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AN *IN VITRO* MODEL FOR THE STUDY OF PSYCHOTROPIC DRUGS AND AS A CRITERION OF ANTIDEPRESSANT ACTIVITY

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Abstract—A crude preparation of synaptosomes from rat brain exhibits the phenomenon of "re-uptake" of biogenic amines across the neuronal membrane. Exogenous serotonin (5HT) is concentrated by a process that is saturable, temperature dependent, linked to the activity of the Na^+K^+-ATPase system and inhibited by chlorimipramine and reserpine.

A number of psychotropic agents have been examined for their ability to inhibit the uptake of ^{14}C-5HT into the crude synaptosome preparation. Using this system it is possible, firstly, to broadly distinguish the site of action of these agents, whether at the neuronal membrane level or the synaptic vesicle level, and secondly to judge their ability to cross the blood–brain barrier. Thus tetrabenazine, like reserpine, has been shown to act at the vesicle level, while chlorpromazine acts preferentially at the neuronal membrane level, as do the imipramine-like tricyclics. Methoserpidine has the same effect as reserpine on the *in vitro* system but appears incapable of traversing the blood–brain barrier.

The inhibitory effect of imipramine-like tricyclics has a direct relation to their efficacity as antidepressants. A lack of correspondence between clinical antidepressant activity and classical pharmacological tests suggests that the system described may serve as a valuable model for antidepressant activity.

BIOGENIC amines are concentrated in central neurons by two general processes. The first is an active transport or re-uptake process by which amines normally released into the synaptic cleft are recaptured by the neuronal membrane. This process is blocked by imipramine-like tricyclic antidepressants. The second is a storage process in the synaptic vesicles and is inhibited by the neuroleptic agent reserpine.

The overall uptake process, transport plus storage, can be studied by measuring the incorporation of labelled amines either into brain slices[1–3] or into synaptosomes (pinched-off nerve endings).[4–15] These latter particles exhibit the biochemical and histological characteristics of *in vivo* nerve endings and can thus serve as an excellent *in vitro* model.[16,17]

The present report describes the effect of various psychotropic agents on the uptake of ^{14}C-serotonin (5HT) into a crude or partially purified synaptosome preparation.

MATERIALS AND METHODS

All reagents used were of analytical grade. ^{14}C-serotonin (5-hydroxy-3-indolyl (ethyl-2-amino-1 ^{14}C) creatinine sulphate monohydrate; 55 mCi/mmole) was purchased from the Radiochemical Centre (Amersham, Bucks, England). Radioactivity measurements were made using a Packard Tricarb liquid scintillation spectrometer (Model 3320) and a toluene–methoxyethanol (3:2) based scintillation fluid containing

naphthalene (8%) and Butyl-PBD (Ciba Ltd) (0·4%). Quenching was corrected by external standardization.

Preparation of crude synaptosome suspension. All operations were conducted at 0–4°. Whole brain from an immature female rat (19–21 days), Charles River strain, was excised, weighed and homogenized in 0·32 M sucrose (20 ml) according to the method of Whittaker.[16] The supernatant (S_1) from the 900 *g* debris centrifugation was diluted to 100 ml with 40 mM Na phosphate buffer, pH 7·0, containing 100 mM NaCl, 4mM KCl and 11 mM D-glucose.[8] Aliquots (5 ml) of this suspension were incubated with ^{14}C-5HT in the presence or absence of various psychotropic agents as described. After incubation the samples were immediately cooled in ice, an aliquot removed for radioactivity measurement and the remainder centrifuged (Beckman, model L2 75B ultracentrifuge) at 100,000 *g* for 10 min at 4° in a 50 Ti rotor. The pellet (P_2) was rinsed twice with cold phosphate buffer (1 ml) and extracted with 0·4 N perchloric acid (300 μl). After removal of precipitated proteins by centrifugation the radioactivity in the extract was measured.

Preparation of purified synaptosomes. The pellet P_2 was resuspended in 0·32 M sucrose (2 ml). An aliquot (1 ml) of the suspension was layered on a two phase sucrose gradient (equal vol. 1·2 and 0·8 M sucrose) and centrifuged at 50,000 *g* for 2 hr at 4° in the SW 50·1 rotor. The gradients were fractionated by piercing the bottom of the tube. To each fraction were added water (200 μl) and scintillation fluid (10 ml) and the radioactivity measured.

For isolation of synaptosomes the opaque layer at the 1·2–0·8 M interface was recovered, diluted with an equal volume of distilled water and centrifuged at 100,000 *g* for 1 hr at 4° in the 50 Ti rotor.

Lysis of synaptosomes by osmotic shock. The pellet P_2 was resuspended in water (2 ml) and an aliquot (1 ml) layered on a two phase gradient (equal vol. 1·2 and 0·8 M sucrose) which was centrifuged and fractionated as previously described.

Assay of ^{14}C-5HT and ^{14}C-5-hydroxyindolacetic acid (5HIAA). ^{14}C-5HT in crude or purified synaptosomes was assayed after extraction with ethanol containing carrier 5HT and 5HIAA (40 μg/ml) and subsequent thin-layer chromatography on Silica gel (Merck F 240) in an acetic acid–butanol–water (3:12:5) solvent system. Plates were scraped and Silica gel fractions counted directly.

Assay of lactate dehydrogenase (LDH) activity. LDH activity was assayed in fractions of gradients of whole or lysed synaptosomes, using the procedure of Kornberg.[18] The decrease in NADH absorption at 340 nm was measured with a Cary Spectrophotometer, model 1605. Protein was estimated by the method of Lowry.[19]

RESULTS

Part 1. Characterization of the synaptosome preparation

Sucrose gradient separation of synaptosomes. After incubation of the crude synaptosome preparation with ^{14}C-5HT, the 100,000 *g* pellet (P_2) was resuspended in sucrose and layered on a two phase sucrose gradient. As shown in Fig. 1a, incorporated radioactivity is clearly associated with the synaptosome fraction which sediments at the interface.[16,17]

An assay of incorporated ^{14}C-5HT after 5 min incubation was carried out by ethanol extraction of the crude synaptosomes or the purified synaptosomes and subse-

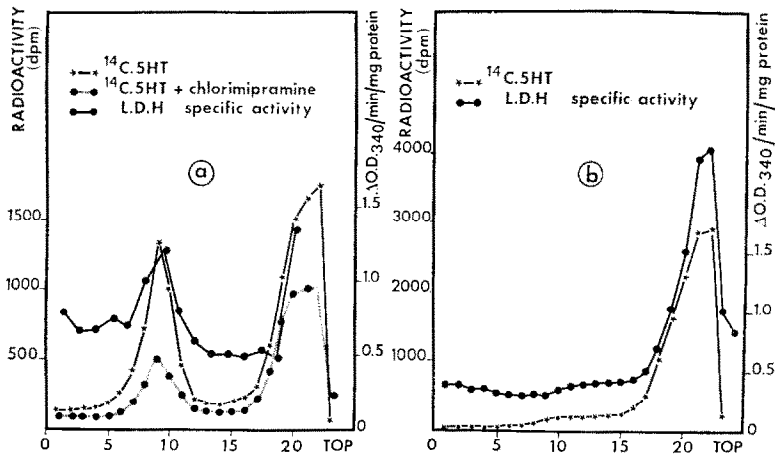

FIG. 1. (a) Distribution of 5HT and LDH activity after sucrose gradient separation of synaptosomes. Effect of chlorimipramine. ^{14}C-5HT ($3{\cdot}6 \times 10^{-7}$ M) was incubated for 15′ at 37° with the crude synaptosome suspension with or without chlorimipramine (4×10^{-6} M). The pellet P_2 obtained by centrifugation (10′, 100,000 *g*) was resuspended in sucrose (0·32 M) and layered on a two phase gradient (1·2, 0·8 M sucrose) which was centrifuged and fractionated as described in Materials and Methods. LDH activity in the gradient fractions was assayed as described. (b) Distribution of 5HT and LDH activity after lysis of synaptosomes.

After incubation of ^{14}C-5HT as for 1 (a), pellet P_2 was resuspended in distilled water and layered on an identical gradient.

quent analysis by thin-layer chromatography. 80–95 per cent of the extracted radioactivity was associated with 5HT and 5HIAA, and of this activity, crude synaptosomes contained 60 per cent associated with 5HT and purified synaptosomes, 70 per cent.

Lysis of synaptosomes by osmotic shock. Suspension of the pellet (P_2) in distilled water resulted in lysis of the synaptosomes. The profile of the subsequent gradient (Fig. 1b) shows radioactivity no longer at the 1·2 and 0·8 M interface, but with soluble proteins and synaptic vesicles at the surface. The same effect was observed when the cytoplasmic marker enzyme, LDH, was assayed.[20] Enzymatic activity originally associated with whole synaptosomes (Fig. 1a) was recovered at the gradient surface after lysis (Fig. 1b). It is to be noted that, after lysis, little radioactivity is associated with the heavier membrane fragments and emptied synaptosomes which still sediment at the 1·2 and 0·8 M interface. This is to be compared with the autoradiographic studies of Aghajanian and Bloom[21] where, after *in vivo* incorporation of ^{14}C-5HT, radioactivity was observed in the vicinity of synaptic membranes as well as in association with the synaptic vesicles of serotoninergic neurons.

Incorporation of radioactivity as a function of temperature. As shown in Fig. 2 the uptake process is temperature dependent and shows a maximum at 37°.

Incorporation of radioactivity as a function of time. The rate of uptake of radioactivity was measured as a function of time at 37° (Fig. 3). The initial rate of incorporation is very rapid. After 5 min there is little variation up to 30 min when there is a progressive diminution. This latter is due partly to monoamine oxidase (MAO) activity as shown by the effect of an inhibitor (IMAO), iproniazid (Table 1) and partly to an autolysis of synaptosomes.[16]

Incorporation of radioactivity as a function of serotonin concentration. As in the experiments of Bogdanski *et al.*[12] with rabbit brain stem preparation, the plot of

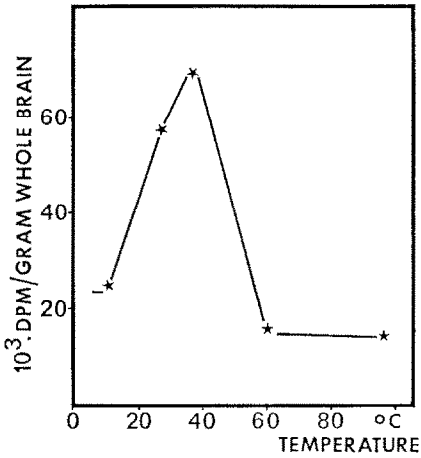

FIG. 2. Uptake of ^{14}C-5HT as a function of temperature. ^{14}C-5HT ($0{\cdot}9 \times 10^{-7}$ M) was incubated with the crude synaptosome suspension for 5 min. Radioactivity in the pellet P_2 was extracted and measured as described.

incorporation of radioactivity in the pellet as a function of initial serotonin concentration at 37° (Fig. 4a, curve 1) reveals two distinct uptake phenomena: an unsaturable linear process (NS) clearly visible at higher concentrations and a saturable process (S).

The presence of both these systems led us to represent the results as a proportion graph[22] which gives a graphical estimation of the uptake parameters. In this particular instance, the fraction of bound radioactivity, b, was taken as the radioactivity of the pellet over the total radioactivity, no attempt being made to distinguish between 5HT and its metabolites. As shown in Fig. 4b, the experimental points may be fitted with precision by an S + NS curve (1), which on analysis gives for the S system a kinetic constant of 0·7 (± 0·2) 10^{-7} M and a maximum uptake capacity of 0·28 (± 0·06) 10^{-7} M. Isotopic dilution experiments (Table 2) confirm the saturability of this system

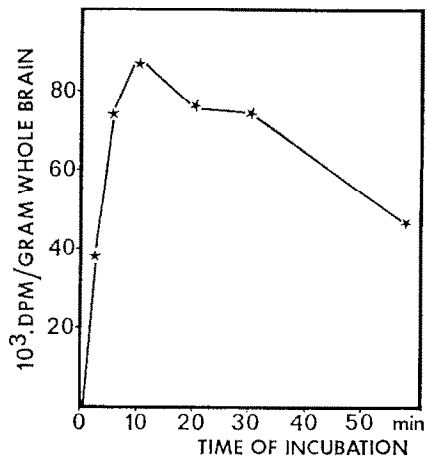

FIG. 3. Uptake of ^{14}C-5HT as a function of incubation time. ^{14}C-5HT ($0{\cdot}9 \times 10^{-7}$ M) was incubated with the crude synaptosome suspension at 37°. Radioactivity was extracted from the pellet P_2 with 0·4 N $HClO_4$.

TABLE 1.

Addition	Incubation time (min)	Uptake
None	5	100
None	60	60
Iproniazid (10^{-3} M)	60	75

The uptake of ^{14}C-5HT into a non-purified synaptosome preparation was measured as described. Incubation was at 37° with ^{14}C-5HT concentration $0{\cdot}9 \times 10^{-7}$ M. Iproniazid was incubated simultaneously with ^{14}C-5HT.

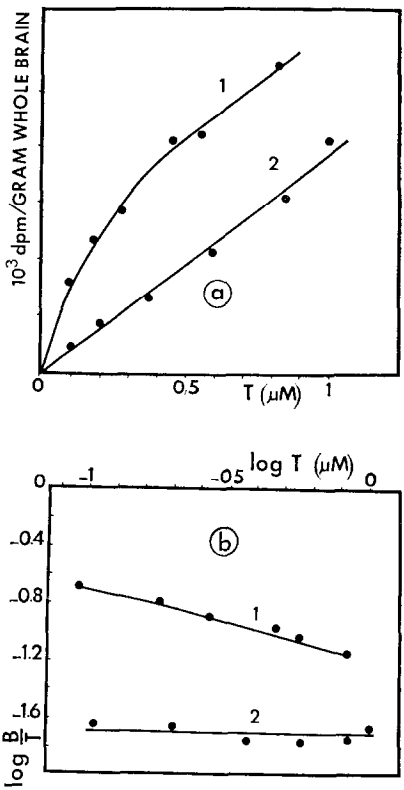

FIG. 4. (a) Uptake of ^{14}C-5HT as a function of concentration. Curve (1). Varying concentrations of ^{14}C-5HT were incubated at 37° for 5 min with the crude synaptosome suspension. Radioactivity in the pellet P_2 was extracted and measured as described, correction being made for the efficiency (50 per cent) of extraction with $HClO_4$. Curve (2). The procedure was carried out as for curve (1) after the synaptosome suspension had been heated at 100° for 15 min. (b) Proportion graph. Log b (the proportion of radioactivity bound) is plotted against log T (the total 5HT concentration, expressed in micromoles). Curve (1) can be fitted by an S + NS system from which an initial estimate of the uptake parameters has been graphically deduced and subsequently evaluated more precisely using the computer method described in [22] Curve (2) is characteristic of an S system only.

since uptake decreases as the 5HT concentration increases. Its specificity towards 5HT was demonstrated by addition of 5HIAA or 5HTP (Table 2), which causes no decrease in uptake. From the S + NS curve it is also possible to evaluate the uptake accounted for by the NS system and given by the parameter $K_{ns}N_{ns}$, in this case equal to 0·053 ± 0·009.

TABLE 2.

Addition	Concentration (M)	Uptake
None		100
5HT	10^{-6}	45
5HT	10^{-5}	25
5HT	10^{-4}	15
5HIAA	10^{-5}	100
5HTP	10^{-5}	90

The uptake of ^{14}C-5HT into a non-purified synaptosome preparation was measured as described. Incubation was at 37° for 5 min with ^{14}C-5HT concentration $0{\cdot}9 \times 10^{-7}$ M in the presence of various amounts of 5HT, 5HIAA and 5HTP.

The curve (Fig. 4a and b, curve 2) obtained after heating the preparation for 15 min at 100° gives a value of $K_{ns}N_{ns}$ (0·047 ± 0·002) identical to that obtained previously. This implies that only the S system is denatured by heating and that the NS system is consequently due to random absorption.

Effect of various inhibitors (*Table* 3)

Ouabain. When the crude synaptosome suspension was pre-incubated for 15 min at 37° with the ATPase inhibitor, ouabain, there was a substantial inhibition of ^{14}C-5HT

TABLE 3. EFFECT OF VARIOUS DRUGS ON ^{14}C-5HT UPTAKE

Addition	Concentration (M)	Uptake
None		100
Ouabain	10^{-5}	75
Ouabain (Preincubation 15 min 37°)	10^{-5}	50
Ouabain	10^{-6}	95
Chlorimipramine	4×10^{-6}	30
Reserpine	10^{-5}	60
Iproniazid	10^{-3}	100

The uptake of ^{14}C-5HT into a non-purified synaptosome preparation was measured as described. Incubation was at 37° for 5 min with ^{14}C-5HT concentration $0{\cdot}9 \times 10^{-7}$ M. Drugs were incubated simultaneously with ^{14}C-5HT.

uptake. This observation has already been recorded[11] and indicates that the saturable uptake system is linked to the NA^+, K^+-dependent ATPase.

Chlorimipramine. The tricyclic antidepressant, chlorimipramine, has been established as a powerful inhibitor of 5HT uptake into blood platelets,[23] brain slices,[24,25] and synaptosomes.[26] The overall inhibitory effect of chlorimipramine on ^{14}C-5HT uptake into the crude synaptosome preparation is due to inhibition specifically at the synaptosome level, as shown by the gradient profile in Fig. 1a.

Reserpine. The neuroleptic reserpine, which interferes with the storage of biogenic amines in synaptic vesicles[27,28,10] but has no effect on the initial uptake of amine,[13] has a certain inhibitory effect on the incorporation of radioactivity into the non-purified system (see later).

To summarize thus far, these results show that the synaptosome preparation retains the characteristics of the phenomenon of "re-uptake" of biogenic amines across the presynaptic membrane and their storage in synaptic vesicles. That is, the synaptosomes are capable of concentrating exogenous 5HT by a process that is saturable, temperature dependent, closely linked to the activity of the Na^+, K^+-ATPase system and inhibited by chlorimipramine and reserpine.

Part 2. Action of psychotropic agents

Antidepressant drugs. A number of psychotropic agents (Table 4) have been examined for their inhibitory action on the active uptake of ^{14}C-5HT into the synaptosome preparation described above. The concentration IC_{50}, of a given compound required for 50 per cent inhibition, has been calculated in each case by measuring the incorporation of radioactivity at various concentrations of inhibitor (Table 5).

The action of different antidepressants tested with the system correlates well with their action observed *in vitro* on brain slices,[30,31] synaptosomes,[26] and blood platelets[23,29] and *in vivo* studied by histofluorescence.[32] Thus the observed order of activity is: chlorimipramine > imipramine > amitriptyline > protriptyline = nortriptyline > desipramine.

TABLE 4. PERCENTAGE INHIBITION OF ^{14}C-5HT UPTAKE IN THE PRESENCE OF VARIOUS ANTIDEPRESSANTS

Drugs	Concentration			
	4×10^{-8}	4×10^{-7}	4×10^{-6}	4×10^{-5}
Imipramine	25	40	65	75
Desipramine	5	15	40	70
Chlorimipramine	35	60	70	75
Amitriptyline	5	40	65	75
Nortriptyline	5	20	55	70
Protriptyline	5	20	55	70

The uptake of ^{14}C-5HT into a non-purified synaptosome preparation was measured as described. Incubation was at 37° for 5 min with ^{14}C-5HT concentration $0{\cdot}9 \times 10^{-7}$ M. Drugs were incubated simultaneously with ^{14}C-5HT.

TABLE 5. INHIBITION OF ^{14}C-5HT UPTAKE BY IMIPRAMINE-LIKE ANTIDEPRESSANTS

Drugs	Synaptosomes non purified IC_{50} (10^{-6} M)	Slices[1] IC_{50} (10^{-6} M)	Slices[2] IC_{50} (10^{-6} M)	Slices[2] ED_{50} (mg/kg ip)	Histofluorescence[3] ED_{50} (mg/kg ip)
Imipramine	0·6	0·5	0·6	24	20
Desipramine	6	5	4	>60	>50
Chlorimipramine	0·1	0·1			7
Amitriptyline	0·8		2	36	12
Nortriptyline	4		5	>60	20
Protriptyline	4				>25

[1] A. CARLSSON, *J. Pharm. Pharmac.* **22**, 729 (1970).
[2] S. B. ROSS *et al.*, *Eur. J. Pharmac.* **7**, 270 (1969).
[3] A. CARLSSON *et al.*, *Eur. J. Pharmac.* **3**, 357 (1969).

As already noted in the literature,[25,30,32] compounds having a tertiary amino side-chain prove superior to those carrying a secondary amino side-chain, although the difference is sometimes only slight. In the case of noradrenaline (NA) uptake, the converse applies, that is secondary amino compounds are more active than tertiary amino.[30,32]

Neuroleptic agents: action of an IMAO. As shown in Table 6, reserpine, tetrabenazine, chlorpromazine and haloperidol inhibit the uptake of 5HT to a much lesser extent than the antidepressants.

3-isoreserpine,[27] and D-reserpine (communicated result) have no *in vivo* action on the central nervous system or periphery and correspondingly have no action on the *in vitro* system.

Methoserpidine (10-methoxydeserpidine) also has no *in vivo* action at the central nervous system level, but at the periphery however, it exerts a considerable effect.[33]

TABLE 6. PERCENTAGE INHIBITION OF ^{14}C-5HT UPTAKE IN THE PRESENCE OF VARIOUS NEUROLEPTICS

Drugs	Concentration 10^{-7} M	10^{-6} M	10^{-5} M
Reserpine	0	25	40
Dextro-reserpine		0	0
3-iso-reserpine			0
Methoserpidine	0	25	35
Tetrabenazine	0	30	40
Chlorpromazine	0	15	45
Haloperidol	0	0	25

The uptake of ^{14}C-5HT into a non-purified synaptosome preparation was measured as described. Incubation was at 37° for 5 min with ^{14}C-5HT concentration $0{\cdot}9 \times 10^{-7}$ M. Drugs were incubated simultaneously with ^{14}C-5HT.

Like reserpine, methoserpidine inhibits to a similar extent the *in vitro* uptake of 5HT into non-purified synaptosomes (Table 6). This latter effect is not observed when rats are treated with methoserpidine (5 or 10 mg/kg, i.p.),[33] 4 hr before sacrifice, while in the case of reserpine (5 mg/kg, i.p.), similarly administered, 5HT uptake into synaptosomes is inhibited to the extent of 40 per cent. Garattini *et al.*[34] have likewise shown that 4 hr after administration of methoserpidine, the overall level of brain 5HT remains unchanged, but under the same conditions, reserpine causes significant decrease. Thus, in so far as the tranquillizing effect of reserpine derivatives is related to 5HT, the lack of central action of methoserpidine is more likely to be due to an inability to cross the blood–brain barrier, rather than to an intrinsic lack of activity.

It has been shown that reserpine acts by preventing the storage of exogenous biogenic amines in synaptic vesicles thus causing a depletion of endogenous stocks. Serotonin remaining unbound is rapidly metabolized by monoamine oxidase (MAO) to HIAA which diffuses out through the external membrane.[30] The observed action of reserpine on the synaptosomal preparation should therefore reflect a part of the overall uptake measured that is associated with storage of 5HT in synaptic vesicles. According to this hypothesis, the inhibitory action of reserpine should be less marked in the presence of an IMAO because unbound ^{14}C-5HT remaining unmetabolized is not lost from the synaptosome. Using the IMAO, iproniazid, this was indeed the result obtained. As shown in Table 7 and Fig. 5 a higher retention of radioactivity was observed.

Two other neuroleptic agents, tetrabenazine and chlorpromazine, were tested. The same result was obtained using tetrabenazine (Fig. 5) in the presence of iproniazid, showing that both reserpine and tetrabenazine have a similar mode of action.[28] Conversely, the mechanism of action of chlorpromazine is radically different. When the incubation was carried out in the presence of iproniazid the incorporation of activity remained unchanged (Table 7), thus chlorpromazine does not seem to have

TABLE 7. EFFECT OF AN INHIBITOR ON ^{14}C-5HT UPTAKE IN THE PRESENCE OF IPRONIAZID

Addition	Concentration (M)	Uptake
None		100
Iproniazid	10^{-3}	105
Reserpine	10^{-5}	35
Reserpine + iproniazid	10^{-5}	60
Tetrabenazine	10^{-5}	40
Tetrabenazine + iproniazid	10^{-5}	65
Chlorpromazine	10^{-5}	54
Chlorpromazine + iproniazid	10^{-5}	53
Chlorimipramine	4×10^{-6}	35
Chlorimipramine + iproniazid	4×10^{-6}	30

The uptake of ^{14}C-5HT into a non-purified synaptosome preparation was measured as described. Iproniazid, where present, was 10^{-3} M. In all experiments there was a 15 min pre-incubation at 37° and subsequent incubation for 15 min at 37° with ^{14}C-5HT at concentration $0{\cdot}9 \times 10^{-7}$ M.

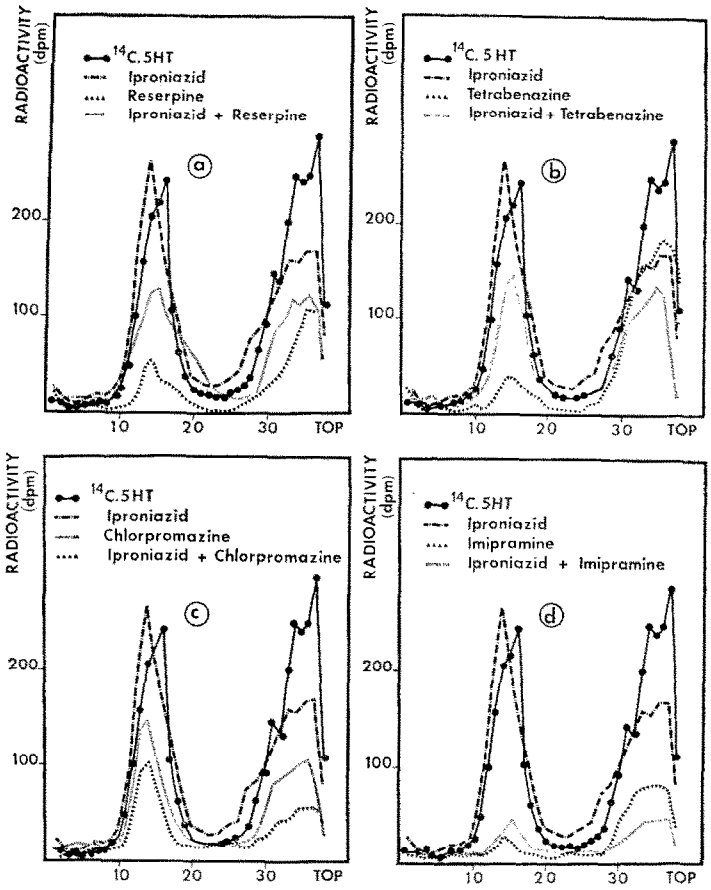

FIG. 5. Distribution of ^{14}C-5HT after sucrose gradient separation of synaptosomes. Effect of various psychotropic agents. In all experiments there was a 15 min pre-incubation and subsequent incubation for 15 min at 37° with ^{14}C-5HT ($0{\cdot}9 \times 10^{-7}$ M). Pellet P_2 was resuspended in sucrose (0·32 M) and layered on a two phase gradient (1·2 and 0·8 M sucrose) which was centrifuged and fractionated as described in Materials and Methods.

an inhibitory effect at the vesicle level. Indeed, in the case of adrenergic neurons,[35] chlorpromazine has been shown to act on the synaptic membrane, which is not surprising considering its structural similarity with imipramine-like tricyclics.

When the antidepressants chlorimipramine and imipramine were incubated in the presence of iproniazid, uptake was, as expected, not modified (Fig. 5 and Table 7).

DISCUSSION

It has been known for a long time that a relation exists between tricyclic antidepressants and the biogenic amines, NA[37] and 5HT.[38] Since then, certain authors have stressed the importance of the role of NA in depression.[38] More recently it has been accepted that 5HT is at least equally important[39] and a specific role has been attributed to each amine: NA being mainly responsible for drive and 5HT for mood.[32] This concept is compatible with the clinically recognized components of endogenous

depression,[40] namely, inhibition (lack of drive), mood (sadness) and anxiety (correlated with central cholinergic action[43]) and corresponds to a certain extent to the classification of antidepressants by Kielhoz,[41] Bente,[42] Benesova[43] and others (cf. ref. 40).

Many antidepressant compounds are believed to exert their effect by blocking the "re-uptake" of released NA and 5HT, which results in an elevated concentration of amine at the synapse. It seemed of interest to study the action of antidepressants on the uptake of 5HT by biochemical methods, since their action on this process is difficult to measure pharmacologically[26,45] and is not evaluated by the classical tests for antidepressant activity.[44] This may explain moreover the lack of correlation between pharmacological and clinical activity of antidepressants.[46] That the degree of inhibition of 5HT uptake may serve as a more reliable criterion of antidepressant activity is supported by the observation that chlorimipramine and amitriptyline, antidepressants clinically very active but having only an average profile of activity according to pharmacological tests, both appreciably inhibit the uptake process (Table 8).

TABLE 8. BIOCHEMICAL, PHARMACOLOGICAL AND CLINICAL ACTIVITIES OF IMIPRAMINE-LIKE ANTIDEPRESSANTS

Drugs	Inhibition uptake[1] ED_{50} (mg/kg ip) NA	5HT	Antireserpine ptosis[2] ED_{50} (mg/kg ip)	Inhibition[4]	Mood[4]	Anxiety[4]
Imipramine	>25	20	≤5	+	+++	+
Desipramine	15	50	2–5	+++	+	0
Chlorimipramine	>25	7	>50	[++][5]	[+++][5]	[++][5]
Amitriptyline	25	12	>20	0	>++	++
Nortriptyline	>25	20	[10][3]	>++	+	0
Protriptyline	4	>25	≤5	++	+	0

[1] A. CARLSSON *et al.*, *Eur. J. Pharmac.* **5**, 357 (1969).
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For a more complete evaluation of an antidepressant compound, it is evident that the *in vitro* system alone is insufficient and must at least be supplemented by the same study after *in vivo* administration of the compound. This is clearly demonstrated by the result obtained with methoserpidine.

More generally however, the crude or purified synaptosome preparation can give a preliminary indication of the site and mechanism of action of various psychotropic agents. It has been possible, for example, to detect a basic difference in the mechanism of action of the neuroleptic chlorpromazine and that of reserpine and tetrabenazine.

Using this model system, it is thus possible to differentiate the action of various psychotropic agents acting on serotoninergic neurons, when their effect is exerted preferentially at either neuronal membrane or synaptic vesicle level.

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