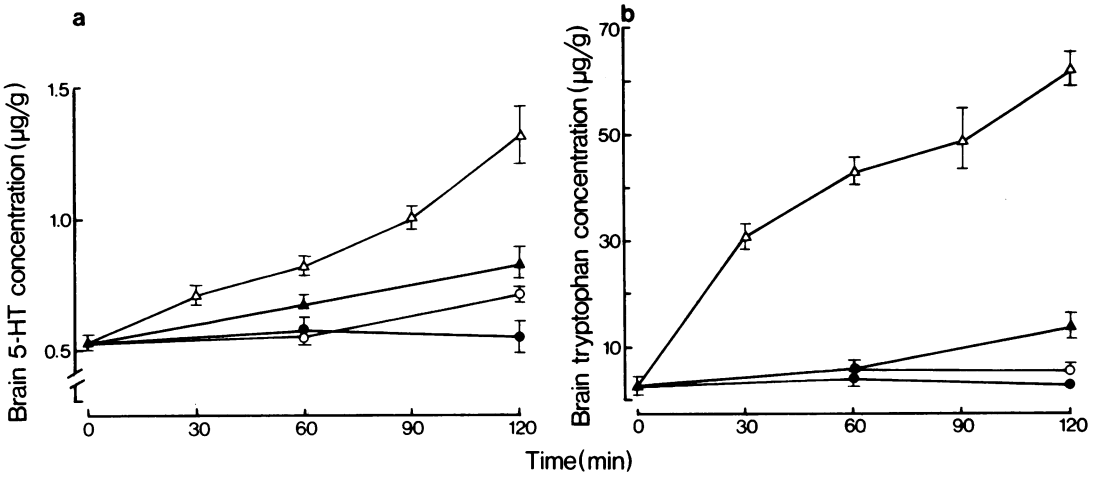

Figure 1 Brain 5-Hydroxytryptamine (Figure 1a) and L-tryptophan (Figure 1b) concentrations in the isolated perfused rat brain. Brains were perfused with either the basal medium which contained glucose (10 mmol/l) alone (●—●) or a medium containing tranylcypromine (1 mmol/l) (○—○). In other experiments the medium contained tranylcypromine (1 mmol/l) + L-tryptophan (0.1 mmol/l) (▲—▲) or tranylcypromine (1 mmol/l) + L-tryptophan (1.0 mmol/l) (△—△). Each point represents the mean ± S.E.M. for 3-7 observations.

Brain 5-HT concentrations were maintained at the control values (0.53 μg/g) during perfusion for 2 h with the basal medium which contained no added tranylcypromine or tryptophan (Figure 1a) (the initial tryptophan concentration being < 2 μg/ml). Addition of tranylcypromine (1 mmol/l) caused increase in brain 5-HT during the second h at a rate of 0.16 $\mu g\, g^{-1}\, h^{-1}$. When tryptophan was added with tranylcypromine the rate of 5-HT accumulation increased with tryptophan concentration being 0.16 $\mu g\, g^{-1}\, h^{-1}$ with 0.1 mmol/l and 0.4 $\mu g\, g^{-1}\, h^{-1}$ with 1.0 mmol/l.

Following perfusion with tryptophan the brain tryptophan concentration rose, the rate of accumulation increasing with the increasing initial concentrations (Figure 1b).

These results compare favourably with rates of 5-HT accumulation measured *in vivo* following loading with 100 mg/kg tryptophan. This model provides a means of studying brain 5-HT metabolism in a situation where there is a high degree of control over the experimental conditions.

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Distribution of chlorpromazine and its metabolites in subfractions of rat brain

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The distribution of chlorpromazine (CPZ) in the central nervous system was measured autoradiographically in the cat by Cassano, Sjöstrand & Hansson (1965) using large amounts of ^{35}S-CPZ. Earlier work by Sjöstrand, Cassano & Hansson (1965) investigating whole body distribution of CPZ in mice showed a concentration of label in the cerebral and cerebellar cortex. In order to study the area and subcellular distribution, rats were injected (8 mg/kg i.p.) with ^{3}H-CPZ at various times before being killed. Brains were removed, divided into cortex, mid-brain and hind-brain, all subsequent procedures being carried

out on each area independently. Subcellular fractions were prepared from a 10,000 *g* pellet on a discontinuous sucrose gradient based on a method by Marchbanks & Whittaker (1967) and purity of fractions ascertained by electron microscopy. Radioactivity of each sample was measured by liquid scintillation counting. Subsequent experiments measuring the ability of isolated subfractions to accumulate CPZ were attempted by incubating the subfractions in medium containing 10^{-4} M ^{3}H-CPZ at 37°C for 15 minutes. The reaction was terminated by centrifugation, the supernatant decanted, tubes wiped dry and pellet resuspended in 10% Triton X100. Samples were counted by liquid scintillation counting as in the earlier experiments.

A time course study following the injection of CPZ indicated an initial rise in all areas of rat brain rising to a maximum at about 15 min and then levelling off from 20-30 min, the highest concentration accumulating in the cortex and the smallest in the hind brain. There were surprisingly high levels in the membrane/myelin fraction compared to that in the synaptosomes in all areas, which was apparent after 15 minutes. It was found that there was a differential distribution of CPZ in the subfractions in the different areas at 10 min and 60 min after injection. At 10 min a relatively high concentration was found in the mitochondria which may be explained by our earlier work (Livingston & Phillips, 1974) on the effects of CPZ on oxidative phosphorylation in synaptosomes and mitochondria, although after 60 min the highest concentrations were found in the membrane/myelin fraction.

Experiments in which CPZ was incubated with subcellular fractions for 32 min showed similar results to whole animal experiments incubated for 60 min, the main difference being in the hind brain where there was a high accumulation in the synaptosomes relative to the other subfractions. However, in the cortex and mid-brain the previous finding of a high concentration in the membrane/myelin subfraction is reinforced, there being approximately twice as much CPZ accumulated in this fraction as in the synaptosomes and mitochondria in the cortex.

The relatively high concentration of CPZ found in the membrane/myelin fraction poses an interesting question as to the site of action of this drug in the central nervous system.

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Change in sensitivity to pentobarbitone and halothane induced by acute administration of central nervous system depressant drugs

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A withdrawal hyperexcitability, as manifested by a reduction in the duration of anaesthesia produced by an intracerebroventricular (i.c.v.) injection of pentobarbitone is seen in rats abruptly withdrawn from a number of central nervous system (CNS) depressant drugs following their chronic administration (Stevenson & Turnbull, 1974). However, since such experiments are necessarily time-consuming and because each animal can only be used once, we have investigated the possibility that CNS excitability might be altered by administration of large doses of depressant drugs over a much shorter period of time and have assessed the usefulness of other indices of CNS excitability.

First we attempted to keep male rats anaesthetized for approximately 8 h by beginning an i.p. infusion of pentobarbitone (30 mg kg^{-1} h^{-1}) immediately animals had lost their righting reflex following an i.p. injection of 50 mg/kg pentobarbitone. The rats were killed on awakening and the brain barbiturate levels were determined. Higher brain levels (23.6 ± 1.7 (5) mean ± s.d. μg/g) were found in these animals compared with rats killed on awakening after a single i.p. injection of 50 mg/kg administered at