further test, EOS at 240 μg was found to significantly increase brain GABA concentrations from 2 to 72 h after drug ($P < 0.05$, $n = 3$ to 6).

In the apomorphine test EOS at 240 and 320 μg injected i.v.c. under brief halothane anaesthesia 24 h previously failed to antagonize gnawing induced by apomorphine (5 mg kg^{-1} s.c.) given 30 min prior to observation. In contrast, CPZ given 1 h previously, completely antagonized apomorphine-induced gnawing ($ED_{50} = 2.3$ mg/kg s.c.).

In the shock avoidance conditioning test (shuttle boxes) trained rats received 1 h blocks of conditioning trials (trial interval 1 min) after administration of EOS at 160, 200 or 240 μg ($n = 6$ per treatment) through an indwelling intraventricular cannula. Mean hourly response latencies (RL) were significantly increased ($P \leqslant 0.05$) at 5, 24 and 48 h by 200 and 240 μg. EOS at 160 μg was ineffective. CPZ (2.5 mg/kg s.c.) tested at 1, 3 and 5 h post-drug significantly increased ($P = 0.01$) RL values at all times. No obvious relationship between elevated brain GABA concentrations and behavioural depression was revealed in this test.

EEG studies were undertaken in rats chronically implanted with skull electrodes and an indwelling intraventricular cannula (Goff, Miller, Smith, Smith & Wheatley, 1975). The parietal EEG, recorded on magnetic tape, was analysed (10 s periods at 10 s intervals) by passing it through four broad wave band filters which measured the voltage within each of the following frequencies: 2.4 to 4.0, 4.0 to 7.5, 7.5 to 13.5 and 13.5 to 26.0 Hz (Nos. 1 to 4 respectively). The mean voltage, in hourly blocks was calculated for pre- (2 h) and post-drug periods (CPZ at 0–4 h; EOS at 0–4, 24, 48 h and 7 days). CPZ ($n = 4$) at 8.4 mg/kg s.c., (the ED_{95} in the apomorphine test), significantly increased ($P \leqslant 0.05$) voltages in Filters 1 and 2 and total voltage at all times, but voltages in Filters 3 and 4 were only significantly increased at 1 to 4 h and 2 to 4 h respectively. EOS at 240 μg ($n = 3$) significantly increased ($P < 0.05$) total voltage and voltages in Filters 1 to 3 (at 24 and 48 hours).

The studies have revealed that the behavioural depression associated with increased brain GABA concentrations induced by EOS in rats differs from CPZ-induced depression in some important respects.

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The effects of three tricyclic antidepressants on arterial ^{3}HNA uptake and arterial responsiveness to noradrenaline (NA)

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The tricyclic antidepressant clomipramine has been used in the therapy of obsessional neurosis in which it is demonstrably more effective than either imipramine or amitriptyline (Rack, 1973). Both imipramine and amitryptiline are potent inhibitors of noradrenaline (NA) uptake (Iversen, 1967) and in this study the effects of imipramine, amitriptyline and clomipramine on arterial NA uptake and arterial responsiveness to NA were investigated.

Rat mesenteric arteries were prepared and perfused as previously described (George & Leach, 1973). To measure the uptake of [^{3}H]-NA, the preparation was perfused for 30 min with normal Krebs solution containing (–)-[^{3}H]-NA 0.42 μCi/ml and carrier (–)-NA to give a final NA concentration of 200 ng/ml. Ascorbic acid (20 mg/l) and disodium E.D.T.A. 10 mg/l were added to stabilize (–)-NA. The [^{3}H]-NA content of the arteries was determined as described by Iversen (1963) and radioactivity counted as described by George & Leach (1975). Dose response curves were obtained to NA alone and, to NA in the presence of each of the tricyclic compounds separately. The perfusion concentrations used were 1×10^{-6} M and 1×10^{-8} M. [^{3}H]-NA uptake was measured in the absence of any drug and the effect of each drug on [^{3}H]-NA uptake was determined separately using a range of perfusion concentrations (5×10^{-6} M–1×10^{-8} M). Each of the drugs,

when present in the perfusion solution caused a potentiation of the responses to NA above the control values. The control ED_{50} response to NA was potentiated by 60% in the presence of imipramine and by 50% and 40% respectively in the presence of amitriptyline and clomipramine (1×10^{-6} M). At a perfusion concentration of 1×10^{-8} M, however, the ED_{50} NA response was potentiated by 30% in the presence of clomipramine, by 20% in the presence of imipramine and by 10% when amitriptyline was present. Each of the three drugs inhibited NA uptake when compared to control values in the absence of any drug. At a concentration of 1×10^{-8} M clomipramine inhibited NA uptake by 30% while amitriptyline and imipramine inhibited NA uptake by 15% and 20% respectively, compared to control values. During perfusion with imipramine (1×10^{-6} M) NA uptake was inhibited by 80% while in the presence of clomipramine and amitriptyline respectively, NA uptake was depressed by 55% and 65% respectively.

These results suggest that all three tricyclic depressants are potent inhibitors of NA uptake. Clomipramine is the most potent inhibitor of NA uptake at a perfusion concentration of 1×10^{-8} M, while imipramine is the most potent inhibitor of NA uptake at a concentration of 1×10^{-6} M. There was a direct correlation between the effects of each drug on NA uptake and the effects on arterial responsiveness to NA. The differences in potencies between clomipramine and the other tricyclic compounds at different perfusion concentrations might explain the greater effectiveness of clomipramine in some disorders.

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Stereoselective uptake of L-homocysteate by rat brain slices

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On microelectrophoretic administration around mammalian central neurones, D-homocysteate appears to be a more potent and longer-acting excitant than L-homocysteate (Curtis & Watkins, 1963). In potency and in time course of action, the latter amino acid resembles L-glutamate, which is well known to be actively taken up by central nervous tissue. Since the time course of concentration changes around receptor sites may be influenced by such uptake systems, and thus affect the excitation characteristics of an amino acid, a study has been conducted on the relative rates of uptake of D- and L-homocysteate by rat brain slices.

[^{35}S]-L-Homocysteic acid was prepared by oxidation of [^{35}S]-L-homocysteine thiolactone with bromine. Unlabelled D- and L-homocysteic acids were prepared in a similar way from the appropriate isomers of homocystine (Watkins, 1962). Rat cerebral cortex slices were preincubated for 40 min at 37°C in Krebs bicarbonate medium (mM: NaCl, 124; KCl, 5; KH_2PO_4 1.2; $MgSO_4$ 1.3; $CaCl_2$ 2.8; $NaHCO_3$, 26; D-glucose 10, adjusted to pH 7.4). The slices were transferred to fresh medium containing various concentrations of amino acids and further incubated at 37°C for periods of 0 to 20 minutes. The tissue content of [^{35}S]-L-homocysteate was estimated directly by scintillation counting of the hyamine-digested slices, and unlabelled D-, L- or DL-homocysteate were determined by ninhydrin reaction after ion exchange separation from endogenous amino acids. Metabolism of [^{35}S]-L-homocysteate was assessed by high voltage paper electrophoresis and by paper chromatography of an aqueous ethanol extract of the tissue.

On incubation of brain slices with unlabelled D- or L-homocysteate (2.5 mM) for 10 min, only the L form was actively accumulated. Two transport systems for [^{35}S]-L-homocysteate were recognized, these exhibiting low and high affinity characteristics (apparent Km 7 ± 2 mM and 10 ± 3 μM; Vmax 4 ± 1 μmol. g wet wt.$^{-1}$ min^{-1} and 8 ± 3 nmol. g wet wt.$^{-1}$ min^{-1}, respectively). Low affinity uptake of [^{35}S]-L-homocysteate (0.1 mM) was inhibited 20–50% by 1 mM L-glutamate, D-glutamate, L-aspartate and D-aspartate, and 61% by 1 mM *p*-chloromercuriphenylsulphonate. D-Homocysteate (1 and 10 mM) did not