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Effect of neuroleptics on the disappearance rate of [^{14}C] labelled catecholamines formed from [^{14}C]tyrosine in mouse brain

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The accumulation and disappearance of [^{14}C] labelled dopamine and noradrenaline formed from [^{14}C]tyrosine in mouse brain has been investigated. After reaching peak concentrations the [^{14}C]dopamine and noradrenaline concentration declined exponentially with half-lives of 2·5 and 6·7 h respectively. The effect of some known neuroleptics belonging to different chemical groups as well as of a new neuroleptic compound, Lu 10-022 [2-trifluormethyl-6-fluoro-9-(3-(4-(2-hydroxyethyl) piperazin-1-yl)propyl) thioxanthen], on the disappearance rate of [^{14}C]catecholamines between 1·5 and 3 h after administration of [^{14}C]tyrosine was compared. All neuroleptics tested, except clozapine, increased the disappearance rate of [^{14}C]dopamine in a dose-dependent manner at the lower dose intervals. However, above a certain dose the disappearance rate was not elevated further. Haloperidol, fluphenazine and Lu 10-022 increased the disappearance of [^{14}C]dopamine more strongly than the rest of the neuroleptics. The disappearance rate of [^{14}C]noradrenaline was also increased by all the neuroleptics, except clopenthixol, although the change was less than for [^{14}C]dopamine disappearance, resulting in a rather poor dose-response relation. Pimozide and Lu 10-022 influenced the [^{14}C] noradrenaline disappearance less than the other neuroleptics. The hypothermic effect caused by the neuroleptics was not related to the change in the disappearance rate of the catecholamines.

The rate of disappearance of labelled catecholamines *in vivo* after an injection of radioactive tyrosine has been taken as an index of their turnover rates in brain (Nybäck & Sedvall, 1968). The disappearance rate of labelled dopamine (^{14}C-DA) has been shown to increase after treatment with neuroleptics (Nybäck & Sedvall, 1968, 1970). Sedvall (1969) showed an increased disappearance of [^{14}C]noradrenaline (^{14}C-NA) from rat submaxillary gland on nerve stimulation after injection of [^{14}C]tyrosine. Furthermore, nerve impulse flow seems to be necessary for the neuroleptics to increase central dopamine turnover, as shown by Andén, Corrodi & others (1971) using the dopamine-depleting effect of α-methyl tyrosine and by Nybäck (1972) using the accumulation and disappearance of ^{14}C-DA formed from [^{14}C]-tyrosine. Carlsson & Lindqvist (1963) proposed that the increase in catecholamine turnover after neuroleptics most likely results from the neuroleptic-induced receptor blockade, which by a feed-back mechanism activates the presynaptic neurons. Furthermore, the hypothermic effect elicited by the neuroleptics has been demonstrated not to be responsible for the change in amine turnover caused by the neuroleptics (Nybäck, 1971). Although many experiments have been performed to investigate the influence of neuroleptics on the synthesis and turnover of brain

catecholamines (Carlsson & Lindqvist, 1963; Andén, Butcher & others, 1970; Andén, Corrodi & Fuxe, 1972; O'Keefe, Sharman & Vogt, 1970; Nybäck, 1971; Bartholini, Haefely & others, 1972), a comparison between more than a few neuroleptics has been reported only by Andén & others (1970), Stille & Lauener (1971) and Sedvall & Nybäck (1972). Also rather high doses of neuroleptics have been used. The present study on the disappearance of labelled catecholamines in brain was undertaken to investigate the dose-response relation in a pharmacologically appropriate dose range for neuroleptics belonging to different chemical groups. Furthermore, a new neuroleptic compound (Møller Nielsen, unpublished data) Lu 10-022 [2-trifluormethyl-6-fluoro-9-(3-(4-(2-hydroxyethyl)piperazin-1-yl)propyl)thioxanthen, dihydro chloride] has been compared with the known neuroleptics.

METHODS

Male albino mice, NMRI/BOM, SPF, 18–27 g, were used at 21–24°. For the time course study of the accumulation and disappearance of [^{14}C] labelled catecholamines the mice were given intravenous injections of [^{14}C]-L-tyrosine (The Radiochemical Centre, Amersham, 507 mCi mmol^{-1}, 10 μCi in 0·5 ml of saline per 25 g of body weight) and killed after various periods of time.

To determine the influence of neuroleptics on the disappearance of [^{14}C] labelled catecholamines, the animals were given injections of [^{14}C]-L-tyrosine as described above. Drug (or saline to controls) was injected subcutaneously 90 min later, and after a further 90 min the rectal temperature was measured and the animals were killed by cervical dislocation.

The brain was removed, frozen on dry ice, weighed and homogenized in perchloric acid containing EDTA and ascorbic acid. Approximately 10 μg of noradrenaline and dopamine was added as carrier substances. After centrifugation an aliquot of the supernatant was taken for determination of total radioactivity. The catecholamine contents in the remaining supernatant were adsorbed on alumina (prepared as described by Anton & Sayre, 1962) and subsequently eluted with 0·2N HCl (Nybäck & Sedvall, 1968).

^{14}C-DA and ^{14}C-NA were separated by cation exchange chromatography on a Dowex 50W × 4 column (Bertler, Carlsson & Rosengren, 1958 as modified by Häggendal, 1962, 1963). The acid eluates from this column, containing noradrenaline (N HCl) and dopamine (2N HCl) respectively, were evaporated to dryness at 70° in a stream of air. The dry residues were dissolved in 0·2 ml of 0·1N HCl and 1 ml of ethanol. After the addition of 10 ml of Instagel (Packard Inst. Co.) to these samples and to the aliquots of the supernatants the radioactivity was determined by liquid scintillation spectrometry. A correction for the relative efficiency of counting was made by recounting the samples after the addition of known amounts of [^{14}C]-toluene. The recovery of labelled dopamine and noradrenaline was 70–80%. The results have not been corrected for this recovery.

RESULTS

The total radioactivity was high immediately after the injection of [^{14}C]tyrosine and declined rapidly (Fig. 1A). The content was 17% of the peak concentration after 1·5 h and declined to approximately 10% after 3 h.

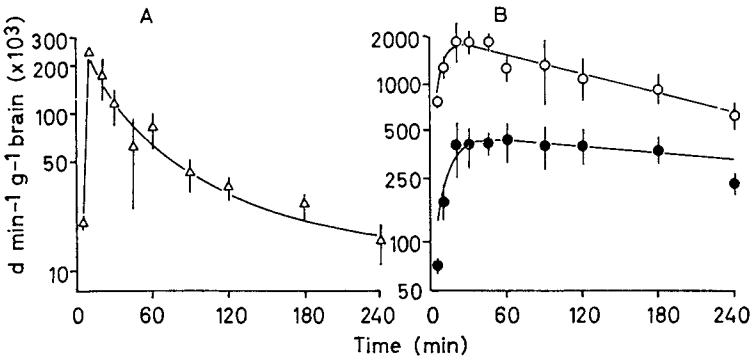

FIG. 1. Time course of total radioactivity (A) and labelled catecholamines (B) in mouse brain following a single i.v. injection of [^{14}C]-L-tyrosine (10 μCi per 25 g weight). Mice were killed 5, 10, 20, 30, 45, 60, 90, 120, 180 and 240 min after the injection. △Total radioactivity. ○ [^{14}C] dopamine. ● [^{14}C] noradrenaline.
Each point is the mean value ± s.d. (disintegrations min^{-1} g brain^{-1}) of 2–40 determinations.

Since the brain [^{14}C]amine data indicated that a one compartment model with first order accumulation and elimination might be applicable for kinetic evaluation, the best fitting curves according to such a system were calculated by a non-linear least squares curve fitting procedure. Furthermore, when the disappearance data alone were considered the decline in radioactivity was found to be exponential (method of least squares. F-test for linearity: $P>0{\cdot}10$ for both dopamine and noradrenaline; t-test for regression coefficient different from 0: $P<0{\cdot}001$ and $P = 0{\cdot}02$ for dopamine and noradrenaline data respectively).

^{14}C-DA and ^{14}C-NA increased rapidly and reached maximal values 26 and 53 min after the injection (Fig. 1B). The rate constants of synthesis were 7·9 and 4·4 h^{-1} respectively. The rate constants of elimination were 0·28 and 0·10 h^{-1}, giving half lives of ^{14}C-DA and ^{14}C-NA of 2·5 and 6·7 h respectively. The turnover times—the time required for the total pool size of the amines to be renewed—were therefore (1/k elimination) 3·6 and 9·7 h for the two amines. The results are in accordance with Nybäck (1971), who found k-values of 0·26 and 0·16 h^{-1} for dopamine and noradrenaline respectively.

The contents of ^{14}C-DA ^{14}C-NA in mouse brain 3 h after injection of [^{14}C]tyrosine and 1·5 h after neuroleptics are shown in Tables 1 and 2. The significance of the differences between the controls and treated groups was tested by two tailed Student's t-tests.

All the tested neuroleptics, except clozapine, increased the disappearance rate of ^{14}C-DA (Table 1). Above a certain dose the disappearance rate was not elevated further by increasing the dose; below this dose, however, the effect was dose-related. With haloperidol, fluphenazine and Lu 10-022, the ^{14}C-DA level was reduced to 30–40% of the controls, which represents at least a four-fold decrease in its half-life. With the remaining neuroleptics, except clozapine, the ^{14}C-DA level was reduced by the higher doses to 50–60% of the controls.

With ^{14}C-NA a different picture was obtained. A dose-response relation did not seem to exist for its disappearance to the same extent as for ^{14}C-DA disappearance. Also the increase in ^{14}C-NA disappearance rate was lower than for ^{14}C-DA. With the higher doses of chlorpromazine, haloperidol, fluphenazine, α-flupenthixol, chlor-

Table 1. Effect of neuroleptics on the level of [^{14}C]dopamine in mouse brain. Mice received [^{14}C]-L-tyrosine (10 μCi per 25 g weight) i.v. and neuroleptics or saline (control) s.c. 90 min later. After a further 90 min the mice were killed. Figures represent the mean ± s.d. (per cent of control) of (n) animals. Shown in brackets is the content of [^{14}C]dopamine in the control group (disintegrations min^{-1} g $brain^{-1}$). Statistics: two tailed Student's *t*-test. $P < 0.05$ (a), $P < 0.01$ (b), $P < 0.001$(c) *vs* saline group.

Dose mg kg^{-1} s.c.	Chlorpromazine 2HCl	Fluphenazine 2HCl	Chlorprothixene HCl	Clopenthixol 2HCl	α-Flupenthixol 2HCl
0	100±22(14) [915±205]	100±22(17) [947±208]	100±22(15) [922±205]	100±23(17) [889±205]	100±22(21) [934±208]
20					
5	54±25(6)c	32±17(4)c	50± 7(4)c	58± 6(4)c	51± 7(4)c
2·5	65± 5(3)a	44±20(3)b	52±11(4)c	53±0·4(2)c	48±13(3)c
1·25	75±11(5)a	37±15(4)c	70±19(4)a	37±1 (2)c	48±10(3)c
0·63	88±25(4)	36±15(4)c	72±10(4)a	63±36(4)a	45± 4(4)c
0·31	—	—	80±28(4)	76±19(4)	49± 6(4)c
0·16	—	48±19(4)c	106±13(4)	99± 9(4)	70±18(4)a
0·08	—	76±14(4)a	—	—	94±14(4)
0·04	—	90±0·4(4)	—	—	—
0·02	—	—	—	—	—

Dose mg kg^{-1} s.c.	Lu 10-022 2HCl	Haloperidol	Pimozide	Clozapine
0	100±12(14) [928±112]	100±21(24) [926±195]	100±20(18) [922±186]	100±24(14) [811±193]
20				99±10(3)
5	32±16(3)	35±11(4)c	65±10(4)b	126±17(3)
2·5	42± 6(3)c	42± 7(2)c	57±13(3)b	129±30(5)
1·25	45±24(3)c	38±12(5)c	50± 5(4)c	116± 9(3)
0·63	45± 5(3)c	29±14(4)c	—	85±34(5)
0·31	77± 7(3)b	29±16(3)c	49± 9(5)c	92±22(6)
0·16	64±30(6)a	43±24(4)c	71± 2(4)c	89±14(6)
0·08	84±14(4)a	57±18(4)c	102± 7(3)	94±28(4)
0·04	83±16(4)a	68± 7(4)c	—	79±13(3)
0·02	98±19(4)	97±15(4)	—	—

prothixene and probably also with clozapine (except 20 mg kg^{-1}) the ^{14}C-NA level was reduced to 60–70% of the controls. With pimozide and Lu 10-022 the level was reduced to approximately 80% of the controls, whereas clopenthixol was without effect. The minimal effective doses (MED) i.e. the doses after which the ^{14}C-DA or ^{14}C-NA contents were significantly ($P<0.05$) lower than the control values, are shown in Table 3, together with the level of [^{14}C]amine obtained with the respective doses, expressed as per cent of control.

The ratios between the doses changing ^{14}C-NA and ^{14}C-DA disappearance (Table 3) illustrate that the neuroleptics influenced the activity in dopaminergic and noradrenergic neuron systems to different degrees. Most neuroleptics were rather potent in changing ^{14}C-DA disappearance, and much higher doses were required for changing

Table 2. *Effect of neuroleptics on the level of* [^{14}C]*noradrenaline in mouse brain.* Mice received [^{14}C]-L-tyrosine (10 μCi per 25 g weight) i.v. and neuroleptics or saline (control) s.c. 90 min later. After a further 90 min the mice were killed. Figures represent the mean $\pm$ s.d. (per cent of control) of (n) animals. Shown in brackets is the content of [^{14}C] noradrenaline in the control group (disintegrations min^{-1} g brain^{-1}). Statistics: two tailed Student's *t*-test. $P < 0{\cdot}05$(a), $P < 0{\cdot}01$(b), $P < 0{\cdot}001$(c) *vs* saline group.

Dose mg kg^{-1} s.c.	Chlorpromazine HCl	Fluphenazine 2HCl	Chlorprothixene HCl	Clopenthixol 2HCl	α-Flupenthixol 2HCl
0	100±18(16) [361±64]	100±18(16) [406±75]	100±19(14) [411±79]	100±23(16) [382±88]	100±21(20) [391±81]
20					
5	61±29(6)b	61±20(4)b	60±18(4)b	88±17(4)	64±12(4)b
2·5	91±20(3)	75± 8(3)a	54±16(4)c	78± 0(2)	79± 3(3)c
1·25	98±24(5)	87±26(4)	68±17(4)b	91± 9(2)	86±19(4)
0·63	111± 8(4)	91±25(4)	86±27(4)	101± 8(4)	86±15(4)
0·31	—	—	99±15(4)	115±21(4)	82±12(4)
0·16	—	108±40(3)	112±14(4)	121±15(4)	103±33(4)
0·08	—	129±38(4)	—	—	102±18(4)
0·04	—	105± 7(4)	—	—	—
0·02	—	—	—	—	—

Dose mg kg^{-1} s.c.	Lu 10-022 2HCl	Haloperidol	Pimozide	Clozapine
0	100±12(14) [373+46]	100±18(26) [365+64]	100±23(18) [391±91]	100±22(14) [364±79]
20				37+ 8(3)c
5	86±16(3)	54±14(5)c	100±10(4)	66± 4(3)c
2·5	82±10(3)a	87±19(4)	82± 6(3)	91±29(5)
1·25	80±23(3)a	92±28(5)	75± 7(4)c	96±27(3)
0·63	109±30(3)	100± 7(4)	—	74±18(4)a
0·31	117±14(3)	103±32(4)	74± 6(5)c	74±20(6)a
0·16	100± 9(6)	124±50(4)	91±16(4)	74±10(6)a
0·08	96±13(4)	100±22(4)	113±15(3)	86±30(4)
0·04	94±20(4)	114±19(4)	—	73±19(3)
0·02	106±20(4)	112±29(4)	—	—

^{14}C-NA disappearance. Clozapine differs from the rest of the neuropleptics, by not enhancing the disappearance of ^{14}C-DA. At the higher dose levels (especially 2·5 mg kg^{-1}) the disappearance of dopamine was, if anything, decreased. On the other hand, clozapine increased the disappearance of noradrenaline.

The rectal temperatures of non-treated mice and [^{14}C]tyrosine-treated mice were 38·0 $\pm$ 0·5° (173 determinations). All neuroleptics except pimozide produced hypothermia in higher doses (Table 4). There was no correlation ($P > 0{\cdot}05$) between the MED_{DA} or MED_{NA} and the lowest doses, which decreased the rectal temperature more than 1° compared to controls (Spearman rank correlation coefficients (r) = −0·446 and −0·386 respectively).

Table 3. *Influence of neuroleptics on the disappearance of* [^{14}C] *catecholamines formed from* [^{14}C] *tyrosine in mouse brain.* Shown are the minimal effective doses (MED) i.e. the doses after which the [^{14}C]dopamine or noradrenaline contents are significantly ($P < 0.05$) lower than the control values. Shown in parentheses are the [^{14}C]amine contents as per cent of the control.

		Minimal Effective Dose mg kg^{-1} s.c.				MED_{NA}
Chemical group	Drug	[^{14}C]dopamine		[^{14}C]noradrenaline		MED_{DA}
Phenothiazines	Chlorpromazine	1·25	(75)	5·0	(61)	4
	Fluphenazine	0·08	(76)	2·5	(75)	32
Thioxanthenes	Chlorprothixene	0·63	(72)	1·25	(68)	2
	Chlopenthixol	0·63	(63)	>5·0	—	>8
	α-Flupenthixol	0·16	(70)	2·5	(79)	16
	Lu 10-022	0·04	(83)	1·25	(80)	32
Butyrophenones	Haloperidol	0·04	(68)	5·0	(54)	125
Diphenylbutylamines	Pimozide	0·16	(71)	0·31	(74)	
Dibenzodiazepines	Clozapine	>20	—	0·16	(74)	<0·008

Table 4. *Effect of neuroleptics on the rectal temperature of mice.* Mice received [^{14}C]-L-tyrosine (10 μCi per 25 g of body weight) i.v. and neuroleptics or saline (control) s.c. 90 min later. Temperature was measured 90 min after neuroleptics. Figures represent the mean ± s.d. (°C) of (n) determinations. Rectal temperature of control mice was 38·0 ± 0·5° (173 determinations). All temperatures below 37° differs from control ($P < 0.05$, Student's *t*-test).

Dose mg kg^{-1} s.c.	Chlorpromazine HCl	Fluphenazine 2HCl	Chlorprothixene HCl	Clopenthixol 2HCl	α-Flupenthixol 2HCl
20					
5	30·4±1·3(4)	35·3±0·2(2)	33·0±1·3(2)	32·9±3·0(2)	33·3±0·3(2)
2·5	32·8±0·4(6)	36·0±0·7(3)	33·0±1·6(4)	36·2±0·2(2)	35·3±0·9(3)
1·25	36·1±0·4(5)	37·3±1·2(4)	31·8±1·4(4)	36·6±0·6(2)	34·9±1·3(4)
0·63	36·4±0·4(4)	37·1±0·2(4)	33·0±3·0(4)	37.4±0·4(4)	36·5±0·6(4)
0·31	—	—	35·0±2·8(4)	37·6±0·1(4)	37·3±0·3(4)
0·16	—	37·2±0·6(4)	37·0±0·2(4)	37·6±0·2(4)	37·4±0·4(4)
0·08	—	38·1±0·4(4)	—	—	37·9±0·1(4)
0·04	—	37·3±0·4(4)	—	—	—
0·02	—	—	—	—	—

Dose mg kg^{-1} s.c.	Lu 10-022 2HCl	Haloperidol	Pimozide	Clozapine
20				31·7±0·4(3)
5	36·1±0·2(3)	33·3±0·6(4)	37·8±0·3(4)	32·5±1·9(3)
2·5	37·1±0·2(3)	36·7±0·3(4)	37·7±1·4(3)	36·5±1·3(5)
1·25	37·5±0·2(3)	37·2±0·4(5)	37·9±0·2(4)	37.4±0·6(3)
0·63	37·4±0·3(3)	37·5±0·5(4)	—	37·4±0·3(5)
0·31	37·8±0·3(4)	37·2±1·0(4)	37·5±0·5(5)	37·5±0·3(6)
0·16	37·8±0·3(6)	36·7±0·3(4)	37·5±0·4(4)	37·6±0·4(6)
0·08	37·8±0·2(4)	37·3±0·2(4)	37·7±0·2(3)	37·2±0·3(4)
0·04	37·5±0·2(4)	37·5±0·4(4)	—	37·4±0·3(4)
0·02	37·3±0·3(4)	37·8±0·3(4)	—	—

DISCUSSION

In the present study the rate constants for synthesis and elimination of ^{14}C-DA and ^{14}C-NA were calculated, assuming that the catecholamines are found in a single open compartment. Due to the inhomogeneity of the catecholamine stores, this assumption can be questioned, but the calculated curves according to this model fit the experimental data closely. The rate constants of synthesis and elimination therefore represent mean values for the total amount of amines in the brain, and the corresponding values in the active pool and in the storage pool probably differ from these.

The decline in [^{14}C] labelled catecholamines between 1·5 and 3 h after the [^{14}C]-tyrosine injection is predominantly determined by their rate of disappearance, since the synthesis of labelled amines from remaining [^{14}C]tyrosine is negligible (cf. Nybäck & Sedvall, 1968, 1970 and Fig. 1 A). The influence of neuroleptics on the disappearance of labelled amines probably reflects an activation of the turnover rate of brain catecholamines, because several neuroleptics have been shown not to change the endogenous level of brain amines in the low doses used in the present study (Carlsson & Lindqvist, 1963; Andén & others, 1970; Nybäck & Sedvall, 1970; Scheel-Krüger, 1972).

The decline in [^{14}C]amines after treatment with neuroleptics in all probability is not exponential because the drug concentration changes and with it the receptor blockade and turnover of amines. Therefore, in the present work the effect of neuroleptics is not expressed as a change in half life or rate constant but rather as a relative value, namely as the content of labelled amines in per cent of the content in control animals 1·5 h after treatment with neuroleptics.

Since no correlation was found between the change in disappearance and the hypothermic effect elicited by the neuroleptics, the lowered body temperature after neuroleptics is probably not responsible for the change in disappearance rate. This is in agreement with Nybäck (1971), who found no difference in the synthesis of labelled amines between saline-treated mice at normal or high ambient temperature or between normothermic and hypothermic chlorpromazine-treated mice.

All neuroleptics, except clozapine, increase the disappearance of ^{14}C-DA in a dose-dependent manner. However, above a certain dose the disappearance rate is not elevated further. This probably means that the different neuroleptics are able to cause blockade to a certain extent and therefore only activate the proposed feed-back mechanism (Carlsson & Lindqvist, 1963; Andén & others, 1971; Nybäck, 1972) to operate to a certain degree. With haloperidol, fluphenazine and Lu 10-022, the level of ^{14}C-DA is reduced to 30–40% of the controls, whereas with the other neuroleptics, except clozapine, which is without effect, the level is reduced to 50–60% only. This might indicate that the three first mentioned neuroleptics possess a stronger dopamine receptor blocking effect, i.e. a stronger intrinsic activity or a greater affinity for the dopamine receptor than the other neuroleptics. By measuring the rise in striatal homovanillic acid Stille & Lauener (1971) also found haloperidol and fluphenazine to be much more potent than chlorpromazine and chlorprothixene.

Also the disappearance of ^{14}C-NA is increased by all the neuroleptics except clopenthixol, but the change in disappearance is much less than the change in ^{14}C-DA disappearance. A dose-response relation was not obtained to the same extent as for ^{14}C-DA disappearance. This probably indicates that the increase in ^{14}C-NA disappearance is not elicited solely by a feed-back mechanism caused by a noradrenaline receptor blockade, but other mechanisms may be involved. Since a clear dose-

response relation was obtained only with the ^{14}C-DA and not with the ^{14}C-NA disappearance, the ratio MED_{NA}/MED_{DA} (Table 3) must be taken with caution. The ratio for pimozide, especially, is uncertain, because an effect on ^{14}C-NA disappearance was obtained with 1·25 and 0·63 mg kg^{-1} but not with the higher doses, 2·5 and 5 mg kg^{-1}. However, the neuroleptics most potent in changing ^{14}C-DA disappearance (haloperidol, fluphenazine and Lu 10-022) also seem to have the highest ratio, which probably indicates a greater specificity for these compounds than for the rest of the neuroleptics. Clozapine is the only compound having a ratio less than one, because only ^{14}C-NA disappearance is elevated.

The results are in good accordance with those of Sedvall & Nybäck (1972) who used much higher doses. In their study pimozide changed the turnover of dopamine but had no effect on noradrenaline. In contrast to the other neuroleptics clozapine in their study had an effect on both ^{14}C-DA and ^{14}C-NA accumulation. An influence on both noradrenaline and dopamine turnover was also found by Bartholini & others (1972), who showed that after 50 mg kg^{-1} of clozapine the α-methyl-*p*-tyrosine (α-MT) induced decrease in cerebral noradrenaline was much more accelerated than the decrease in dopamine. Andén & others (1970, 1972) have examined the functional effects of several neuroleptics on the dopamine receptors in the corpus striatum and the noradrenaline receptors in the spinal cord of rats, and have compared these effects with the effects on dopamine and noradrenaline turnover. With few exceptions they found that blockade of the dopamine or noradrenaline receptors observed in the functional models after treatment with neuroleptics was correlated with turnover changes observed in the respective neurons. One of the more interesting exceptions was pimozide, which in the functional models was absolutely specific, because only the dopamine receptors were blocked. However, pimozide increased the turnover of dopamine as well as of noradrenaline. This latter observation is supported by the present study.

From Tables 1, 2 and 3, it appears that within the phenothiazine and within the thioxanthene group, neuroleptics with quite different activities are found both when the effect on ^{14}C-DA and ^{14}C-NA disappearance and when the ratio between the MED's are considered. No inferences can be drawn about the general effect of neuroleptics belonging to the other three groups, butyrophenones, diphenylbutylamines and dibenzodiazepines.

Finally, the compound, Lu 10-022, appears to be as potent as haloperidol and fluphenazine in effecting an increase in ^{14}C-DA disappearance, and like these compounds does so in doses much lower than those, which influence the disappearance of ^{14}C-NA.

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