Potentiation by cocaine of responses of the guinea-pig isolated tracheal chain to ethylnoradrenaline and α-methylnoradrenaline

Ethylnoradrenaline and α-methylnoradrenaline (corbasil) differ in structure from noradrenaline only by substitution of an ethyl or methyl group on the α-carbon atom of the ethylamine side-chain. The potencies of these two compounds in relaxing the guinea-pig isolated tracheal chain preparation and the influence of 10^{-5}M cocaine on their potency has been compared with noradrenaline. The preparation of tracheal chain and determination of the mean concentration to give 50% of the maximum relaxation to isoprenaline (EC50) have been described previously (Chahl & O'Donnell, 1967; O'Donnell, 1968). Two preparations from each animal were set up so that noradrenaline could be examined on one chain and ethylnoradrenaline or α-methylnoradrenaline on the other. The same experimental design was used on both preparations, i.e. a control concentration–response line to the amine, a line after 10^{-5}M cocaine had been in contact with the tissue for 0·5 h, and a further line after 10^{-5}M cocaine and 10^{-6}M propranolol had been in contact for 1 h. In another series of experiments, the shift of the normal concentration–response line to each drug by 10^{-6}M propranolol, after 1 h contact with the tissue, was determined.

In the absence of cocaine, ethylnoradrenaline was more potent than α-methylnoradrenaline or noradrenaline, which were equipotent (Table 1). All three drugs were potentiated by cocaine but not to the same extent (Table 1). Thus, in the presence of cocaine, noradrenaline became more potent than the other two drugs, which were now equipotent.

An aim of the study was to assess the true potency of the three drugs on the β-adrenoceptors of the tissue. If it is assumed that cocaine blocks the loss of drug to neuronal uptake sites, then the potency found with cocaine present should be a truer representation of the potency on β-adrenoceptors. All three drugs were potentiated by cocaine. However, the study was made on the (−)-isomer of noradrenaline and racemic (*erythro*) ethyl- and methyl-noradrenaline. If the (−)-isomer is the active component of the racemic mixture and if the (+)-isomer contributes little to the response and does not antagonize neuronal uptake, then potentiation by cocaine of the racemic mixture and the (−)-isomer should be the same. On the other hand, potency values would require correction for the presence of inactive (+)-isomer. The simplest correction is to double the estimated potency of ethyl- and methyl-noradrenaline. This type of correction has been previously applied by Foster (1966).

Table 1. *Effect of cocaine* (10^{-5}M) *on noradrenaline, methylnoradrenaline and ethylnoradrenaline potency on the guinea-pig tracheal chain.*

	Negative mean log EC50		Potentiation by cocaine (log units)
	Control	Cocaine	
(−) Noradrenaline	6·16 ± 0·29* (36)†	7·34 ± 0·25 (11)	1·18 ± 0·29
(±) α-Methylnoradrenaline ..	6·23 ± 0·32 (17)	6·94 ± 0·31 (9)	0·71 ± 0·33
(±) Ethylnoradrenaline	6·60 ± 0·22 (32)	7·02 ± 0·13 (14)	0·42 ± 0·20

* Standard deviation.
† Number of experimental concentration-response lines contributing to the mean log EC50.

Table 2. *Effect of propranolol on noradrenaline, methylnoradrenaline and ethylnoradrenaline potency on the guinea-pig tracheal chain.*

	Negative mean log EC50		Degree of block by propranolol (log units)	
	In presence propranolol (10^{-6}M)	In presence cocaine (10^{-5}M) and propranolol (10^{-6}M)	No cocaine	Cocaine
(±) Ethylnoradrenaline	3·94 ± 0·14* (5)†	4·01 ± 0·23 (15)	2·66 ± 0·22	3·01 ± 0·20
(−) Noradrenaline ..	4·68 ± 0·19 (5)	4·87 ± 0·29 (14)	1·48 ± 0·29	2·47 ± 0·28
(±) α-Methylnoradrenaline	4·70 ± 0·16 (7)	4·74 ± 0·20 (10)	1·53 ± 0·30	2·20 ± 0·27

* Standard deviation,
† Number of experimental concentration-response lines contributing to the mean log EC50.

Application of this correction to the potencies obtained in the presence of cocaine showed that the three drugs became equipotent, suggesting that substitution of an ethyl or methyl group on the α-carbon in the *erythro* configuration of noradrenaline might have little effect on its potency on β-adrenoceptors in this preparation. In contrast, this substitution resulted in a decrease in the potentiation by cocaine which could be interpreted as a loss of affinity for the cocaine-sensitive uptake mechanism in this tissue.

The block of the concentration–response line by propranolol (10^{-6}M) was examined in the absence and presence of cocaine, and ethylnoradrenaline was always blocked more than α-methylnoradrenaline or noradrenaline (Table 2). If it is assumed that, when uptake is blocked by cocaine, the control concentration–response line to ethylnoradrenaline is positioned correctly, then the greater block might be explained by the concentration–response line in the presence of propranolol and cocaine being positioned incorrectly. This could result from other effects of the high concentrations of drug used in the presence of 10^{-6}M propranolol, e.g. additional block of β-adrenoceptors by high concentrations of the (+)-isomer of ethylnoradrenaline. Alternatively, it could reflect differences in extraneuronal uptake of the three drugs and this could affect receptor concentration.

Ethylnoradrenaline and corbasil were generously donated by Sterling-Winthrop. This work was supported by grants from the National Health & Medical Research Council of Australia and the Asthma Foundation of Queensland.

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July 13, 1971

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