Pharmacological characterization of presynaptic α-adrenoceptors which regulate cholinergic activity in the guinea-pig ileum

G.M. DREW

Department of Pharmacology, Allen & Hanburys Research Ltd, Ware, Hertfordshire SG12 0DJ, U.K.

Field stimulation of the guinea-pig ileum releases acetylcholine from cholinergic nerves and causes contraction of the longitudinal muscle. The contraction is inhibited by α- and β-adrenoceptor agonists. β-Adrenoceptor agonists stimulate β-adrenoceptors located on the smooth muscle, thereby causing muscle relaxation, whereas α-adrenoceptor agonists act by reducing the release of acetylcholine from the cholinergic nerves. The α-adrenoceptors involved are located on the cholinergic nerve terminals (Knoll & Vizi, 1971; Kosterlitz & Lees, 1972).

The release of noradrenaline from sympathetic nerves is modulated by α-adrenoceptors located at the nerve terminals. These presynaptic α-adrenoceptors differ from postsynaptic α-adrenoceptors in their sensitivity to agonists (Starke, Endo & Taube, 1975; Drew, 1976) and to antagonists (Dubocovich & Langer, 1974; Blakely & Summers, 1976; Drew, 1976). The presynaptic α-adrenoceptors are characteristically less sensitive than the postsynaptic α-adrenoceptors to the agonist effects of phenylephrine and methoxamine and to the antagonist actions of thymoxamine, labetalol and phenoxybenzamine. Langer (1974) has suggested, therefore, that α-adrenoceptors should be subclassified as α_1 (postsynaptic type) and α_2 (presynaptic type).

The differential sensitivity of pre- and postsynaptic adrenoceptors to α-adrenoceptor agonists and antagonists has been used to characterize the α-adrenoceptors located on the cholinergic nerve terminals in the guinea-pig ileum. Segments of ileum were suspended under 0.5–1.0 g tension in Krebs solution, at 37°C, containing propranolol (0.3 μg/ml). Field stimulation (0.1 Hz; 1 ms; supramaximal voltage) was delivered using platinum electrodes, 12 mm apart, and the resulting twitch responses were recorded isometrically.

Agonists were added to the bathing fluid in a cumulative-concentration schedule. Clonidine (0.1–10 ng/ml), oxymetazoline (0.1–100 ng/ml) and xylazine (0.1–100 ng/ml) caused concentration dependent reductions in the twitch response. The maximum effects of these drugs corresponded to 85–95% inhibition of the twitch response. Phenylephrine and methoxamine were 1000–10,000 times less potent than clinidine.

Phentolamine (0.01, 0.1 and 1.0 μg/ml) and piperoxan (0.03, 0.1 and 0.3 μg/ml) were potent antagonists of the inhibitory effect of clonidine. In contrast, thymoxamine (1, 3 and 10 μg/ml) was only weakly active and labetalol (0.3 and 1 μg/ml) was inactive against clonidine.

These results suggest that the presynaptic α-adrenoceptors located on the parasympathetic nerve terminals in the guinea-pig ileum are of the same type as those located on cholinergic nerve terminals—that is α_2.

References

BLAKELY, A.G.H. & SUMMERS, R.J. (1976). The effects of AH 5158 on the overflow of transmitter and the uptake of [^{3}H]-(–)-noradrenaline in the cat spleen. *Br. J. Pharmac.*, **56**, 364P–365P.

DREW, G.M. (1976). Effects of α-adrenoceptor agonists and antagonists on pre- and postsynaptically located α-adrenoceptors. *Eur. J. Pharmac.*, **36**, 313–320.

DUBOCOVICH, M.L. & LANGER, S.Z. (1974). Negative feedback regulation of noradrenaline release by nerve stimulation in the perfused cat's spleen: differences in potency of phenoxybenzamine in blocking the pre- and post-synaptic adrenergic receptors. *J. Physiol. (Lond.)*, **237**, 505–519.

KNOLL, J. & VIZI, E.S. (1971). Effect of frequency of stimulation on the inhibition by noradrenaline of the acetylcholine output from parasympathetic nerve terminals. *J. Physiol. (Lond.)*, **41**, 263–272.

KOSTERLITZ, H.W. & LEES, G.M. (1972). Interrelationships between adrenergic and cholinergic mechanisms. In *Catecholamines, Handb. exp. Pharmac.* ed. Blaschko, H. & Muscholl, E., pp. 762–812. N.S., vol. **33**. Berlin and Heidelberg: Springer-Verlag.

LANGER, S.Z. (1974). Presynaptic regulation of catecholamine release. *Biochem. Pharmac.*, **23**, 1793–1800.

STARKE, K., ENDO, T. & TAUBE, H.D. (1975). Relative pre- and postsynaptic potencies of α-adrenoceptor agonists in the rabbit pulmonary artery. *Naunyn-Schmiedebergs Arch. Pharmac.*, **291**, 55–78.