak outflow after 60–100 s. This difference in efflux patterns was seen in four experiments. In two further experiments it was found that the specific activities of the ^{3}H-NA and of the ^{14}C-NA released during electrical stimulation were 2–3 times greater than the specific activities of the corresponding labels in the tissue.

The variation of endogenous NA output with frequency and train length was determined in the rabbit vas deferens treated with 5 μg/ml phenoxybenzamine (Hughes, 1971). The NA output per pulse increased more than fifty-fold when the number of pulses per train were increased from 10 to 300 ; for the same number of pulses however the output per pulse was always greater at 16 Hz than at 2 Hz. It was calculated that the fraction of the total tissue NA which was released per pulse varied from 4×10^{-6} to 4×10^{-4}, depending on the stimulus frequency and train length.

These results suggest that separate 'pools' of NA may be labelled by ^{3}H-NA and ^{14}C-tyrosine. Both of these 'pools' are available for release but they show temporal differences in mobilization which may reflect different functions. The mechanisms underlying the variations in fractional release with frequency and train length are unknown ; these mechanisms may represent an important means of controlling sympathetic nerve function.

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Effects of calcium and manganese on acetylcholine release from the myenteric plexus of guinea-pig and rabbit ileum

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Morphine depresses the evoked acetylcholine (ACh) release from the myenteric plexus of the ileum of the guinea-pig but not of the rabbit (Greenberg, Kosterlitz &

Waterfield, 1970; Lees, Kosterlitz & Waterfield, 1972). If calcium ions play an important role in the morphine-sensitive mechanism of ACh release, variations in calcium concentration should have different effects on evoked ACh release from the myenteric plexus of the guinea-pig and rabbit. Myenteric plexus-longitudinal muscle preparations of the two species were immersed in Krebs solution containing physostigmine (7·7 μM) and choline (20 μM). ACh release was evoked by supramaximal field stimulation with a fixed number of pulses (1–540) at 1 and 10 Hz. $CaCl_2$ concentrations were 2·54, 1·27, 0·64 and 0·32 mM. In the guinea-pig, single pulses induced a large release which was depressed by a reduction in calcium concentration from 2·54 to 0·64 mM; in the rabbit, the amount of ACh which was released by single pulses was below the sensitivity of the bioassay. The ACh release evoked by trains of 20 to 540 pulses at 1 and 10 Hz was depressed by lowering of the calcium concentration; this effect was more marked in the guinea-pig than in the rabbit.

$MnCl_2$ (1mM) depressed ACh output from the guinea-pig myenteric plexus, the reduction being greater at low than at high frequencies of stimulation. A depressant effect on the evoked release of ACh at the neuromuscular junction of the frog was demonstrated recently (Kajimoto & Kirpekar, 1972).

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AH 8165: A new short-acting, competitive neuromuscular blocking drug

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In the conscious mouse and chick 1,1′-azobis[3-methyl-2-phenyl-1H-imidazo(1,2-a) pyridinium]dibromide (AH 8165), 0·05–0·2 mg/kg i.v., caused a short lasting flaccid paralysis without sign of muscle fasciculations. These results indicated that AH 8165 could be a short lasting competitive neuromuscular blocking agent and further experiments were carried out, primarily in the anaesthetized cat, dog and monkey, to investigate the mechanism of action of this compound in more detail.

In the chloralose anaesthetized cat maintained on artificial ventilation AH 8165, 0·2 mg/kg i.v., caused a $74·0 \pm 8·3\%$ depression of maximal twitches of the tibialis anterior muscle elicited indirectly at 1 Hz. The blockade occurred within 10 s, it was not preceded by potentiation of the twitch response or accompanied by muscle fasciculations and recovery took 2–4 min. The degree of blockade was related to the frequency of nerve stimulation, at high rates (5 Hz) the blockade was more effective. In all subsequent experiments muscle twitches were elicited at a frequency of 1 Hz. AH 8165, 0·4 mg/kg i.v., caused almost complete neuromuscular blockade and during the recovery period responses of the muscle to indirect tetanic stimulation