Inhibition of the re-uptake of neuronally liberated noradrenaline and α-receptor blocking action of some ergot alkaloids.

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On the isolated, perfused spleen preparation of the cat with sympathetic postganglionic nerve stimulation (Thoenen, Hürlimann & Haefely, 1963), ergotamine and dihydroergotamine increase the content of neuronally liberated noradrenaline in the perfusate (Salzmann & Pacha, 1968; Salzmann, Pacha, Taeschler & Weidmann, 1968). This effect is observed with numerous other compounds including α-receptor blocking agents. Brown & Gillespie (1957) have suggested that blockade of α-receptors is a possible explanation of the phenomenon, but more recently inhibition of the re-uptake of noradrenaline into the stores was considered to be mainly responsible (Thoenen, Hürlimann & Haefely, 1964).

The ergot alkaloids possess a wide spectrum of pharmacological activities with great differences in potency. Some, for example, have high α-receptor blocking activity, whereas others have little or no activity. This was the reason to study some other ergot alkaloids, and also phenoxybenzamine on the spleen preparation, and to relate their effect on the noradrenaline content of the perfusate to their α-blocking activity. The results are listed in Table 1. They show that a marked increase of the content of neuronally liberated noradrenaline can also be produced by ergot alkaloids which have only little α-blocking activity.

These results suggest that the increase of neuronally liberated noradrenaline which is observed with some ergot alkaloids is not due to a blockade of α-receptors, but to

TABLE 1. *α-Receptor blocking action and inhibition of the re-uptake of neuronally liberated noradrenaline by some ergot alkaloids and phenoxybenzamine*

Compounds	*a*-Receptor blocking action				Increase of the noradrenaline content in the perfusate
	Isolated guinea-pig seminal vesicle; ED50 (in ng/ml) for the inhibition of adrenaline (0·5–2 μg/ml) reaction	Blood pressure of the anaesthetized dog (aprobarbital); ED50 (in mg/kg i.v.) for the inhibition of B.P. increase after Adrenaline (0·3–3 μg/kg i.v.)	Noradrenaline (0·3–3 μg/kg i.v.)	Isolated, perfused spleen of the cat; max. % inhibition of the spleen contraction provoked by nervous stimulation after 1 μg/min i.a.†	Isolated perfused spleen of the cat; max. % increase of the content of neuronally liberated noradrenaline after 1 μg/min i.a.†
1-Methyl-ergot-amine	19·6	No inhibition up to 3 mg/kg i.v.		−16	+200
Ergotamine	14·0	No inhibition up to 3 mg/kg i.v.		−25	+136
Hydergine*	0·66	0·13	1·0	−40	+113
Dihydroergotamine	2·00	0·51	1·2	−70	+208
Phenoxybenzamine	0·13	0·50	3·9	−85	+278

*The single components of hydergine—dihydroergocornine, dihydroergocristine and dihydroergokryptine—show the same effects (*a*-receptor blocking action and inhibition of the re-uptake of noradrenaline) as hydergine. (Instead of continuous perfusions, single injections were given in these experiments on the isolated perfused spleen.)

†In addition to 1 μg/min i.a., the effects of continuous infusions with 0·01, 0·05, 0·1, 0·2, 0·5, 2, 5, 10 and 100 μg/min i.a. were also examined.

an inhibition of the re-uptake. This effect of ergot alkaloids, little known to date, might be significant for the pharmacological characterization of these substances.

REFERENCES

BROWN, G. L. & GILLESPIE, J. S. (1957). The output of sympathetic transmitter from the spleen of the cat. *J. Physiol., Lond.*, **138**, 81–102.

SALZMANN, R. & PACHA, W. (1968). Vergleichende Untersuchungen über die Beeinflussung adrenerger Reaktionen durch Ergotamin und Dihydroergotamin an verschiedenen Versuchsmodellen. *Helv. physiol. pharmac. Acta.*, **26**, *CR* 246–*CR* 248.

SALZMANN, R., PACHA, W., TAESCHLER, M. & WEIDMANN, H. (1968). The effect of ergotamine on humoral and neuronal actions in the nictitating membrane and the spleen of the cat. *Naunyn-Schmiedebergs Arch. Pharmak. u. exp. Path.*, **261**, 360–378.

THOENEN, H., HÜRLIMANN, A. & HAEFELY, W. (1963). The effect of postganglionic sympathetic stimulation on the isolated, perfused spleen of the cat. *Helv. physiol. pharmac. Acta*, **21**, 17–26.

THOENEN, H., HÜRLIMANN, A. & HAEFELY, W. (1964). Dual site of action of phenoxybenzamine in the cat's spleen; blockade of *a*-adrenergic receptors and inhibition of re-uptake of neurally released norepinephrine. *Experientia*, **20**, 272–273.

Removal of 5-hydroxytryptamine by rat isolated lung.

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5-Hydroxytryptamine (5-HT) is removed from the circulation by the lung (Axelrod & Inscoe, 1963; Gaddum, Hebb, Silver & Swan, 1953; Thomas & Vane, 1967). The isolated lungs of rat and guinea-pig perfused with Krebs solution will also remove 5-HT; we have studied this removal using the rat isolated lung.

Rats were anaesthetized with pentobarbitone and the pulmonary artery and trachea cannulated. The lungs were then dissected free, inflated and perfused via the pulmonary artery with oxygenated Krebs solution maintained at 37°C. The lung perfusate was superfused over rat stomach strips (Vane, 1957) to estimate the 5-HT present. The amount of 5-HT removed by the lungs was determined by comparing the responses of the rat stomach strip to infusions of 5-HT made directly to the assay tissues with those to infusions of 5-HT made into the pulmonary arterial cannula. Rat lungs removed 90–98% of the 5-HT passing through them, and this degree of removal was maintained when the infusions (3–5 min long) were repeated up to 4 times. The pressure in the pulmonary artery cannula averaged 10 mm Hg and during infusion of 5-HT (10–40 ng/ml) the pressure changes were minimal.

When amitriptyline (10^{-6}–10^{-5}M) or desmethylimipramine (10^{-5}M) were infused into the lungs for 5 min before and during the infusion of 5-HT, more 5-HT (20–50%) appeared in the lung perfusate than under control conditions (2–10%). Reserpine had no effect on the disappearance of 5-HT in rat lung either when the rats were pretreated (2 mg/kg intraperitoneally 48 and 24 hr before use) or when it was infused concomitantly (10^{-5}M) with 5-HT. The monoamine oxidase inhibitors, mebanazine (10^{-5}M) and iproniazid (10^{-4}M) did not increase the peak of the contractions of the rat stomach strip which occurred during infusions of 5-HT into the lungs, but the contractions persisted for 40–50 min compared with 6–9 min during infusions into untreated lungs. All these contractions were antagonized by methysergide (10 ng/ml), suggesting that the prolonged contraction was due to 5-HT reappearing in the perfusate after the initial removal into some structure in the lungs. These two monoamine oxidase inhibitors do not affect uptake of catecholamines by rat heart (Iversen, 1965).