3 and 8 cycles. There were also alterations in tryptophan, tyrosine, normetanephrine and 5-hydroxyindoleacetic acid concentrations.

These findings confirm our earlier observations that female sex hormones alter brain monoamine concentrations, and also suggest that the effects of the chronic administration of oestrogen/progesterone combinations may differ from those produced by acute dosage.

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The uptake of 5-hydroxytryptamine by the rabbit heart *in vitro*

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Hearts from rabbits given heparin (500 units/kg) 5 min before killing were perfused at constant pressure by the Langendorff technique with Tyrode solution at 37° C and set up for recording right ventricular tension and rate (Fozard & Muscholl, 1971). The uptake of 5-hydroxytryptamine (5-HT) was estimated indirectly by measuring the difference between the arterial and venous concentrations of 5-HT in the perfusion fluid, and directly by assaying the 5-HT accumulated by the heart.

After 30 min equilibration with drug-free Tyrode, perfusion with 5-HT (0·25, 0·5 and 1×10^{-8} g/ml) was begun and continued for 55 minutes. The whole of the coronary flow was collected in seven aliquots (0–2, 2–4, 4–6, 6–10, 10–25, 25–40, 40–45 min) and a sample from each was assayed for 5-HT along with two aliquots of the arterial solution taken from the inflow cannula at the beginning and end of the perfusion. After a further 5 min perfusion with drug-free Tyrode, to wash out the extracellular space, the heart was removed from the cannula, cut into small pieces, firmly blotted and weighed. The 5-HT content of perfusates and hearts was assayed by the method of Snyder, Axelrod & Zweig (1965).

Rabbit hearts removed 5-HT from the perfusion fluid with the magnitude of the arterio-venous difference (expressed as % of the arterial concentration) being inversely proportional to the perfusion concentration, and declining slowly over the perfusion period. Between 6 and 10 min after starting 5-HT perfusion, the mean % arterio-venous differences were $34·0\pm4·9$ (mean, S.E. of mean, $n=5$), $16·4\pm2·4$ ($n=6$) and $13·6\pm1·3$ ($n=5$) for the 0·25, 0·5 and 1×10^{-8} g/ml concentration levels respectively. Hearts from non-heparinized rabbits removed a similar quantity of 5-HT from a perfusion solution of 1×10^{-8} g/ml as hearts from animals given heparin, although their endogenous 5-HT content was significantly larger. There was no significant change in the force or rate of cardiac contraction, coronary flow or cardiac water content as a result of 5-HT perfusion. The cumulative removal of 5-HT from the perfusion fluid (expressed as ng/g heart wet weight) was essentially linear for the first 10 min, although the rate of removal declined slowly thereafter. Analysis of the cardiac 5-HT content (expressed as ng/g heart wet weight) after perfusion with 0·25, 0·5 and 1×10^{-8} g/ml gave values of $78·6\pm7·0$ ($n=5$), $121·9\pm18·0$ ($n=6$) and $152·6\pm27·3$ ($n=4$) respectively, which in each case represent an increase over the value obtained in control experiments ($67·8\pm1·9$, $n=7$) in which perfusion was with Tyrode alone. The percentage of 5-HT removed from the fluid which was retained by the heart was 5·6, 17·5 and 18·0 for the 0·25, 0·5 and 1×10^{-8} g/ml concentration levels respectively. Initial rates of removal of 5-HT were calculated from the individual removal curves during the time period 2—10 minutes. When S/v was plotted against S (where S=perfusion concentration of 5-HT and

v = initial rate of 5-HT removal), a straight line was obtained. The K_m was $2{\cdot}52 \times 10^{-8}$M and V_{max} was (11·6 ng/g)/minute.

These preliminary results demonstrate a saturable, high affinity, low capacity, mechanism in the rabbit heart capable of eliminating 5-HT from the fluid perfusing it.

This work was supported in part by a grant from the Migraine Trust.

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Amino acids and inflammation

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Inflammation produced in rats by dextran, carrageenan, or complete Freund's adjuvant has been used to determine the inhibitory actions of some esters of amino acids, one dipeptide, and a few sulphur-containing amino acids. Recently, Gecse, Zslinszky, Lonovics & West (1971) reported that phenylglycine heptyl ester is a powerful antagonist of intradermal dextral in rats and protects guinea-pigs from fatal anaphylactic shock. McArthur, Dawkins & Smith (1971) found that dipeptides such as phenylalanyl-phenylalanine bind to human serum albumin and are displaced by therapeutic concentrations of salicylate and other antirheumatic drugs. Earlier, Bailey & Sheffner (1967) showed that cysteine and certain other thiol-containing compounds are effective anti-inflammatory agents.

In the dextran experiments (1 mg into one hindpaw of Wistar rats), paw volumes were measured on a volume differential meter and dose-response curves were obtained for phenylglycine and phenylalanine heptyl esters. Intraperitoneal doses of 25 mg/kg reduced the oedema by about 50% whereas both the amino acids and the heptanol were inactive. Cysteine (100 mg/kg) inhibited the response but serine (its corresponding non-thiol compound), D-penicillamine (dimethyl-cysteine) and phenylalanyl-phenylalanine were inactive, even at doses of 300 mg/kg. Unlike aspirin, each of the active compounds was ineffective when given orally.

For the carrageenan inflammatory response, 1 mg was injected into one hindpaw and paw volumes were measured over 6 hours. Again, the heptyl esters of phenylglycine and phenylalanine produced about 50% inhibition at 25 mg/kg whereas the inhibitory dose of phenylalanyl-phenylalanine was 300 mg/kg. Cysteine (100 mg/kg), cystine (300 mg/kg), and glutathione (300 mg/kg) were active but serine and penicillamine were not. In this test, higher doses of some of the active compounds produced greater reductions of the response than did the maximally tolerated oral dose of aspirin.

Adjuvant-induced arthritis in rats was markedly reduced (over 35%) by daily doses of 25 mg/kg of cysteine (S.C.) or phenylalanine heptyl ester (I.P.), yet phenylalanyl-phenylalanine (I.P.) and penicillamine (I.P.) exerted little effect. Thus, penicillamine was ineffective in all three tests used, although some clinical improvement in patients with rheumatoid arthritis has been reported with this compound (Jaffe, 1965).

These findings are demonstrated and suggest the possibility of inhibiting inflammatory states with peptides, esters of amino acids with high molecular weight alcohols, or sulphur-containing amino acids.

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