phentolamine, another α-adrenoceptor blocking agent, had no effect on the size of contraction, so it was of interest to investigate if the effect of thymoxamine was due to α-adrenoceptor blockade.

Phenylephrine, a compound thought to act exclusively on α-adrenoceptors (Goodman & Gilman, 1970), increases the contractions of the vas deferens in response to nerve stimulation. α-Adrenoceptor blockade antagonizes this effect and thus displaces the concentration-effect curve for phenylephrine to the right. Although 25 ng/ml thymoxamine reduced the contraction size by 16%, it did not significantly antagonize phenylephrine ($P > 0.05$); however, antagonism was apparent with higher concentrations of thymoxamine. This indicates that thymoxamine has pharmacological actions distinct from α-adrenoceptor blockade. These actions are detectable at extremely low concentrations of the drug and therefore throw doubt on its specificity as an α-adrenoceptor blocking agent. The nature of these actions is being investigated.

I thank D. W. Snowdon for preparing the figure and William Warner & Co. Ltd. for supplying thymoxamine.

REFERENCES

BIRMINGHAM, A. T. & SZOLCSANYI, J. (1965). Competitive blockade of adrenergic α-receptors and histamine receptors by thymoxamine. *J. Pharm. Pharmac.*, **17**, 449–458.

BIRMINGHAM, A. T. & WILSON, A. B. (1963). Preganglionic and postganglionic stimulation of the guinea-pig isolated vas deferens preparation. *Br. J. Pharmac. Chemother.*, **21**, 569–580.

GOODMAN, L. S. & GILMAN, A. (1970). *The Pharmacological Basis of Therapeutics*, pp. 484–485. New York: MacMillan.

MCEWEN, L. M. (1956). The effect on the isolated rabbit heart of vagal stimulation and its modification by cocaine, hexamethonium and ouabain. *J. Physiol., Lond.*, **131**, 678–689.

Effects of sympathomimetic amines on rabbit platelet aggregation *in vitro*

LIISA AHTEE and F. MICHAL*

Department of Pharmacology, University of Helsinki, and Department of Pharmacology, Royal College of Surgeons, Lincoln's Inn Fields, London, WC2

Adrenaline and noradrenaline can produce aggregation of blood platelets and potentiate aggregation induced by adenosine diphosphate; this action is thought to be mediated at sympathomimetic receptors on the platelet membrane (Mills & Roberts, 1967). We have studied the effects of several directly and indirectly acting sympathomimetic compounds to establish the structural specificity of the receptors involved in aggregation and the preceding morphological change of platelets.

Velocities of the morphological change and aggregation were measured in 1 ml volumes of rabbit citrated platelet-rich plasma at 37° C (Michal & Born, 1971). Drugs were dissolved in buffered saline pH 7 and added in volumes not exceeding 20 μl so that the final concentrations were 10^{-8}–2×10^{-3} M.

(−)-Adrenaline (2×10^{-6} M) and (−)-noradrenaline (2×10^{-4} M) caused platelets to aggregate but the morphological change needed only about 1/10 of these concentrations. None of the other catecholamines examined caused aggregation or shape change in concentrations up to 2×10^{-3} M except dopamine, which at 2×10^{-4} M caused platelets to change shape. None of seventeen non-catecholamines aggregated platelets but tyramine (2×10^{-3} M), amphetamine (10^{-4} M), mephentermine (2×10^{-4} M) and phenylethylamine (2×10^{-4} M) induced the morphological change.

Most of the compounds accelerated platelet aggregation caused by low concentrations of ADP but (+)-isoprenaline (2×10^{-4} M) and (±)-orciprenaline (2×10^{-3} M)

only inhibited aggregation. Some compounds potentiated at low concentrations but inhibited at higher concentrations; these compounds included (—)-isoprenaline, octopamine, (—)-metaraminol and mephentermine. The potentiating action of tyramine, synephrine, naphazoline and clonidine also disappeared with increasing concentrations but did not inhibit at the concentrations used.

The substances which potentiated ADP most were (—)-adrenaline (10^{-8} M), (—)-noradrenaline and α-methylnoradrenaline (2×10^{-8} M), clonidine (2×10^{-7} M), phenylephrine (10^{-6} M), dopamine, ethylnoradrenaline and naphazoline (2×10^{-6} M), (+)-amphetamine (5×10^{-6} M), tyramine (10^{-5} M), (—)-metaraminol, (±)-amphetamine and phenylethylamine (2×10^{-5} M). The potentiating effect of most of the compounds rapidly reached a plateau after which no additional increase occurred. The initial rate of aggregation and the maximal extent of aggregation induced by ADP were increased by over 100% by (—)-adrenaline, (—)-noradrenaline, α-methylnoradrenaline, dopamine, (±)-amphetamine, ethylnoradrenaline, (+)-amphetamine and phenylethylamine. Phenylephrine, tyramine and (—)-metaraminol increased aggregation by more than 50%. Although clonidine was effective at low concentration it never enhanced ADP aggregation by more than 40%. Tetrahydrozoline and xylometazoline were inactive.

Our experiments support the conclusion that the catecholamine receptors on blood platelets are α-type. The most active drugs had the catecholamine structure with *para* and *meta* hydroxyl groups, but the hydroxyl group at the *meta* position seems to be the more important for the enhancement of platelet aggregation. The shape change and potentiation of ADP aggregation caused by indirectly acting sympathomimetics could result from the release of platelet constituents.

REFERENCES

MICHAL, F. & BORN, G. V. R. (1971). Effect of the rapid shape change of platelets on the transmission and scattering of light through plasma. *Nature, New Biol.*, **231**, 220–222.

MILLS, D. C. B. & ROBERTS, G. C. K. (1967). Effects of adrenaline on human blood platelets. *J. Physiol., Lond.*, **193**, 443–453.

Possible allosteric interaction between pharmacological receptors in guinea-pig vas deferens

ALLAN T. IIJIMA and R. J. REIFFENSTEIN* (introduced by M. J. NEAL)

Department of Pharmacology, University of Alberta, Edmonton, Canada

Stripped vas deferens preparations were mounted in Krebs solution at 34° C and isotonic contractions obtained under 0·5 g tension. Only supramaximal concentrations of all agonists were used. Differences reported are significant at the 5% level by paired-data *t*-test. Responses to supramaximal doses of noradrenaline ($1–2\times10^{-4}$ M) were completely blocked by exposing the tissue to phenoxybenzamine (10^{-8} to 10^{-7} M) for 5 min, a treatment which reduced but did not block the responses to methacholine ($0·5–3\times10^{-4}$ M). Subsequently, noradrenaline added in the presence of methacholine caused a further contraction. If the agonists were added in the reverse order, the final equilibrium was the same although the response to noradrenaline was absent and the response to methacholine was typical of those due to noradrenaline (Fig. 1). This phenomenon still occurs in the presence of hexamethonium, after pretreatment of the animals with reserpine (after which the tissues did not respond to tyramine), or after cold storage of the tissue for several days. The revived response to nor-