5 min, histamine (3×10^{-4} M to 3×10^{-3} M) produced a concentration-dependent inhibition of both NA and 5-HT accumulation.

Gillespie & Rae (1972) have shown that NA accumulation by the guinea-pig superior mesenteric artery is appreciably less than that observed with the rabbit ear artery. As in the case of NA, accumulation of 5-HT was markedly less in the guinea-pig superior mesenteric artery than in the rabbit ear artery.

The results of this study reveal that 5-HT is accumulated by arterial smooth muscle cells and that drugs which decrease NA accumulation also reduce the accumulation of 5-HT. Furthermore, both amines appear to exhibit the same species selectivity. Such findings, together with the observation that histamine blocks the accumulation of both NA and 5-HT, raise the possibility that amine accumulation by arterial smooth muscle may be mediated via a common mechanism.

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Some unexpected pharmacological effects of *p*-chlorophenylalanine methyl ester (PCPA) methyl ester)

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Effects *in vitro*: PCPA methyl ester contracted the rat's isolated stomach strip (RSS) and uterus, as did 5-hydroxytryptamine (5-HT), these effects were prevented by methysergide but not by mepyramine, hyoscine, phentolamine and propranolol. Cross-tachyphylaxis occurred between β-phenethylamine, dexamphetamine, substances acting on 5-HT receptors in the RSS (Vane, 1960) and PCPA methyl ester, and 5-HT. Contractions of the RSS to PCPA methyl ester were unaffected by changing bath pH from 7.0 to 2.0, reduced at pH 8.0 and abolished at pH 8.5. Pretreatment of rats with an L-aromatic decarboxylase inhibitor Ro4-4602 (N^1-(DL-seryl)-N^2(2,3,4-trihydroxybenzylhydrazine)), 335 μmol/kg, or amine oxidase inhibitors, did not affect response of the RSS to PCPA methyl ester. Contraction of the guinea-pig ileum to 5-HT was immediate, whereas that to PCPA methyl ester occurred only on wash-out to large doses (0.5 mmol/ml). Such contractions last 20 min, being partly dependent on neuronal integrity since they were diminished by tetrodotoxin (3.0 nmol/ml); wash-out contractions were still obtained after doses of acetylcholine (0.2 nmol/ml), that produce maximal membrane permeability changes (Burgen & Spero, 1968). Additionally, PCPA methyl ester (1.0mmol/ml) immediately abolished twitches and tetanus to coaxial excitation of the guinea-pig ileum and the contractions to acetylcholine, histamine, and 5-HT. PCPA methyl ester (6.0 μmol), like 5-HT (60.0 nmol), caused bronchoconstriction of guinea-pig isolated lungs but unlike 5-HT, the effects were not prevented by methysergide (6.0 μmol), nor by mepyramine, hyoscine, phentolamine and propranolol. Effects *in vivo*: Similar effects were obtained with guinea-pig lungs as *in vitro*. In cats, increases in total and free acidity of gastric secretion evoked by histamine (3.0 nmol kg^{-1} min^{-1} i.v.) were markedly reduced by PCPA methyl ester (0.6 μmol kg^{-1} min^{-1}) or 5-HT (2.6 nmol kg^{-1} min^{-1}) infused into the aorta; volume of gastric secretion was reduced to a lesser degree. 5-HT evokes adrenaline secretion in dogs (Eble, Gowdey & Vane, 1972). In abdominally eviscerated cats, 5-HT (0.06 μmol) or PCPA methyl ester (2.0 μmol) injected retrogradely into the ligated superior mesenteric artery, evoked adrenaline secretion from the adrenal medullae, effects prevented by methysergide (0.215 μmol). In chicks, PCPA methyl ester (10 μmol/100 g) induced behavioural and electrocortical sleep and a 1.0-1.5°C fall in body temperature, effects unaltered by methysergide; equimolar doses of *p*-chlorophenethylamine elicited arousal.

Results with PCPA methyl ester on the RSS, rat uterus and cat adrenal medullae, indicate a

5-HT-like action and, assuming hydrolysis of the ester was not immediate, are compatible with a basic charge distribution on the molecule. Although *p*-chlorophenethylamine contracted the RSS, the 5-HT-like results were not attributable to its presence in the PCPA methyl ester, the only contaminant found with thin-layer chromatography (three different solvent systems) being free PCPA (1-2%). Effects on the guinea-pig ileum could be due to PCPA methyl ester affecting calcium influx. In experiments using the superfused RSS and rat colon (Piper & Vane, 1971), bronchoconstriction which developed in guinea-pigs was apparently due to liberation of prostaglandin $F_{2\alpha}$ by PCPA methyl ester.

J.E.W. is an M.R.C. scholar.

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The effect of intraventricular 6-hydroxydopamine on the response of the conscious cat to pyrogen

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Previously it has been shown that in the cat depletion of brain 5-hydroxytryptamine (5-HT) reduces the hyperthermic response to both bacterial pyrogen and prostaglandin E_1 (PGE_1) (Harvey & Milton, 1974). As both noradrenaline (NA) and 5-HT are thought to be concerned with temperature regulation in this species it was of interest, therefore, to determine whether depletion of brain catecholamines would also affect the response to hyperthermic agents.

Hypothalamic NA depletion was produced by injecting 6-hydroxydopamine (6-OH-DA) into the third ventricle via a previously implanted cannula. Three separate doses of 6-OH-DA (500 μg) were administered at 3 day intervals (Milton & Paterson, 1973). Fever was produced by injecting the O-somatic-antigen of *Shigella dysenteriae* (2 μg/kg) into a saphenous vein. All experiments were at an ambient temperature of 20-22° C.

Following the first dose of 6-OH-DA there was a rapid and massive fall in deep body temperature which was accompanied by panting and ear skin vasodilatation and with the animal lying prostrate on the floor of the cage. Approximately 8 h after the 6-OH-DA injection the body temperature had returned to pre-injection level. The second dose of 6-OH-DA also produced a fall in deep body temperature, but the effects were considerably less than after the first injection. The third dose of 6-OH-DA was without significant effect, and at this time body temperature was within the normal range.

In each animal fever was produced both before and after the 6-OH-DA treatment, and it was found that in all experiments there was a significant potentiation of the fever following the 6-OH-DA, both in the total thermal response and in the maximum temperature rise.

The fall in deep body temperature seen after the first dose of 6-OH-DA is consistent with a large outpouring of NA stimulating heat loss pathways. Following the second dose of 6-OH-DA when NA levels would be expected to be markedly reduced the response was small, and after the third dose at a time when not only should depletion be complete but also neuronal degeneration have taken place there was no change in deep body temperature. That the deep body temperature was normal following 6-OH-DA treatment indicates that at an ambient temperature of 20-22° C, in the cat, noradrenergic heat loss is not involved in maintaining body temperature. There is evidence that during fever, which is considered to be due to PGE release (Feldberg, Gupta, Milton & Wendlandt, 1973), heat loss pathways may exert some control (Bligh & Milton, 1973). Therefore, if in the cat, heat loss pathways are noradrenergic, their inactivation by depletion and degeneration