REFERENCES

AGHAJANIAN, G. K., ROSECRANS, J. A. & SHEARD, M. H. (1967). *Science*, **156**, 402–403.

CHASE, T. N., KATZ, R. I. & KOPIN, I. J. (1969). *J. Neurochem.*, **16**, 607–615.

CORRODI, H., FUXE, K., HÖKFELT, T., LIDBRINK, P. & UNGERSTEDT, U. (1973). *J. Pharm. Pharmac.*, **25**, 409–412.

ENERO, M. A., LANGER, S. Z., ROTHLIN, R. P. & STEFANO, F. J. E. (1972). *Br. J. Pharmac.*, **44**, 672–688.

FARNEBO, L.-O. (1971). *Z. Zellforsch.*, **122**, 503–519.

FARNEBO, L.-O. & HAMBERGER, B. (1970). *J. Pharm. Pharmac.*, **22**, 855–857.

FARNEBO, L.-O. & HAMBERGER, B. (1971a). *Br. J. Pharmac.*, **43**, 97–106.

FARNEBO, L.-O. & HAMBERGER, B. (1971b). *Acta physiol. scand., Suppl.* **371**, 35–44.

FARNEBO, L.-O. & HAMBERGER, B. (1973). In: *Frontiers in Catecholamine Research*, Pergamon Press (in the press).

FARNEBO, L.-O. & HAMBERGER, B. (1974). *J. Pharm. Pharmac.*, **26**, 644–646.

FUXE, K., HÖKFELT, T. & UNGERSTEDT, U. (1968). *Advances in Pharmac.*, **6A**, 235–251.

KATZ, R. I. & KOPIN, I. J. (1969). *Pharmac. Res. Comm.*, **1**, 54–62.

MONACHON, M.-A., BURKARD, W. P., JALFRE, M. & HAEFELY, W. (1972). *Naunyn-Schmiedeberg's Arch. Pharmac.*, **274**, 192–197.

STARKE, K. (1971). *Naturwissenschaften*, **58**, 420.

STARKE, K. & MONTEL, H. (1973). *Neuropharmacology*, **12**, 1073–1080.

WERNER, U., WAGNER, J. & SCHÜMANN, H. J. (1971). *Arch. Pharmak.*, **268**, 102–113.

Influence of α- and β-adrenoceptors on the release of noradrenaline from field stimulated atria and cerebral cortex slices

Noradrenaline release from peripheral and central noradrenaline nerves can be influenced by drugs affecting α-adrenoceptors (Häggendal, 1970; Farnebo & Hamberger, 1970, 1971a, b; Starke, 1971; Kirpekar & Puig, 1971; Enero, Langer & others, 1972; Starke & Altmann, 1973). Stimulation of α-adrenoceptors depresses noradrenaline release while blockade of α-adrenoceptors increases it. The release of noradrenaline is under physiologic conditions probably controlled by the synaptic concentration of the amine. It has been suggested that this feed-back control of noradrenaline release is mediated via presynaptic α-adrenoceptors, because drugs affecting α-adrenoceptors have been found to be effective also in heart tissue where the adrenoceptor of the effector cell is of the β type (Farnebo & Hamberger,1971a; Starke, 1971; Enero & others, 1972; Starke & Altmann, 1973).

β-Adrenoceptors seem to be of small significance in the regulation of noradrenaline release in the guinea-pig heart (Werner, Wagner & Shümann, 1971), while little is known about the role of β-adrenoceptors in the regulation of noradrenaline release in the brain. The aim of this investigation was to study the release of noradrenaline from field stimulated mouse atria and rat cerebral cortex slices and to compare the effect of α- and β-adrenoceptor stimulating and blocking drugs on this release.

Mouse isolated atria (N.M.R.I.; weight about 2–3 mg) or rat cerebral cortex slices (Sprague-Dawley; weight about 5 mg) were incubated with (±)-[7-^{3}H] noradrenaline (^{3}H-NA) (5–10 Ci mmol^{-1}, Radiochemical Centre, Amersham) 10^{-7}M for 30 min at 37°. Single atria or slices were then superfused by Krebs-Ringer bicarbonate buffer to which the drug to be tested was added. After 30 min superfusion the tissue was stimulated by an electrical field (10 Hz, 12 mA, 2 ms, biphasic pulses) for 10 min (atria) or 2 min (cortex slices) and then further superfused for 15 or 13 min respectively (Baldessarini & Kopin, 1967; for details see Farnebo & Hamberger, 1970, 1971a,b). Total radioactivity in the superfusate and tissue was

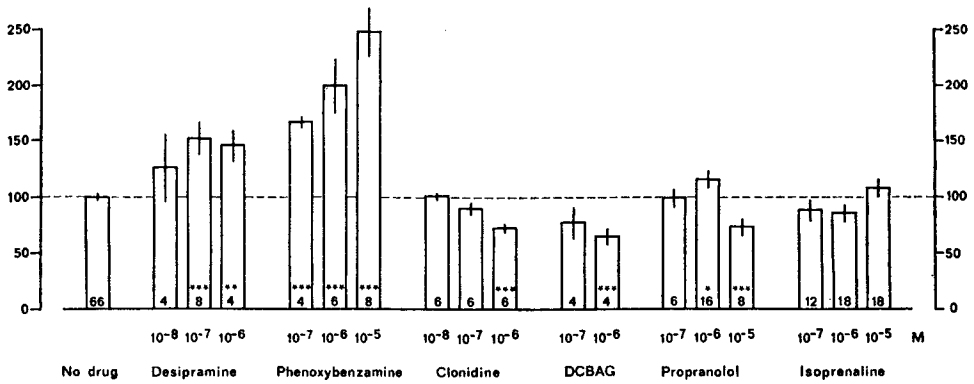

FIG. 1. Stimulation-induced overflow of radioactivity (% drug-free control : ordinate) from mouse isolated atria preincubated with ^{3}H-NA (10^{-7}M). Significance of differences from the control (*t*-test) and number of experiments are given at the bottom of the columns. $*P<0{\cdot}05$, $**P<0{\cdot}01$, $***P<0{\cdot}001$.

determined by liquid scintillation counting. The stimulation-induced overflow of radioactivity was calculated as a percentage of the amount of radioactivity in the tissue at the onset of stimulation (see Farnebo & Hamberger, 1971a). The results are presented as per cent of drug-free controls.

In the mouse atria the effects of membrane pump blockade and α-adrenoceptor blockade or stimulation were found to closely resemble the results obtained in the field-stimulated rat iris (Fig. 1) (Farnebo & Hamberger, 1971a). Thus, desipramine 10^{-7}M increased the stimulation-induced overflow by about 50%. Phenoxybenzamine 10^{-6}M doubled the stimulation-induced overflow. As phenoxybenzamine is a much less potent inhibitor of the membrane pump than desipramine (Farnebo & Hamberger, 1971a) it seems probable that the effect of phenoxybenzamine is to a large extent due to its α-adrenoceptor blocking activity. The α-adrenoceptor stimulating drugs clonidine and DCBAG (2,6-dichlorobenzylidene aminoguanidine) (Bolme, Corrodi & Fuxe, 1973) decreased the stimulation-induced overflow to about 70% of the control. In cerebral cortex slices phentolamine significantly increased and DCBAG significantly decreased the stimulation-induced overflow (Fig. 2).

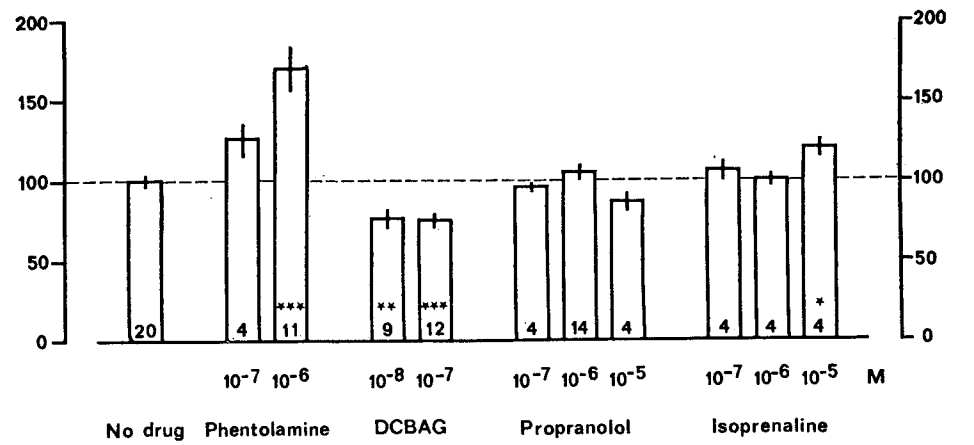

FIG. 2. Stimulation-induced overflow of radioactivity (% drug-free control : ordinate from rat cerebral cortex slices preincubated with ^{3}H-NA (10^{-7}M). Significance of differences from the control (*t*-test) and number of experiments are given at the bottom of the columns. $*P<0{\cdot}05$, $**P<0{\cdot}01$, $***P<0{\cdot}001$.

The effect of clonidine on noradrenaline release is less pronounced in the mouse atria than in the perfused guinea-pig heart (Starke & Schümann, 1971). One probable explanation for this is the higher frequency of stimulation used in this study. When a high frequency of stimulation is used, more noradrenaline will be released. This causes a higher concentration in the synapse and thus the feed-back inhibition of its release will be more effective. Consequently clonidine will in this case cause a less pronounced decrease of noradrenaline release (Starke & Altmann, 1973).

Propranolol 10^{-6}M slightly enhanced the stimulation-induced overflow in the mouse atria, probably due to its uptake inhibiting property (Foo, Jarrett & Stafford, 1968; Werner & others, 1971). Propranolol 10^{-5}M considerably reduced the stimulation-induced overflow. This effect is most likely due to the local anaesthetic property of this drug (Day, Owen & Warren, 1968; Werner & others, 1971). Isoprenaline did not significantly alter the stimulation-induced overflow from the mouse atria. In cerebral cortex slices propranolol was without effect, while isoprenaline 10^{-5}M caused a 20% increase of the stimulation-induced overflow, possibly due to slight inhibition of the membrane pump (Iversen, 1967).

The present results confirm the earlier findings that noradrenaline release also in the heart can be modified by drugs affecting α-adrenoceptors. This seems to speak strongly in favour of the view of a presynaptic localization of the release regulating α-adrenoceptors. It does not seem likely that β-adrenoceptors play any part in the physiologic regulation of noradrenaline release from peripheral or central noradrenaline nerve terminals.

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REFERENCES

BALDESSARINI, R. J. & KOPIN, I. J. (1967). *J. Pharmac. exp. Ther.*, **156**, 31–38.

BOLME, P., CORRODI, H. & FUXE, K. (1973). *Europ. J. Pharmac.*, **23**, 175–182.

DAY, M. D., OWEN, D. A. A. & WARREN, P. R. (1968). *J. Pharm. Pharmac.*, **20**, 130S-134S.

ENERO, M. A., LANGER, S. Z., ROTHLIN, R. P. & STEFANO, F. J. E. (1972). *Br. J. Pharmac.*, **44**, 672–688.

FARNEBO, L.-O. & HAMBERGER, B. (1970). *J. Pharm. Pharmac.*, **22**, 855–857.

FARNEBO, L.-O. & HAMBERGER, B. (1971a). *Br. J. Pharmac.*, **43**, 97–106.

FARNEBO, L.-O. & HAMBERGER, B. (1971b). *Acta physiol. scand., Suppl.* **371**, 35–44.

FOO, J. W., JOWETT, A. & STAFFORD, A. (1968). *Br. J. Pharmac.*, **34**, 141–147.

HÄGGENDAL, J. (1970). In: *New Aspects of Storage and Release Mechanisms of Catecholamines. Bayer Symposium II.* pp. 100–109. Editors: Schümann, H. J. and Kronberg, G. Berlin-Heidelberg-New York: Springer.

IVERSEN, L. L. (1967). *The Uptake and Storage of Noradrenaline in Sympathetic Nerves*, Cambridge University Press.

KIRPEKAR, S. M. & PUIG, M. (1971). *Br. J. Pharmac.*, **43**, 359–369.

STARKE, K. (1971). *Naturwissenschaften*, **58**, 420.

STARKE, K. & ALTMANN, K. P. (1973). *Neuropharmacology*, **12**, 339–347.

STARKE, K. & SCHÜMANN, H. J. (1971). *Experientia*, **27**, 70–71.

WERNER, U., WAGNER, J. & SCHÜMANN, H. J. (1971). *Arch. Pharmak.*, **268**, 102–113.