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EFFECT OF NOMIFENSINE (HOE 984), A NEW ANTIDEPRESSANT, ON UPTAKE OF NORADRENALINE AND SEROTONIN AND ON RELEASE OF NORADRENALINE IN RAT BRAIN SYNAPTOSOMES

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Abstract—Nomifensine (8-amino-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline hydrogen maleate) is a thymoleptic drug with a moderate centrally stimulating component. Its effects on noradrenaline (NA) and serotonin (5-HT) uptake by crude synaptosome preparations from both whole rat brain and from hypothalamus have been studied and compared with those of several tricyclic antidepressants and D-amphetamine. Nomifensine inhibition of NA uptake by synaptosomal fractions from rat hypothalamus ($IC_{50} = 7{\cdot}0 \times 10^{-7}$ M) was similar to that of nortriptyline and protriptyline. In contrast to tricyclic antidepressants, nomifensine was found to be a powerful inhibitor of NA uptake in synaptosomes obtained from whole brain ($IC_{50} = 9{\cdot}0 \times 10^{-8}$ M). Nomifensine had only a moderate effect on 5-HT accumulation ($IC_{50} = 2{\cdot}8 \times 10^{-5}$ M), comparable with that of desipramine. The inhibition of uptake of both NA and 5-HT by nomifensine was of a competitive type. It is suggested that the centrally stimulating component of nomifensine, which is lacking in most thymoleptic drugs, is based upon its strong inhibition of catecholamine re-uptake into noradrenergic as well as dopaminergic nerve endings. Nomifensine has no releasing effects on the efflux of NA from rat brain synaptosomes, thus differing clearly from D-amphetamine and other indirectly acting sympathicomimetic agents.

NOMIFENSINE (Hoe 984, Fig. 1) was selected from the series of 8-amino-4-phenyl-1,2,3,4-tetrahydroisoquinolines, a new group of antidepressant psychotropic drugs,[1] for further pharmacological and biochemical studies because it revealed a favourable therapeutic index in animal experiments and because it has a good and uniform effect after oral administration. According to the results of animal experiments, the compound is a thymoleptic drug with a moderate centrally stimulating component.[2] Moreover, nomifensine was shown to potentiate the noradrenaline effect. In clinical trials, nomifensine has proved to be a particularly well tolerated antidepressant.

It is a favoured view today that thymoleptics owe their antidepressant activity to a blockade of the amine transport system at the level of the neuronal cell membrane, commonly referred to as the membrane pump. The neuronal membrane transport system appears to play a major role in terminating the effects of catecholamines and serotonin released at synapses. Blockade of the membrane pump should lead to an increase in the neurotransmitter concentrations at receptor sites in the brain.[3–6]

Studies with brain synaptosomes[7,8] demonstrate that this preparation can serve as an excellent *in vitro* model for analyzing the effects of agents on these uptake mechanisms.[9–17] In the present study we have compared the effects of nomifensine,

tricyclic antidepressants and D-amphetamine on the uptake of ^{14}C-noradrenaline (NA) and ^{14}C-serotonin (5-HT) into crude synaptosome preparations obtained from rat whole brain and hypothalamus. Furthermore, we have compared the effect of nomifensine with tyramine and D-amphetamine on the release of ^{14}C-NA from rat brain synaptosomes.

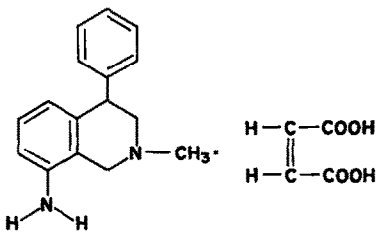

FIG. 1. Nomifensine (Hoe 984). 8-Amino-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline hydrogen maleate.

MATERIALS AND METHODS

Chemicals. ^{14}C-Serotonin (5-hydroxy-3-indolyl(ethyl-2-amino-1-^{14}C)creatinine sulphate monohydrate; 57 mCi/m-mole) and D,L-^{14}C-noradrenaline(carbinol-^{14}C) D.L-bitartrate (54 mCi/m-mole) were purchased from the Radiochemical Centre (Amersham, Buckinghamshire, England). All reagents used were of analytical grade.

Tissue preparation. Our methods for determining catecholamine uptake were similar to those of Snyder and Coyle.[10] All procedures prior to incubation were performed at 0–4°. Immature female rats (18–21 days), Wistar strain, were sacrificed by decapitation, and whole brains were removed immediately, weighed and homogenized in 9 vol of ice-chilled 0·32 M sucrose according to the method of Whittaker.[7] The homogenate was centrifuged at 1000 *g* for 10 min to remove the nuclei and cell debris as a pellet (P_1), and 10-ml portion of the supernatant (S_1) was diluted to 100 ml with Krebs–Henseleit bicarbonate buffer,[18] pH 7·4, containing 11 mM glucose and half-strength calcium. This synaptosome suspension obtained from whole brain was equivalent to 10 mg of original tissue per ml (averaging 0·42 mg protein/ml), and was used for ^{14}C-NA uptake studies. When ^{14}C-5-HT uptake was measured this synaptosome suspension was further diluted with an equal volume of buffer (5 mg tissue/ml).

The hypothalamus was dissected from rat brain using the technique described in detail by Glowinski and Iversen.[19] The tissue, collected from ten rats (about 700 mg) was homogenized in 7 vol of 0·32 M sucrose and centrifuged as described above. The supernatant was decanted and diluted with 9 vol of Krebs–Henseleit bicarbonate buffer, yielding a final synaptosomal fraction equivalent to 12·5 mg tissue/ml.

Uptake of biogenic amines. Aliquots were taken from the carefully stirred synaptosome suspensions, 5 ml from whole brain suspension and 1 ml from hypothalamus suspension respectively. The samples were incubated at 37° in a shaking water bath with ^{14}C-NA or ^{14}C-5-HT in the presence or absence of various antidepressant drugs. When the uptake of noradrenaline was examined. ascorbic acid (0·2 mg/ml). EDTA disodium salt (0·025 mg/ml) and iproniazid phosphate (1×10^{-4} M) were also added to the incubation medium.

After 3 min of pre-incubation, either ^{14}C-NA or ^{14}C-5-HT was added to produce a final concentration of $0{\cdot}9 \times 10^{-7}$ M and incubation was continued for an additional 5 min. Drugs were incubated simultaneously with the radioactively labelled amine. Control samples were incubated also at 0° and under otherwise identical conditions to determine the nonspecific uptake[20] which was not affected by antidepressant agents. The difference between uptake at 37° and 0° was taken as a measure for the high affinity transport activity.[13–15]

At the end of the incubation period, the reaction was terminated by cooling the tubes in ice, and the further procedure for the measurement of accumulated radioactivity in the synaptosomal fraction was conducted according to Kannengiesser *et al.*,[16] except that two extractions of pellet P_2 were carried out with 0·3 ml of 0·4 N perchloric acid each time. 0·4 ml of the combined acidic extracts were transferred to counting vials containing 15 ml scintillation fluid of the following composition: dioxane (600 ml), toluene (400 ml), methanol (100 ml), 2,5-diphenyloxazole (5 g) and 1,4-bis[2-(4-methyl-5-phenyloxazolyl)]-benzene (120 mg). Radioactivity was measured in a Packard Tricarb liquid scintillation spectrometer (Model 3380).

IC_{50} Values were determined as the concentration of drug that inhibits the five minute uptake of either ^{14}C-NA or ^{14}C-5-HT by 50 per cent. Four or five different concentrations of the drug were used in triplicate, and the results were plotted on semi-logarithmic paper.

Release of noradrenaline. The experimental conditions are essentially the same as described by Ng *et al.*[21] Synaptosome suspensions in Krebs–Henseleit bicarbonate buffer were obtained from whole brain as described above. Five-millilitre samples (equivalent to 50 mg of tissue used) were incubated with ^{14}C-NA at $3{\cdot}6 \times 10^{-7}$ M in the presence of ascorbic acid (0·2 mg/ml), EDTA disodium salt (0·025 mg/ml) and iproniazid phosphate (1×10^{-4} M) for 20 min at 37°, and uptake was stopped by cooling the tubes in ice. After centrifugation at 16,000 *g* for 10 min at 4°, the synaptosomal pellets were gently resuspended in fresh bicarbonate buffer and incubated at 37° for 5 min to allow equilibration. At this moment (zero time) drugs (1×10^{-4} M) were added. After further incubation for 5, 10, 20, 25 or 30 min at 37°, the samples were cooled in ice and centrifuged at 60,000 *g* for 10 min. The radioactivity remaining in the synaptosomes was counted after extracting the pellets with 0·4 N perchloric acid as described for the uptake studies.

RESULTS

The time course of accumulation of ^{14}C-NA and ^{14}C-5-HT by crude synaptosome preparations from whole rat brain is shown in Fig. 2. Zero-time values, which were determined by preparing the incubation mixture at 0° and centrifuging it immediately are not subtracted in this case, in order to demonstrate the magnitude of the blanks. The rate of uptake of both neurotransmitters was almost linear for the first 4 min. After 4 min incubation, the percentage of accumulation was 5·5 for ^{14}C-NA and 8·6 for ^{14}C-5-HT.

The lower amount of radioactivity per gram brain for ^{14}C-NA accumulation is due to a greater amount of synaptosomes in the incubation medium (10 mg original tissue per ml). Moreover, our studies were performed with D,L-noradrenaline, and in homogenates of different areas of rat brain, except corpus striatum, the uptake

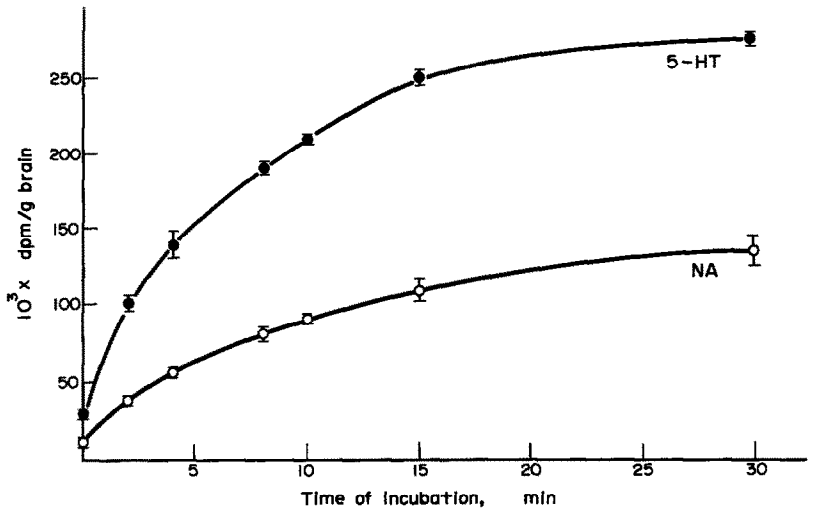

FIG. 2. Uptake of ^{14}C-5-HT and of ^{14}C-NA as a function of incubation time. Reaction mixture consisted of 5 ml Krebs-bicarbonate buffered medium at pH 7·4. ^{14}C-5-HT ($0{\cdot}9 \times 10^{-7}$ M) was incubated with the crude synaptosome suspension equivalent to 5 mg whole brain per ml. D,L-^{14}C-NA ($0{\cdot}9 \times 10^{-7}$ M) was incubated with the crude synaptosome suspension equivalent to 10 mg whole brain per ml to which ascorbic acid (0·2 mg/ml), EDTA disodium salt (0·025 mg/ml) and iproniazid phosphate (1×10^{-4} M) were added. Incubation temperature was 37°. Radioactivity was extracted from the pellet P_2 with 0·4 N $HClO_4$ and measured as described in the text. Each point represents mean value ± S.D. of three determinations.

of noradrenaline is stereospecific with a marked preference for L-noradrenaline; K_i values for L-noradrenaline were found to be about one-fourth those for D-noradrenaline.[11]

Nomifensine, D-amphetamine and a number of tricyclic antidepressants have been examined for their inhibitory action on the uptake of ^{14}C-NA (Table 1) and ^{14}C-5-HT (Table 2) into the synaptosome preparation obtained from whole brain. The ^{14}C-NA accumulation was strongly inhibited by nomifensine and D-amphetamine. The percentage inhibition proved to be the same for these two drugs within the range of concentrations used. ^{14}C-NA uptake into synaptosomes from whole rat brain was

TABLE 1. PERCENTAGE INHIBITION OF ^{14}C-NA UPTAKE INTO SYNAPTOSOMES FROM WHOLE RAT BRAIN IN THE PRESENCE OF NOMIFENSINE AND OTHER ANTIDEPRESSANTS

Drugs	Concentration (M)						
	4×10^{-9}	4×10^{-8}	4×10^{-7}	4×10^{-6}	1×10^{-5}	2×10^{-5}	4×10^{-5}
Nomifensine	14 ± 3	38 ± 5	68 ± 4	83 ± 2			
Imipramine			<5	18 ± 7	37 ± 5	47 ± 5	62 ± 4
Chlorimipramine			<5	15 ± 2	38 ± 4	55 ± 3	72 ± 3
Amitriptyline			<5	32 ± 2	47 ± 4	64 ± 4	75 ± 1
Desipramine			<5	8 ± 2	20 ± 2	35 ± 3	50 ± 3
Nortriptyline			<5	31 ± 3	48 ± 3	61 ± 6	70 ± 4
Protriptyline			<5	33 ± 3	47 ± 4	61 ± 2	71 ± 6
D-Amphetamine	14 ± 1	37 ± 3	66 ± 3	80 ± 1			

The uptake of ^{14}C-NA into a crude synaptosome preparation was measured as described. Incubation was performed at 37° for 5 min with $0{\cdot}9 \times 10^{-7}$ M ^{14}C-NA. Drugs were incubated simultaneously with ^{14}C-NA. Percentage inhibition was evaluated in triplicate at each concentration.

The results are given as mean values ± S.D.

TABLE 2. PERCENTAGE INHIBITION OF ^{14}C-5-HT UPTAKE INTO SYNAPTOSOMES FROM WHOLE RAT BRAIN IN THE PRESENCE OF NOMIFENSINE AND OTHER ANTIDEPRESSANTS

Drugs	Concentration (M)					
	4×10^{-8}	4×10^{-7}	4×10^{-6}	1×10^{-5}	2×10^{-5}	4×10^{-5}
Nomifensine		<5	19 ± 1	33 ± 5	43 ± 5	57 ± 3
Imipramine	10 ± 3	39 ± 4	55 ± 7			75 ± 3
Chlorimipramine	39 ± 4	51 ± 5	59 ± 4			68 ± 2
Amitriptyline		30 ± 6	48 ± 7	55 ± 5	65 ± 2	72 ± 3
Desipramine		<5	28 ± 6	50 ± 4	60 ± 2	72 ± 5
Nortriptyline			53 ± 5	61 ± 3	66 ± 1	72 ± 1
Protriptyline			46 ± 5	58 ± 3	68 ± 3	74 ± 6
D-Amphetamine		<10	36 ± 1	48 ± 3	60 ± 2	69 ± 2

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

The results are given as mean values ± S.D.

less impaired by tricyclic antidepressants, and no marked differences in the inhibitory properties of these compounds were observed.

Synaptosomes from whole brain are not as useful as synaptosomes obtained from the hypothalamus for inhibitory studies of NA uptake by tricyclic antidepressants;[22] they include a large number of dopaminergic nerve terminals from the corpus striatum which can also accumulate NA *in vitro*. In the striatum the K_m for ^{3}H-D,L-NA uptake was found to be $2{\cdot}0 \times 10^{-6}$ M, whereas the K_m for ^{3}H-dopamine uptake in this region and the K_m for ^{3}H-D,L-NA in the hypothalamus was $4{\cdot}0 \times 10^{-7}$ M.[10]

Striatal synaptosomes with their high dopaminergic content are less sensitive to nonplanar tricyclic compounds than synaptosomes from the noradrenergic rich hypothalamus. Horn *et al.*[12] found that desipramine was 1000 times more potent in inhibiting hypothalamic than striatal catecholamine uptake.

Table 3 summarizes the results of our studies with nomifensine and other antidepressants on the inhibition of the hypothalamic NA uptake mechanism. Desipramine was the most potent inhibitor. Nomifensine resembled nortriptyline and protriptyline closely, and its potency in inhibiting hypothalamic NA uptake was some-

TABLE 3. PERCENTAGE INHIBITION OF ^{14}C-NA UPTAKE INTO SYNAPTOSOMES FROM RAT HYPOTHALAMUS IN THE PRESENCE OF NOMIFENSINE AND OTHER ANTIDEPRESSANTS

Drugs	Concentration (M)						
	4×10^{-8}	1×10^{-7}	4×10^{-7}	1×10^{-6}	4×10^{-6}	1×10^{-5}	2×10^{-5}
Nomifensine	22 ± 4	31 ± 4	43 ± 5	51 ± 7	68 ± 7		
Chlorimipramine		<10	21 ± 3		46 ± 4	54 ± 3	64 ± 6
Desipramine	28 ± 6	36 ± 5	55 ± 2	64 ± 6			
Nortriptyline	26 ± 4		49 ± 2	55 ± 3			
Protriptyline	29 ± 5		48 ± 6	54 ± 6			
D-Amphetamine		31 ± 3	51 ± 3	61 ± 8	77 ± 5		

The uptake of ^{14}C-NA into a crude synaptosome preparation from rat hypothalamus was measured as described. Incubation was performed at 37° for 10 min with $0{\cdot}9 \times 10^{-7}$ M ^{14}C-NA. Drugs were incubated simultaneously with ^{14}C-NA. Percentage inhibition was evaluated in triplicate at each concentration.

The results are given as mean values ± S.D.

TABLE 4. CONCENTRATION OF DRUG CAUSING 50 PER CENT INHIBITION OF ^{14}C-NA AND ^{14}C-5-HT UPTAKE (IC_{50}) INTO RAT BRAIN SYNAPTOSOMES

Drugs	^{14}C-NA Whole brain IC_{50} (M)	^{14}C-NA Hypothalamus IC_{50} (M)	^{14}C-5-HT Whole brain IC_{50} (M)
Nomifensine	$9{\cdot}0 \times 10^{-8}$	$7{\cdot}0 \times 10^{-7}$	$2{\cdot}8 \times 10^{-5}$
Imipramine	$2{\cdot}2 \times 10^{-5}$	—*	$1{\cdot}6 \times 10^{-6}$
Chlorimipramine	$1{\cdot}6 \times 10^{-5}$	$6{\cdot}0 \times 10^{-6}$	$4{\cdot}0 \times 10^{-7}$
Amitriptyline	$1{\cdot}0 \times 10^{-5}$	—*	$4{\cdot}5 \times 10^{-6}$
Desipramine	$4{\cdot}0 \times 10^{-5}$	$2{\cdot}8 \times 10^{-7}$	$1{\cdot}1 \times 10^{-5}$
Nortriptyline	$1{\cdot}2 \times 10^{-5}$	$5{\cdot}0 \times 10^{-7}$	$3{\cdot}0 \times 10^{-6}$
Protriptyline	$1{\cdot}2 \times 10^{-5}$	$5{\cdot}5 \times 10^{-7}$	$5{\cdot}5 \times 10^{-6}$
D-Amphetamine	$1{\cdot}1 \times 10^{-7}$	$4{\cdot}0 \times 10^{-7}$	$1{\cdot}0 \times 10^{-5}$

IC_{50} values are calculated from the data in Tables 1–3 by plotting the results on semi-logarithmic paper.
* Not determined.

what lower than that of D-amphetamine. Chlorimipramine was the least potent inhibitor of this uptake process.

Nomifensine was only a weak inhibitor of 5-HT uptake in synaptosome preparations from whole brain (Table 2), whereas chlorimipramine was the most active compound.

The concentration IC_{50} of a given drug required for 50 per cent inhibition of amine uptake was calculated, and the values are shown in Table 4. Nomifensine was about 10 times more potent in inhibiting NA uptake by synaptosomes from whole brain than by synaptosomes from hypothalamus.

As to the tricyclic antidepressants, our experiments confirm the stronger influence of the secondary amines (desipramine, nortriptyline, protriptyline) on NA uptake

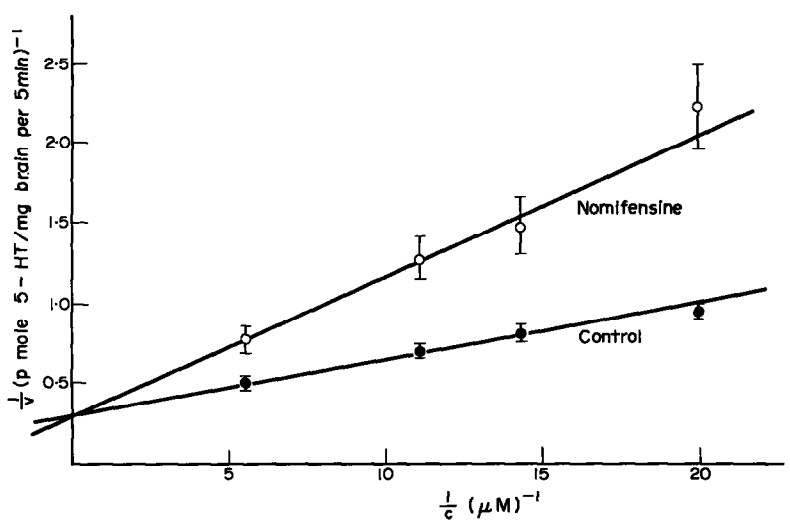

FIG. 3. Competitive inhibition of ^{14}C-5-HT uptake by nomifensine as illustrated by the Lineweaver–Burk method. Reaction conditions were the same as in Fig. 2 except that 2×10^{-5} M nomifensine (○) was incubated simultaneously with ^{14}C-5-HT during a 5 min period (● indicates control rates). Concentration range of ^{14}C-5-HT was 0·05–0·18 μM. Uptake was evaluated in triplicate and each point represents mean value ± S.D.

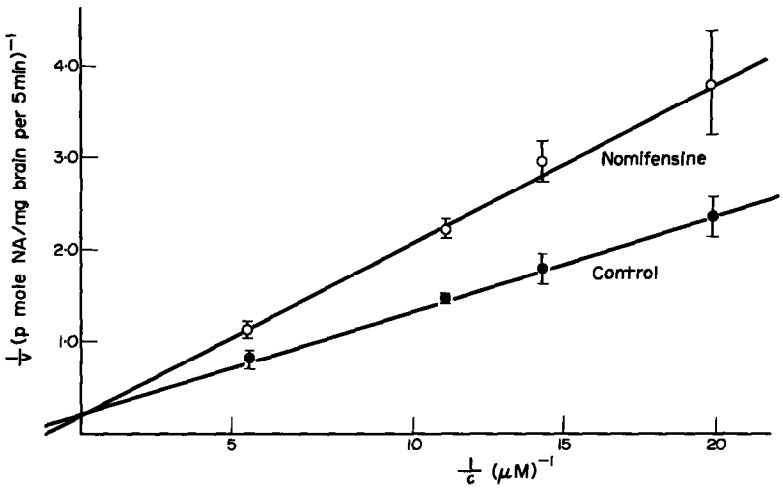

FIG. 4. Competitive inhibition of ^{14}C-NA uptake by nomifensine as illustrated by the Lineweaver–Burk method. Reaction conditions were the same as in Fig. 2 except that 1×10^{-7} M nomifensine (○) was incubated simultaneously with ^{14}C-NA during a 5 min period (● indicates control rates). Concentration range of ^{14}C-NA was 0·05–0·18 μM. Uptake was evaluated in triplicate and each point represents mean value ± S.D.

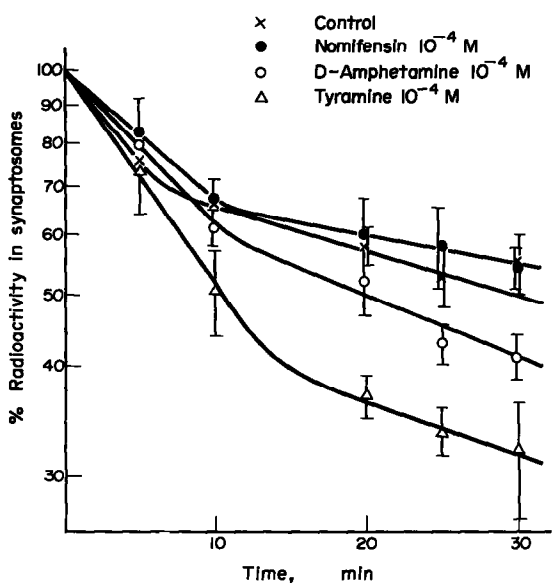

FIG. 5. Effects of nomifensine, D-amphetamine and tyramine on release of ^{14}C-NA from synaptosomes. Total radioactivity remaining in synaptosomes following uptake of ^{14}C-NA after varying times of incubation without drugs and with drugs was measured as described in Materials and Methods. Each value is the mean ± S.D. of at least three determinations. The radioactivity at zero time (100 per cent) was $295 \times 10^3 \pm 49 \times 10^3$ dis/min per g brain (n = 20).

and the stronger influence of the tertiary amines (chlorimipramine, imipramine, amitriptyline) on 5-HT uptake, reported by others,[16,23–27] except that under our experimental conditions amitriptyline was slightly less active than nortriptyline in inhibiting the 5-HT uptake process.

Nomifensine inhibited the uptake of both NA and 5-HT into synaptosomes from whole brain competitively (Figs. 3 and 4). A competitive pattern of inhibition has also been found for tricyclic antidepressants in the hypothalamus, whereas catecholamine uptake in the striatum was inhibited noncompetitively by these drugs.[12]

Whilst nomifensine appears to resemble D-amphetamine in its inhibition of the NA and 5-HT uptake processes, it differs from amphetamine in so far as it has no effect on the release of NA from synaptosomes (Fig. 5).

The efflux of ^{14}C-NA which was determined by assaying radioactivity retained in the particulate fraction was exponential with time. During the first 10 min, there was a rapid loss of accumulated radioactivity which was then followed by a slow release phase. The efflux of NA occurred more rapidly when incubation was performed in the presence of D-amphetamine (10^{-4} M) or tyramine (10^{-4} M) which are known to induce a release of catecholamines from storage sites.[28,29] Nomifensine did not enhance significantly the spontaneous release of NA or its metabolites from synaptosomes.

DISCUSSION

In the last few years there has been a great interest in the possible roles of NA and 5-HT in mental illness. It has been suggested that there may be some dysfunction of these biogenic amines in depressive states.[30–32]

The relationship between the therapeutic value of antidepressants and their pharmacological and biochemical actions in experimental animals and in various tissue preparations has received much attention. Many antidepressant compounds are believed to exert their effect by blocking the re-uptake of released NA and 5-HT, thus increasing the concentrations of transmitter substances at receptor sites of the synapse.

Kielholz and Pöldinger[33] distinguished several components in the clinical actions of antidepressants such as mood elevation and psychomotor activation. Comparing this differentiation with the results of the inhibition of monoamine uptake by tricyclic antidepressants, it was concluded that mood elevation is related to an inhibition of 5-HT re-uptake in central neurons, whereas blockade of NA re-uptake promotes drive in the depressed patient.[23,26] Assuming that these relationships between antidepressant action and the influence on neurotransmitter uptake are significant, our results suggest that nomifensine acts relative to 5-HT mainly by blockade of catecholamine re-uptake in the central nervous system, leading to more pronounced psychomotor activation rather than mood elevation. This has been confirmed by the clinical results obtained so far.

According to the pharmacological studies in animal experiments, nomifensine has been classified as a thymoleptic drug with a centrally stimulating component.[2] This component, which is lacking in most thymoleptic drugs may be due to the strong inhibition of catecholamine re-uptake into noradrenergic as well as dopaminergic nerve endings. In contrast to the tricyclic antidepressants which act predominantly on hypothalamic noradrenergic synaptosomes, nomifensine has also proved to be a

potent inhibitor of NA uptake in whole brain synaptosomes. Nomifensine has about the same activity as nortriptyline and protriptyline on NA uptake into synaptosome preparations from the hypothalamus, but it is 130 times as potent as these tricyclic compounds in synaptosome preparations from whole brain. It may be concluded that nomifensine, like amphetamine,[11] is also active on dopamine uptake into striatal synaptosomes. This assumption has been confirmed by Hunt *et al.*[34]

Kinetic analysis of the mechanism of inhibition of catecholamine uptake by tricyclic antidepressants indicated that inhibition was competitive in the hypothalamus and noncompetitive in the corpus striatum.[12] It is still not known what features of the noradrenaline and dopamine neurons may account for the differing types of inhibition. As nomifensine inhibits NA uptake into synaptosomes from whole brain competitively, presumably it inhibits catecholamine uptake competitively in hypothalamus and corpus striatum as well. Amphetamine inhibits catecholamine uptake competitively in both brain regions[12] and, moreover, it proved to be a competitive inhibitor of 5-HT accumulation into synaptosomes from whole rat brain.[17] 5-HT uptake inhibition by nomifensine was also competitive.

Nomifensine seems to be similar to D-amphetamine in its inhibitory properties on catecholamine and 5-HT uptake mechanisms of brain synapses but it differs clearly from amphetamine in so far as it has no releasing effects on the efflux of NA from rat brain synaptosomes. Although nomifensine, like amphetamine, strongly inhibits catecholamine uptake processes, it does not show the characteristic features of a sympathicomimetic drug. In animal experiments and clinical studies concerning the influence of nomifensine on the body functions, especially on the cardiovascular system, no side-effects have been observed.

In contrast to nomifensine, other 1,2,3,4-tetrahydroisoquinolines which have been suggested to be formed in man through a condensation reaction of the catecholamines and acetaldehyde,[35] are only weak inhibitors of both NA and 5-HT uptake processes in synaptosomal fractions.[36,37] With salsolinol, the condensation product of dopamine and acetaldehyde, IC_{50} values of approximately 3×10^{-4} M have been obtained for NA and 5-HT uptake; this compound also causes a release of ^{3}H-catecholamines from brain tissue *in vitro*.[36]

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