the acute administration of morphine has recently been reported (Yarbrough, Buxbaum & Sanders-Bush, 1971). The present studies were undertaken to determine first, if such an effect is shared by other acutely administered analgesics and, secondly, if pretreatment with the narcotic antagonist naloxone prevents the morphine-induced increase in rat brain 5-HT turnover.

Male Sprague-Dawley rats weighing 200–250 g were used and brain levels of 5-HT and 5-hydroxyindole acetic acid (5-HIAA) were assayed fluorometrically. Drug-induced changes in the increased brain levels of 5-HT and 5-HIAA following the administration of pargyline and probenecid respectively were used as an index of alteration in brain 5-HT turnover (Neff, Lin, Ngai & Costa, 1969).

The I.P. injection of morphine (20 mg/kg), methadone (10 mg/kg), pethidine (50 mg/kg) and pentazocine (60 mg/kg) doses expressed as free base, 1 h prior to sacrifice had no effect on rat brain 5-HT steady state levels. Pentazocine and methadone had no effect on the brain content of 5-HIAA but the levels were significantly increased by morphine. Conversely, a significant decrease in 5-HIAA levels was produced by pethidine. The increase in brain 5-HIAA content following probenecid administration was significantly increased by morphine. Further evidence of a drug-induced increase in 5-HT turnover was the finding that the increase in brain 5-HT content following pargyline administration was significantly augmented by morphine. Unlike the situation with morphine, rat brain 5-HT turnover was unaffected by methadone, pethidine and pentazocine as indicated by the lack of drug-induced alterations in either the increased 5-HT or 5-HIAA levels following pargyline or probenecid administration.

The ability of morphine to potentiate the increases in brain levels of both 5-HT and 5-HIAA following the injection of pargyline and probenecid was antagonized by pretreatment with naloxone (5 mg/kg).

The results of this study confirm the reported ability of acutely administered morphine to increase rat brain 5-HT turnover. Furthermore, the morphine-induced increase in 5-HT turnover is prevented by the specific narcotic antagonist naloxone. Finally, rat brain 5-HT turnover is unaltered by acutely administered methadone, pethidine and pentazocine.

REFERENCES

NEFF, N. H., LIN, R. C., NGAI, S. H. & COSTA, E. (1969). In: *Advances in Biochemical Psychopharmacology*, Vol. 1, ed. Costa, E. & Greengard, P., pp. 91–109. Raven Press, New York.

SAMANIN, R., GUMULKA, W. & VALZELLI, L. (1970). Reduced effect of morphine in midbrain raphé lesioned rats. *Eur. J. Pharmac.*, **10**, 339–343.

TENEN, S. S. (1968). Antagonism of the analgesic effect of morphine and other drugs by p-chlorophenylalanine, a serotonin depletor. *Psychopharmacologia*, **12**, 278–285.

YARBROUGH, G. G., BUXBAUM, D. M. & SANDERS-BUSH, E. (1971). Increased serotonin turnover in the acutely morphine treated rat. *Life Sci.*, **10**, Part 1, 977–983.

Desmethylimipramine and the hypotensive action of clonidine in the rabbit

ROBIN H. BRIANT* and J. L. REID (introduced by C. T. DOLLERY)

Department of Clinical Pharmacology, Royal Postgraduate Medical School, London W12

Clonidine reduces arterial pressure both when administered systemically and when introduced directly into the cisterna magna. It has been proposed that its hypo-

tensive effects are mediated by a direct α-adrenoceptor agonist action on the central nervous system (Bolme & Fuxe, 1971). The effect of pre-treatment with desmethylimipramine (DMI) 20 min before intravenous clonidine (3–100 μg/kg) and intracisternal clonidine (1 and 3 μg/kg) was investigated in groups of normotensive rabbits (n=4–7). Arterial pressure was measured directly with a strain gauge transducer via a catheter in the central artery of the ear.

DMI (2·5 mg/kg, i.v.) caused a transient reduction in mean arterial pressure. Clonidine was given twenty min after DMI. At this time, the arterial pressure was not significantly different in control and DMI pre-treated groups, but the pressor sensitivity to intravenous noradrenaline was increased in DMI treated animals (mean dose ratio 4·3 : 1, n=4). The hypotensive action of intravenous clonidine in unanaesthetized rabbits was markedly reduced at all doses tested. The acute transient pressure rise after clonidine did not differ significantly in the two groups (control 24·8 ± S.E. of mean 3·28 mmHg; DMI pretreated 25·6 ± S.E. of mean 2·68 mmHg). Clonidine 30 μg/kg reduced the mean arterial pressure by 17·6 ± S.E. of mean 3·57 mmHg in controls, and 5·3 ± S.E. of mean 0·99 mmHg in DMI pretreated animals. Clonidine 1 μg/kg injected intracisternally in sodium pentobarbitone anaesthetized rabbits reduced the mean arterial pressure by 37·0 ± S.E. of mean 2·33 mmHg in controls while in DMI pretreated animals, the fall was only 10·2 ± S.E. of mean 2·67 mmHg.

These results indicated that the hypotensive effect of intravenous and intracisternal clonidine is greatly reduced by DMI. It is proposed that clonidine exerts its depressor effect by an action on noradrenergic neurones and not as a direct receptor agonist. This hypothesis is supported by observations that clonidine inhibits the release of noradrenaline following nerve stimulation from the isolated rabbit heart (Werner, Starke & Schümann, 1972) and that destruction of central noradrenergic neurones with 6-hydroxydopamine abolishes the hypotensive effect of centrally administered clonidine (Reid & Dollery, 1972).

This work was supported by the Wellcome Trust (R.H.B.) and the Medical Research Council (J.L.R.).

REFERENCES

BOLME, P. & FUXE, K. (1971). Pharmacological studies on the hypotensive effects of clonidine. *Eur. J. Pharmacol.*, **13**, 168–174.

REID, J. L. & DOLLERY, C. T. (1972). Central noradrenergic neurones and the hypotensive actions of clonidine. In the press.

WERNER, U., STARKE, K. & SCHÜMANN, H. J. (1972). Actions of clonidine and 2(2 methyl 6 ethyl cyclohexylamino)-2-Oxazoline on postganglionic autonomic nerves. *Arch. Int. Pharmacodyn.*, **195**, 282–290.

Mode of action of permeability factor obtained from the spleen

H. ff. S. DAVIES, ROSE HARTLEY* and H. O. SCHILD

Department of Pharmacology, University College, London

Spleen permeability factor (SPF) is a protein fraction obtained from rat spleen by homogenization of the sliced tissue followed by ammonium sulphate fractionation. When injected intradermally in rats it causes an increase in capillary permeability demonstrable by dye extravasation. Dye leakage was quantitatively