Treatment with L-dopa is reported to produce psychotomimetic side-effects (Jenkins & Schweiger, 1971). In schizophrenia, the high dopamine levels in the extrapyramidal system could produce sufficiently high levels of DMPEA for hallucigenic activity and at the same time antagonize the akinetic effects as seen in animal studies (Ernst, 1965). This is supported by the fact that neuroleptic drugs used in the treatment of schizophrenia, effectively reduce dopamine levels by increasing its turnover rate and are well known to produce a parkinsonian syndrome as a side-effect (Ayd, 1961).

School of Pharmacy, J. A. SMITH*
University of Bradford, R. HARTLEY
Bradford BD1 1DP, Yorkshire, U.K.

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Blood-brain barrier to carbidopa (MK-486) and Ro 4-4602, peripheral dopa decarboxylase inhibitors

L-α-Methyldopa hydrazine (α-methyl-α-hydrazino L-3,4-dihydroxyphenylpropionic acid, MK-486, carbidopa, Merck) and *N'*-(DL-seryl)-N^2-(2,3,4-trihydroxybenzyl) hydrazine Ro 4-4602 are powerful inhibitors of dopa decarboxylase *in vitro* and *in vivo*. Previous studies have indicated that these compounds do not cross the blood-brain barrier easily (Bartholini & Pletscher, 1969; Bartholini, Blum & Pletscher, 1969; Kuruma, Bartholini & others, 1972; Lotti & Porter, 1970). Porter, Watson & others (1962) found little or no radioactivity in the brains of rats given 5 mg kg^{-1} 1-[^{14}C]-DL-carbidopa intraperitoneally. For this reason they have been used to advantage in patients with Parkinson's disease receiving L-dopa, because they reduce peripheral loss of L-dopa and markedly reduce the doses of L-dopa needed for therapeutic effects.

We thought that it would be useful to directly measure their ability to cross the blood-brain barrier.

One approach to the problem of drug permeability is the oil-water partition coefficient method described by one of us (Dewhurst & Marley, 1965). It is based on the

Table 1. *Partition coefficients derived from paper chromatography.*

Compound	Mean R_F*	Standard deviation	Partition coefficient
Carbidopa	0·22	0·01	0·55
Ro 4-4602	0·07	0·02	0·15
5-HT	0·12	0·01	0·26
Tryptamine	0·29	0·01	0·78

* Means of 8 runs.

premise that where special transport mechanisms do not exist, the penetration of substances through cell lipoprotein membranes is proportional to their partition coefficient between the aqueous and lipoprotein phases at the surface of cells. Bush (1961) pointed out that partition coefficients could be derived from paper chromatography and and this technique was applied here. The mobile phase chosen consisted of a mixture of oleyl alcohol 50%, ethanol 40% and ammonium acetate buffer pH 7·4, 10%. Oleyl alcohol was chosen as a representative constituent of cell membranes. The detailed technique is described by Dewhurst & Marley (1965).

Application of this technique to the substances in question gave the results shown in Table 1. The results indicate that both decarboxylase inhibitors show much less penetration of the brain than tryptamine and their partition coefficients fall in the range of substances which show little or no entry. Ro 4-4602 indeed penetrates to an even less degree than 5-HT whereas the position of α-methyldopa hydrazine suggests that although it penetrates more than 5-HT, it does not reach a partition coefficient of 0·7 associated with ready cell membrane penetration (Dewhurst & Marley, 1965).

One of us has described a simple and accurate direct way of measuring the blood-brain barrier *in vivo* (Oldendorf, 1970, 1971a,b). Essentially it consists of measuring the ratio of $^{14}C/^{3}H$ of rat brain 15 s (one brain circulation time) after the rapid intracarotid injection of a 0·2 ml bolus of buffered Ringer containing the [^{14}C]labelled material to be studied, along with [^{3}H]water as a highly diffusible internal standard of reference against which the uptake of the [^{14}C]test substance is measured. The $^{14}C/^{3}H$ ratio in the brain tissue is divided by the same ratio in the Ringer's mixture and expressed as a percentage of the water uptake as an arbitrary brain uptake index (BUI).

We were able to obtain side-chain 2-[^{14}C]labelled carbidopa, 3·3 μCi mg^{-1} through the generosity of Dr. Clement Stone, Merck Institute for Therapeutic Research, West Point, Pennsylvania; and 2-^{14}C-labelled Ro 4-4602, 5·1 μCi mg^{-1} through the generosity of Dr. Alfred Pletscher, F. Hoffman-La Roche & Co., Ltd., Basel, Switzerland. In the case of the MK-486, the concentration injected was 1·2 mM in the 0·2 ml bolus of "pipes" buffer [piperazine-*NN'-bis* (2-ethane sulphuric acid), monosodium monohydrate, Calbiochem], pH 6·6–6·8; and with Ro 4-4602 it was 0·84 mM. Three rats were used for each compound. The B.U.I.'s averaged 2·11 ± 0·18 for carbidopa and 1·09 ± 0·19 for Ro 4-4602, both of which are background levels and signify no penetration into the brain.

These results confirm in a direct way the claims that both of these substances do not cross the blood-brain barrier, justifying the wide spread use of the term "peripheral dopa decarboxylase inhibitor".

Psychopharmacology Research Laboratory, W. G. CLARK*
Veterans Administration Hospital, Sepulveda,
California 91343; and
Department of Biological Chemistry,
Center for Health Sciences, University of California,
Los Angeles (UCLA).

* From whom reprints should be requested.

Research Service, Veterans Administration Center, Los Angeles; and Department of Neurology, Reed Neurological Research Center, University of California (UCLA).

W. H. OLDENDORF

Department of Psychiatry, University of Alberta, Edmonton, Alberta, Canada.

W. G. DEWHURST

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A note on the effect of (+)- and (−)-amphetamine on lipid metabolism

Both (+)- and (−)-amphetamine have anorectic properties (Lawlor, Trivedi & Yelnosky, 1969; Mantegazza, Müller & others, 1970). However, while the effect of (+)-amphetamine on plasma free fatty acids (FFA) and triglycerides is well established, data on the effect of the (−)-isomer on lipid metabolism are scanty. We have compared, (+)- and (−)-amphetamine for their effects on plasma FFA and triglycerides, on triglyceride absorption, and on body temperature, intestinal transit and food intake.

Charles River male rats, 200 g, four to a cage, were used. Except where specified, food was available until the experiments began. (+) and (−)-Amphetamine sulphate (obtained by courtesy of Recordati, Milan) were administered intraperitoneally; all doses refer to the salt. Controls received saline. Rectal temperature was recorded before treatment and after 30, 60, 120, 180, 240, 300 and 360 min. Food intake was measured in rats fasted for 18 h. Pellets were made available to the animals just after the treatment. The amount of food consumed during the subsequent 4 h was recorded.

The intestinal motility was measured according to De Feo, Piccinelli & Silvestrini (1971). Photoluminescent pigment and drug were given at the same time, rats were killed 60 min after treatment.

Triglyceride absorption was determined as follows: 2 h after amphetamine, the animals received 20 ml kg^{-1} of olive oil by stomach tube and 2 h later, they were decapitated and plasma triglycerides measured according to Van Handel, Zilversmit & Bowman (1957). Plasma FFA were measured according to Dole (1956).

(+)-Amphetamine, at 5 and 10 mg kg^{-1}, caused hyperthermia, up to 120 min after