Relative potencies of some false transmitters on isolated human smooth muscle.

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Certain amines accumulate in sympathetic nerve endings and can be released by nerve stimulation. Alpha-methylnoradrenaline is formed in animals and man after administration of α-methyldopa, octopamine after monoamine oxidase inhibitors or tyramine, metaraminol from α-methyl-*m*-tyrosine, and *p*-hydroxynorephedrine from hydroxyamphetamine (Kopin, 1968) or from (+)-amphetamine (Thoenen, Hurlimann, Gey & Haefely, 1966).

The hypotension produced by monoamine oxidase inhibitors and α-methyldopa has been attributed to the production of sympathetic transmitters inferior in potency to noradrenaline. However, since the potency of α-methylnoradrenaline is of the same magnitude as noradrenaline in some experimental situations (Muscholl & Maitre, 1963; Conradi, Gaffney, Fink & Vangrow, 1965) but less in others (Day & Rand, 1964), the potencies of some of these so called "false transmitters" have been measured relative to noradrenaline on isolated human smooth muscle preparations by the method previously described (Coupar & Turner, 1969).

Potencies of (−)-α-*methylnoradrenaline* (α-*MN*), (−)-*octopamine* (*O*), (−)-*metaraminol* (*M*), (±)-*p-hydroxynorephedrine* (*pHNE*) *and* (−)-α-*methyloctopamine* (α*MO*) *relative to* (−)-*noradrenaline* (1·0) *as free bases on some human smooth muscle preparations.*

	Tissue	No. of specimens used	Response	Mean relative potencies			
				αMN	O	M	pHNE
Vein	Circular saphenous muscle	3	Contraction	0·6	0·08	0·04	
		3					0·004
Ileum	Longitudinal muscle	2	Relaxation	1·0	0·05	0·03	
		2		0·4	A	A	
		2					0·002
Colon	Longitudinal muscle	1	Relaxation	0·4	0·002	A	
		3		0·5	A	A	A
Stomach	Pyloric antrum longitudinal muscle	1	Inhibition of acetylcholine contractions	<1			

Autoinhibition (A) occurred in ileum and colon where O, M, and pHNE effects were smaller than the control noradrenaline maxima and caused inhibition of subsequent noradrenaline responses.

In all tissues studied the potency of α-methylnoradrenaline was the same as or slightly less than noradrenaline. The potencies of the other false transmitters on vein, ileum, and colon were much lower, the order being octopamine≏metaraminol> *p*-hydroxynorephedrine. Octopamine, metaraminol and *p*-hydroxynorephedrine sometimes induced autoinhibition of their effects, but autoinhibition did not occur in saphenous vein.

The results suggest that the antihypertensive effect of α-methyldopa is not due to α-methylnoradrenaline being less potent at adrenoceptive receptors.

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REFERENCES

CONRADI, E., GAFFNEY, T., FINK, D. & VANGROW, J. (1965). Reversal of sympathetic nerve blockade: a comparison of dopa, dopamine and norepinephrine and their α-methylated analogues. *J. Pharmac. exp. Ther.*, **150**, 26–33.

COUPAR, I. M. & TURNER, P. (1969). Relative potencies of sympathetic amines in human smooth muscle. *Br. J. Pharmac.*, **36**, 213*P*.
DAY, M. D. & RAND, M. J. (1964). Some observations on the pharmacology of *a*-methyldopa. *Br. J. Pharmac. Chemother.*, **22**, 72–86
KOPIN, I. J. (1968). False adrenergic transmitters. *Ann. rev. Pharmac.*, **8**, 377–393.
MUSCHOLL, E. & MAITRE, L. (1963). Release by sympathetic stimulation of *a*-methylnoradrenaline stored in the heart after administration of α-methyldopa. *Experientia*, **19**, 658–659.
THOENEN, H., HURLIMANN, K. F., GEY, K. F. & HAEFELY, W. (1966). Liberation of *p*-hydroxynorephedrine from the cat spleen by sympathetic nerve stimulation after pretreatment with an amphetamine. *Life Sci., Oxford*, **5**, 1715–1722.

Further evidence for an electrogenic sodium pump in a mammalian sympathetic ganglion.

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After ganglion cells of superior cervical ganglia from rabbit, rat or kitten have been depolarized by acetylcholine or carbachol, removal of the depolarizing agent results in a large hyperpolarization (Pascoe, 1956; Brown, 1966; Kosterlitz, Lees & Wallis, 1968). Since Kosterlitz *et al.* (1968) found that the rates of onset and decay of this hyperpolarization recorded by the sucrose-gap method were reduced in a potassium-free solution, they suggested that the potential was generated as a result of active extrusion of Na^+ by an electrogenic sodium pump, which requires extracellular K^+.

Further evidence shows that: (*a*) the hyperpolarization is still present when the membrane potential approaches E_K and its magnitude is not linearly related to the ratio $[K^+]_i/[K^+]_o$; (*b*) it cannot be attributed to movement of Cl^-; (*c*) is prevented by ouabain (10 μM); (*d*) it is reduced when $[Na^+]_o$ or $[Ca^{2+}]_o$ is reduced; (*e*) its rates of onset and decay are reduced in a glucose-free solution.

However, a diffusion barrier round the cells might allow an electrically neutral pump to generate the potential if the potassium ion concentration within the barrier fell. This possibility is excluded by the following experiment: in potassium-free solution, acetylcholine causes a depolarization, which is followed slowly by a small hyperpolarization; when now $[K^+]_o$ is raised to 6 mM, a large, rapid hyperpolarization

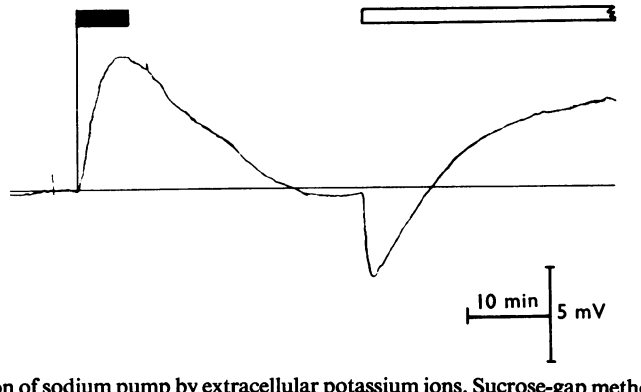

FIG. 1. Activation of sodium pump by extracellular potassium ions. Sucrose-gap method of recording; depolarization of ganglion upwards. Ganglion bathed in potassium-free Krebs solution for 23 min before commencement of record. Eserine (60 μM) present throughout the experiment. Black bar, ganglion exposed to acetylcholine 110 μM. White bar, $[K^+]$ of Krebs solution bathing ganglion raised to 6 mM. Note that the resting potential in the presence of 6 mM K^+ was eventually −4·6 mV, of which about 40% was due to d.c. drift.