effect of clonidine (30 μg/kg s.c.) was determined on acid secretion stimulated by continuous i.v. infusions (2 ml/h) in a tail vein of histamine (1 mg kg^{-1} h^{-1}), pentagastrin (6 μg kg^{-1} h^{-1}), 2 deoxy-*d*-glucose (2 DG, 25 mg kg^{-1} h^{-1}) and methacholine (0.6 mg kg^{-1} h^{-1}). Total acidity was automatically titrated at pH = 8.5 (ATS_1, Radiometer).

Gastric acid output decreased markedly after clonidine in both pylorus ligated and chronic fistula rats under basal conditions. The corresponding ED_{50}s were 27 (15–48) μg/kg, i.p., and 13.6 (5.4–34) μg/kg, s.c. respectively. In contrast the ED_{50} was 5.8 (1.6–21) μg/kg when clonidine was administered in the lateral ventricle of the brain. Furthermore clonidine (30 μg/kg s.c.) produced a very significant ($P < 0.01$) and long lasting (>3 h) inhibition when maximal acid responses were obtained with histamine, pentagastrin or 2 DG infusion. On the contrary no inhibition was seen on the secretion stimulated by methacholine.

Thus clonidine used in the same dose range as that described in dogs for its cardiovascular activities possesses powerful gastric antisecretory properties in basal and stimulated acid secretion of conscious rats. Considering first the marked inhibition obtained on the 2 DG stimulation and the lack of activity on the methacholine, and second the very low ED_{50} registered when clonidine was administered in the lateral ventricle of the brain, it seems very likely that its gastric antisecretory property is of central origin in rats. Work is now in progress to determine more precisely the nature of the central neurone receptors involved in this activity.

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Effects of *p*-chloro-β-phenylethylamine on the uptake and release of putative amine neurotransmitters in rat brain

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The monoamine *p*-chloro-β-phenylethylamine (PCPE), a metabolite of *p*-chlorophenylalanine (PCPA) has been reported by Koe & Weissman (1966) to cause a decrease in brain noradrenaline (NA) and 5-hydroxytryptamine (5-HT) levels following its injection intraperitoneally into rats. Our findings in littermate male Wistar rats, using the assay procedure of Martin & Ansell (1973), are in agreement with this. NA levels were 74.8 ± 3.5% and 5-HT levels 74.7 ± 4.8% of controls (mean ± s.e. mean, $n = 6$) 15 min after PCPE, 40 mg/kg i.p. In the same animals we found no significant change in dopamine (DA) levels from controls.

We have now investigated the effects of PCPE on uptake and release of ^{3}H-labelled DA, NA and 5-HT *in vitro* using methods previously described (Raiteri, Angelini & Levi, 1974; Raiteri, Levi & Federico, 1974). Crude synaptosomal P_2 fractions (Gray & Whittaker, 1962) prepared from rat hypothalamus (NA studies) or striatum (DA and 5-HT studies) were used, and all incubation and superfusion media contained nialamide (1.25×10^{-5} M).

PCPE was a stronger inhibitor of 5-HT and NA uptake than of DA uptake ($IC_{50} = 2.2 \times 10^{-6}$ M, 5.0×10^{-6} M and 1.5×10^{-5} M respectively) and, as shown in Figure 1, showed marked differences in its effect on the release of the three transmitters, being a particularly strong stimulator of 5-HT release. Simultaneous experiments with β-phenylethylamine demonstrate that addition of the *p*-chloro substituent on β-phenylethylamine has little effect on NA release, but has a dramatic influence on 5-HT and DA release, increasing the former and decreasing the latter.

This compound appears to be a useful analogue for studying structure-activity relationships in the effects of phenylethylamine derivatives on the transport of amine neurotransmitters *in vivo* and *in vitro*, although to maintain substantial levels *in vivo* for long periods

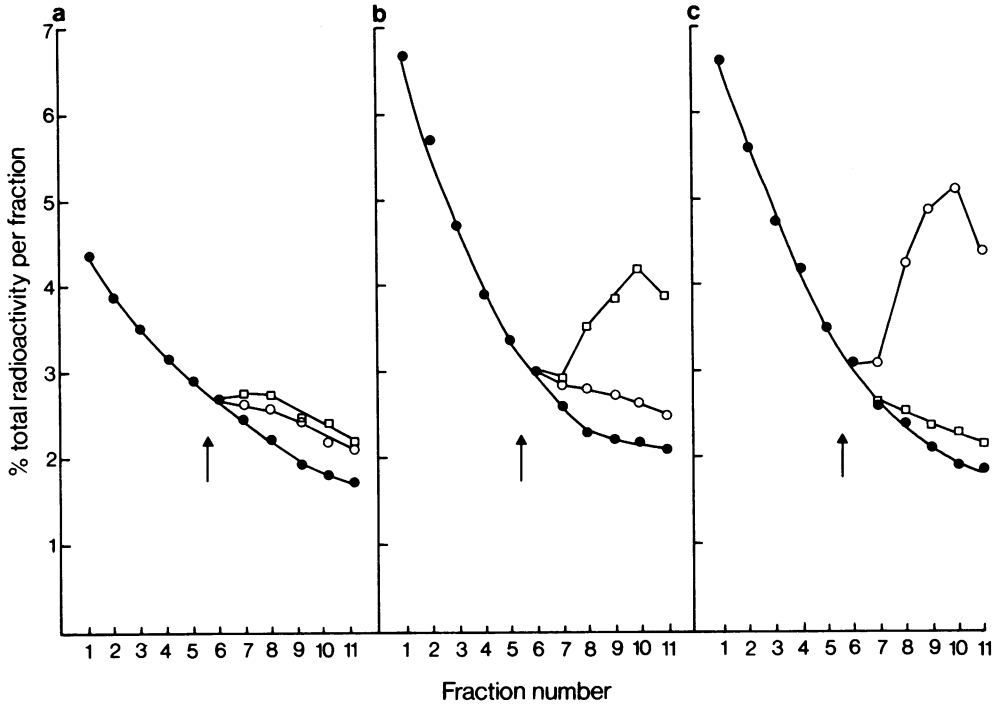

Figure 1 Effect of *p*-chloro-β-phenylethylamine (PCPE) and β-phenylethylamine (PE) on biogenic amine release. P_2 preparations, prelabelled with tritiated noradrenaline (NA), dopamine (DA) or 5-hydroxytryptamine (5-HT) were collected on millipore filters in superfusion chambers and superfused at a rate of 0.5 ml/minute. Fractions of the superfusate were collected at 1 min intervals. The radioactivity of each fraction is expressed as a percentage of the total radioactivity recovered (fractions plus filter) at the end of the superfusion period. The arrow indicates the time of addition of PCPE or PE (final concentration, 10^{-6} M). Each curve is the mean of 3 experiments run in triplicate, and PCPE and PE were tested simultaneously, in parallel superfusion chambers. (a) Hypothalamus, ^{3}H-noradrenaline release; (b) corpus striatum, ^{3}H-dopamine release, (c) corpus striatum, ^{3}H-5-hydroxytryptamine release, ●, control; ○, PCPE; □, PE.

following injection of PCPA or PCPE, it is necessary to do experiments in conjunction with a monoamine oxidase (MAO) inhibitor.

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