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Effects of 5-HT Receptor Subtype-Selective Drugs on Locomotor Activity and Motor Habituation in the DHT Adult Rat Model

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PRANZATELLI, M R , E JAPPAY AND S R SNODGRASS *Effects of 5-HT receptor subtype-selective drugs on locomotor activity and motor habituation in the DHT adult rat model* PHARMACOL BIOCHEM BEHAV **27**(3) 497–504, 1987 —5-Hydroxytryptophan (5-HTP) induces biphasic time and dose dependent effects on locomotor activity (LMA) and motor habituation in rats with 5 7-dihydroxytryptamine (DHT) lesions To identify the role of serotonin (5-HT) receptors in these responses, we studied the effects of 5-HT_2 receptor antagonists on LMA occurring spontaneously and evoked by 5-HTP or putative selective 5-HT agonists in rats injected intracisternally with DHT or vehicle Motor habituation was assessed by analysis of computer-tabulated 10 minute "bins" during hour long recording Neuroleptic 5-HT_2 antagonists prevented 5-HTP stimulation of LMA in DHT-lesioned rats in the rank order of potency pirenperone > pipamperone > ketanserin = cinanserin The non-neuroleptic ritanserin, however, did not reduce LMA stimulated by the 5-HT_{1B} agonist RU24969 but did reverse transient suppression of LMA induced by high dose 5-HTP and by the putative 5-HT_2 agonist DOI RU24969, like 5-HTP, induced a failure of motor habituation which differed from DOI-evoked alteration 8-OH-DPAT did not affect motor habituation at the dose tested These data suggest that the 5-HT_{1B} site mediates 5-HTP-evoked locomotor hyperactivity in the DHT model, that the 5-HT_2 site participates in the transient hypoactivity seen with high doses of 5-HTP, and that 5-HT_1 and 5-HT_2 sites may be functionally linked Both sites differentially influence motor habituation, which appears to be under complex regulation Bin analysis is a sensitive index of these habituation effects

Locomotor activity Bin analysis 5-HT_2 antagonists Motor habituation
5,7-Dihydroxytryptamine (DHT) 5-HT agonists

LOCOMOTOR activity (LMA) and motor habituation may be altered by potentiation of serotonergic neurotransmission in the rat [13,18] A role for both central serotonin (5-HT) [16,18] and dopamine (DA) [2, 7, 10] receptors has been suggested There is evidence that some of the 5-HT receptor sites (5-HT_1 and 5-HT_2) identified by radioligand binding studies in the brain [30] are functionally significant and participate in various forms of motor activity [15, 18, 35, 39]

We previously reported that 5-hydroxytryptophan (5-HTP) alters locomotor activity in rats with 5,7-dihydroxytryptamine (DHT) lesions [31,32], a possible model of denervation supersensitivity of post-synaptic serotonin receptors [37,38] 5-HTP also induces a failure of motor habituation, preventing the normal decline in behavioral frequency or magnitude with repeated stimulus presentation [4,9] Motor habituation can be measured by analysis of sequential epochs or "bins" of activity within a session, which are computer-tabulated while total counts are recorded To test the hypothesis that a single 5-HT receptor subtype mediates the effects of 5-HTP on LMA and motor habituation, we studied the effects of 5-HT receptor subtype-selective drugs in the adult rat with and without DHT lesions

Drugs regarded as most selective for subtypes of 5-HT receptors are 5-HT_2 antagonists and 5-HT_1 agonists Ritanserin, pirenperone, pipamperone, and ketanserin (haloperidol analogs) are selective for 5-HT_2 receptors (10^{-9} M) and lack the agonist activity of "classical" 5-HT antagonists

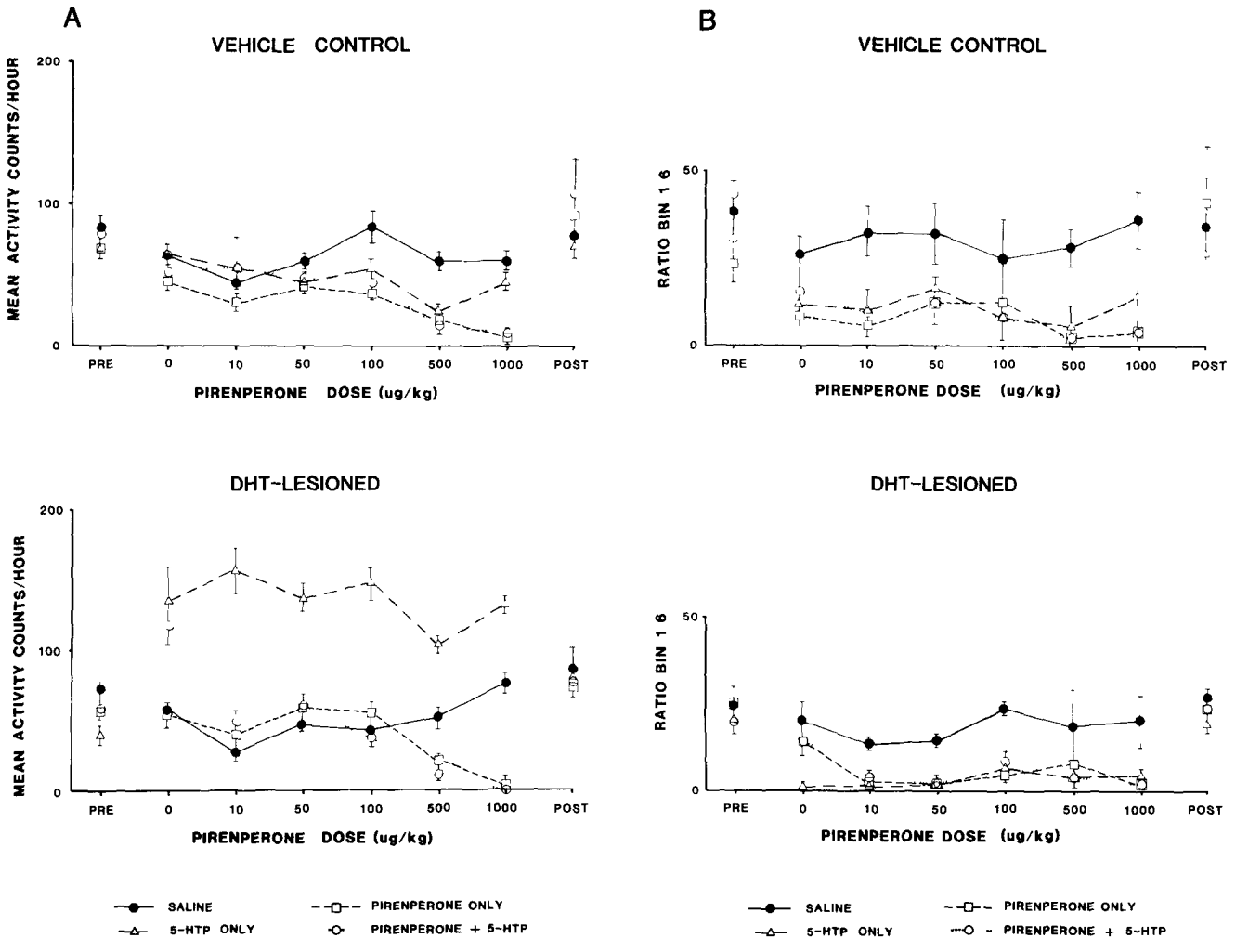

FIG 1 (A) Mean LMA in unlesioned (VEHICLE CONTROL) and DHT-lesioned rats in response to saline (●), 5-HTP (△), pirenperone (□) or pirenperone + 5-HTP (○) Data from ascending and descending dose schedules of pirenperone, which were not statistically different, were combined Spontaneous LMA was measured three days before (PRE) and after (POST) drug treatments The group indicated as 5-HTP received no antagonist (X-axis label applies to all but this group) A non-arithmatic, non-logarithmic scale was used to facilitate visual inspection of dose thresholds (B) Ratio bin 1 6

[6, 24, 25] Except perhaps for ritanserin, they also have potent effects on other receptors (DA, alpha$_1$-adrenergic) [17,25] Cinanserin, a cinnamanilide [11], is a structurally unrelated 5-HT antagonist, which is less selective for 5-HT$_2$ site but has little activity at histamine or alpha-adrenergic sites For agonists, we chose RU24969 (5-methoxy-3(1,2,3,6-tetrahydropyridin-4-yl)1H-indole, 8-OH-DPAT (8-hydroxy-2-(di-n-propylamino) tetralin), and DOI (1-(2,5-dimethoxy-4-iodo-phenyl aminopropane)-2) for selectivity at 5-HT$_{1B}$, 5-HT$_{1A}$, and 5-HT$_2$ receptors, respectively [14, 15, 36, 39]

METHOD

Animals and Drugs

Three hundred and fifty male, 80–100 g, Sprague-Dawley rats (Batin and Kingman, Fremont, CA) were housed four to an 18×34×51 cm plastic cage with free access to food and water Temperature was constant (23°C) and a 12-hour light-dark cycle was provided Drugs were prepared before each experiment and dosages (in 0 5 to 1 ml) were calculated according to body weight as determined on the day of testing 5,7-Dihydroxytryptamine creatinine sulfate (DHT, Sigma), RU24969 (Roussel UCLAF), 8-OH-DPAT (RBI), L-ascorbic acid (Sigma), cinanserin HCl (Squibb), DOI (RBI), pipamperone HCl (Janssen), and desipramine HCl (with warming, Merrell Dow) were dissolved in 0 9% normal saline L-5-hydroxytryptophan (Calbiochem, San Diego, CA) was acidified in saline with HCl Drug vehicles included 20% propylene glycol plus ethanol for ritanserin and pirenperone (Janssen), and 5% dextrose and 0 1% tartaric acid in 50% propylene glycol for ketanserin (Janssen) Phenobarbital (130 mg/ml, Elkins Sinn, Cherry Hill, NJ) was used in manufacturer's vehicle

Lesioning

In our modification [32] of the DHT model [37,38], 5-HT depletion is maximized with multiple DHT injections Under ether anesthesia, rats received two intracisternal injections separated by 3–5 days of DHT (200 μg free base in 25 μl 0 9%

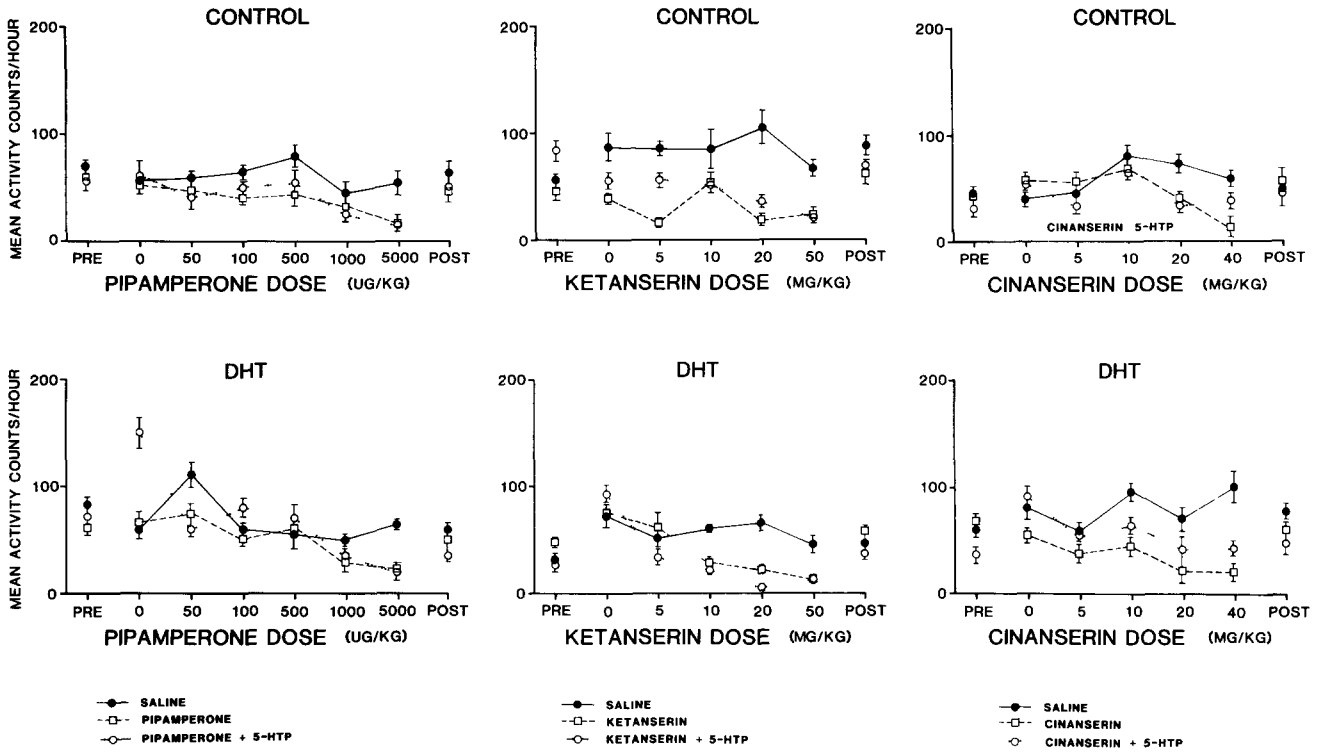

FIG 2 Effect of pipamperone (μg/kg) (N=16), cinanserin (mg/kg) (N=64), and ketanserin (mg/kg) (N=48) alone (□) or in combination with 5-HTP (○) on LMA in unlesioned (CONTROL) and DHT-lesioned rats Spontaneous LMA was measured three days before (PRE) and after (POST) drug treatments

saline) or saline (both with 0 1% w/v ascorbic acid) Rats were pretreated with desipramine (25 mg/kg) (to make lesions selective for 5-HT neurons) and phenobarbital (40 mg/kg) (to reduce convulsions) by intraperitoneal injection This procedure consistently produces large and selective 5-HT depletions in multiple brain regions 92% depletion of 5-HT in neocortex, 90% in cervical spinal cord, 100% in septum/accumbens, 44% in brainstem, and 68% in hippocampus [32]

Measurement of Locomotor Activity in Neuroleptic Studies

LMA was measured two weeks after intracisternal treatments After acclimatizing to test room conditions in their home cages, rats were injected with test drug and placed immediately in plastic 20×22 5×45 cm test cages without food or water

LMA was measured for one hour simultaneously in 16 identical activity cages, each with one photocell 3 cm above the cage floor halfway along the length of the cage Proper functioning of the cages was tested at intervals throughout the study Beam interruptions (counts) were recorded automatically and computer-tabulated as 10 minute epochs or "bins" and totalled hourly Studies were conducted between 1 and 4 p m , when baseline activity in the rat is stable [38], under uniform fluorescent lighting Periodic visual inspection of the rats and attention to on-line bin scores allowed exclusion of the few rats (<2%) whose stereotypic-myoclonic behaviors interrupted the photocell beam and caused spuriously high counts

5-HT_2 antagonists (pirenperone, ketanserin, cinanserin, or pipamperone) were injected intraperitoneally 15–20 minutes prior to 5-HTP (30 mg/kg) or 0 9% saline Therefore, each rat received two injections at each testing session either 5-HTP or saline and either a 5-HT_2 antagonist or its vehicle Rats were randomly assigned to receive all doses of only one 5-HT_2 antagonist (doses selected from preliminary studies) administered in an ascending or descending dose schedule A three day interval separated testing sessions (doses) Each rat served as its own control, tested three days before and after the study Multiple control groups were also used, including the equivalent number of repeated saline or other vehicle injections in unlesioned and DHT-treated rats The possible development of tolerance to 5-HTP was assessed by the use of one additional group of rats treated with 5-HTP only, acting as a control for each of the antagonist experiments

5-HT Agonist and Ritanserin Studies

Different rats received a single dose of one drug (or drug combination) only chosen based on ED_{50}s from the literature [14, 15, 39] RU24969, DPAT, and DOI, injected subcutaneously, were used as selective agonists of 5-HT_{1B}, 5-HT_{1A}, and 5-HT_2 receptors, respectively Ritanserin or vehicle was injected intraperitoneally 45 minutes prior to agonists We chose ritanserin instead of other 5-HT_2 antagonists for these studies, which were conducted last, when it became accepted as a non-neuroleptic selective 5-HT_2 antagonist [15] An observer counted crossings for one hour in the same size cages used in photocell studies Crossings of the longitudinal axis of the cage (as in photocell interruptions) were scored continuously during sequential 10 minute intervals after drug injection

TABLE 1

EFFECTS OF SELECTIVE 5-HT AGONISTS ON LMA IN RATS WITH DHT LESIONS

	LMA	BIN 1 6
Saline	52 5 ± 4 5	23 8 ± 7 3
RU24969	341 0 ± 39 9*	0 7 ± 0 2*
8-OH-DPAT	116 0 ± 14 0*	34 3 ± 21 8
DOI	17 8 ± 3 8*	4 5 ± 2 0*

LMA is the mean ± S E M of total hourly counts, each N=5–7 rats BIN 1 6 is the ratio of counts from the first to the last 10 minutes of an hour recording

*$p<0$ 05 (SNK test)

Measurement of Motor Habituation

The distribution of LMA within the hour was summarized by the ratio of activity during the first to last ten minutes of the hour (ratio bin 1 6) This ratio was found to be the most sensitive indicator of a change in motor habituation [31] In computing bin ratios, counts of zero were changed to a count of one to prevent division by zero Five bin patterns, which were identified by visual inspection, were also used in the analysis decremental (steadily decreasing counts), incremental (steadily increasing counts), continuous (similar counts in every bin), discontinuous (dissimilar counts in each bin without a decreasing or increasing pattern), and not active (0–5 counts in all bins) [31]

Statistics

Statistical analysis used the general linear models (GLM) procedure of the Statistical Analysis System (SAS) [33], which was run on an IBM 3081 computer at the University of Southern California and a Digital Vax 750 computer at Columbia University Health Sciences Multivariate analysis of variance (MANOVA) was used to determine the effect of independent variables (drug, dose, dosing schedule, intracisternal treatment, and pre- and post-study measurements) on dependent variables (LMA, bin ratio, bin pattern) For all significant main effects (F statistic allowed rejection of the null hypothesis), the Student Newman-Keuls (SNK test) multiple range test of the means was used to clarify the nature of difference between individual groups such as determining dose thresholds ($p<0$ 05) [1] Dose thresholds were used to compare drug effects

RESULTS

Effects of 5-HT$_2$ Antagonists on Spontaneous LMA

5-HT$_2$ antagonists significantly reduced total LMA (Figs 1 and 2) pirenperone, $F(11,549)=10$ 41, $p<0$ 0001, pipamperone, $F(1,48)=5$ 59, $p<0$ 02, ketanserin, $F(9,213)=7$ 52, $p<0$ 0001, cinanserin, $F(9,284)=4$ 05, $p<0$ 001 (MANOVA) The effect of dose was highly significant pirenperone, $F(7,549)=14$, $p<0$ 001, pipamperone, $F(6,48)=3$ 74, $p<0$ 004, ketanserin, $F(5,213)=6$ 32, $p<0$ 0001, cinanserin, $F(6,248)=4$ 27, $p<0$ 001 Neuroleptic doses suppressed spontaneous LMA significantly in both lesioned and unlesioned rats (thresholds from SNK test, $p<0$ 05), pirenperone 100 μg/kg (Fig 1), pipamperone 1 mg/kg, ketanserin 20 mg/kg, cinanserin 20 mg/kg (Fig 2) Mean LMA did not differ significantly between ascending and descending dose schedules, which were then combined for subsequent analyses

TABLE 2

EFFECT OF PRETREATMENTS ON 5-HTP- AND RU24969-INDUCED LMA IN BIN 2

Pretreatment	Treatment	LMA
Veh	NS	9 5 ± 1 9
Veh	5-HTP	0*
Rit	5-HTP	7 5 ± 2 6
Rit	NS	8 0 ± 1 4
Veh	RU	65 5 ± 14 0*
Rit	RU	65 3 ± 5 1*

Each group of 4–6 rats was injected IP with 0 5 mg/kg ritanserin (Rit) or vehicle (Veh) one hour prior to 50 mg/kg 5-HTP, saline (NS) or RU24969 (RU) Cage-crossings were counted for 10 minutes by an observer 20 minutes later

*$p<0$ 05 (SNK test)

Effects of 5-HT$_2$ Antagonists on 5-HTP-stimulated LMA

Threshold doses of antagonists were lower for reducing 5-HTP-stimulated LMA than for spontaneous LMA in the DHT group (Figs 1A and 2) Pirenperone and pipamperone were effective at 10 and 50 μg/kg, respectively, but the threshold dose for both cinanserin and ketanserin was 5 mg/kg (SNK test, $p<0$ 05) Dose-response for the latter drugs was poor Saline-treated DHT rats had thresholds similar to control rats treated with saline or 5-HTP 500 and 1000 μg/kg for pirenperone and pipamperone, respectively, and 20 mg/kg both for cinanserin and ketanserin (SNK test, $p<0$ 05) The locomotor response to 5-HTP did not attenuate significantly during intermittent treatment with 5-HTP alone

Effects of Selective 5-HT Agonists on LMA in Rats with DHT Lesions

5-HT agonists had differential effects on LMA and motor habituation in rats with DHT lesions, $F(320)=25$ 39, $p<0$ 001 RU24969 significantly increased LMA in bins 2 through 6 compared to saline and to other agonists (SNK test, $p<0$ 05) Only RU24969 differed from saline from 30 to 60 minutes Total hourly counts for all groups differed significantly from each other (Table 1)

Effects of Ritanserin on Agonist-Induced LMA

Ritanserin (0 5 mg/kg) reversed the suppression of LMA at 20 minutes by 5-HTP but had no intrinsic effect on LMA at the dose tested (Table 2) In contrast, ritanserin did not abate RU24969-induced locomotor hyperactivity

5-HT$_2$-Antagonist Effects on Motor Habituation

Analysis of bin ratios (Fig 1B) and bin patterns (Tables 3 and 4) contributed information on motor habituation Bin ratios were highest in saline groups (control or DHT), reflecting a rapid decline of LMA over the hour Bin ratios were significantly reduced by 5-HTP in DHT-lesioned rats, $F(6,48)=4$ 2, $p<0$ 002, and by pirenperone (with or without 5-HTP) at all doses in control and DHT groups ($p<0$ 005–0 0001) Pirenperone had highly significant drug, $F(11,549)=9$ 10, $p<0$ 001, and dose, $F(7,549)=24$ 87,

TABLE 3

PERCENTAGE OF RATS EXHIBITING EACH BIN PATTERN OF LMA IN RESPONSE TO PIRENPERONE WITH OR WITHOUT 5-HTP

	Control					DHT				
Dose (μg/kg)	Inc	Dec	Cont	Disc	NA	Inc	Dec	Cont	Disc	NA
					Pirenperone Alone					
0	0	90	10	0	0	3	64	8	19	6
10	0	60	20	20	0	0	54	15	31	0
50	0	69	8	23	0	0	57	0	43	0
100	0	69	8	23	0	6	56	19	6	13
500	0	9	9	27	55	0	30	0	14	56
1000	0	9	9	27	55	0	30	0	14	56
					Pirenperone + 5-HTP (30 mg/kg)					
0	0	50	25	25	0	13	33	40	14	0
10	0	39	8	30	16	10	20	30	30	10
50	6	44	19	25	6	22	22	22	22	12
100	15	46	8	23	8	13	13	25	37	12
500	8	8	18	16	50	9	27	0	28	36
1000	0	14	14	29	43	0	0	0	17	83

Inc=incremental, Dec=decremental, Cont=continuous, Disc=discontinuous, NA=no activity All variations of the discontinuous patterns are combined N=8–16 rats (except 0 dose N=64) shown also in Fig 1

TABLE 4

PERCENTAGE OF RATS EXHIBITING EACH BIN PATTERN OF LMA IN RESPONSE TO KETANSERIN WITH OR WITHOUT 5-HTP

	Control					DHT				
Dose (mg/kg)	Inc	Dec	Cont	Disc	NA	Inc	Dec	Cont	Disc	NA
					Ketanserin Alone					
0	0	75	15	5	5	0	58	16	26	0
5	0	55	0	36	9	0	63	12	25	0
10	0	50	0	40	10	10	40	0	40	10
20	0	67	0	16	17	0	33	0	50	17
50	0	17	0	33	50	0	25	12	38	25
					Ketanserin + 5-HTP (30 mg/kg)					
0	6	44	19	25	6	12	24	35	29	0
5	0	15	15	62	8	7	36	7	43	7
10	0	15	16	69	0	7	33	13	34	13
20	0	18	18	46	18	5	18	6	24	47
50	0	8	7	35	50	0	6	0	31	63

See abbreviations in Table 1 Each N=11–17 rats shown also in Fig 2

$p<0.001$, main effects on bin ratios The reduction of bin ratios by pirenperone, unlike by 5-HTP, paralleled the reduction of total counts (Table 3) Pipamperone, ketanserin, and cinanserin had similar effects on bin ratios (not shown)

Bin patterns also revealed neuroleptic effects (Table 3) The 5-HT_2 antagonists introduced a "no activity" pattern not seen with 5-HTP in control or DHT groups At 500 μg/kg pirenperone (SNK test, $p<0.05$), the decremental bin pattern was replaced by inactivity This effect occurred at lower doses of pirenperone in DHT rats also injected with 5-HTP 5-HT_2 antagonists and 5-HTP both decreased the decremental pattern However, 5-HT_2 antagonists induced inactivity, and effect not seen with 30 mg/kg 5-HTP used in this study, and had no clear effect at low doses on the 5-HTP-induced continuous pattern

The bin effects of ketanserin are shown in Table 4

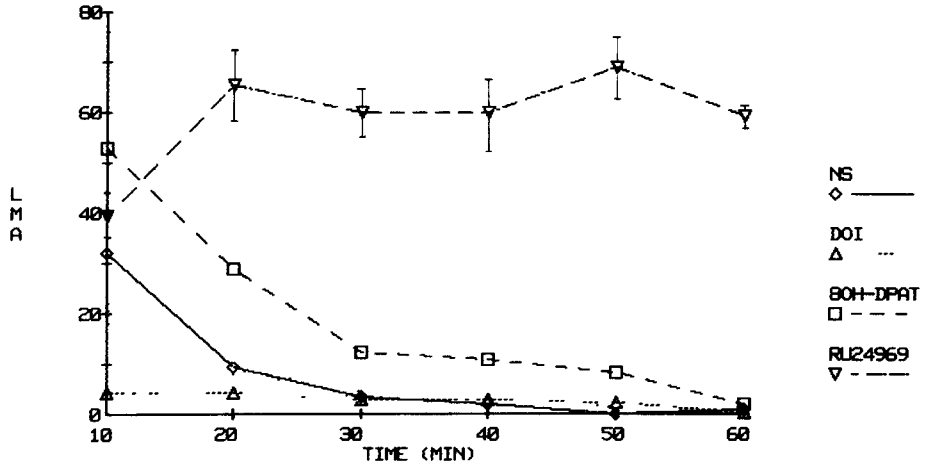

FIG 3 Effect on habituation of locomotor activity of 3 mg/kg normal saline (NS) (◇), RU24969 (▽), 8-OH-DPAT (□), and DOI (△) in rats with DHT lesions Cage-crossings were observer counted for 6 consecutive 10 minute intervals beginning immediately after drug injection Data are means with S E M

Cinanserin had similar effects percentages of each bin pattern in controls (without 5-HTP) were 53 (decremental), 6 (continuous), 35 (discontinuous), and 6 (inactive) at dose 0, and 27, 9, 36, and 28, respectively, at 50 mg/kg In DHT-treated rats, 0 dose percentage were 47 (decremental), 18 (continuous), 29 (discontinuous), and 6 (inactive), compared to values for 50 mg/kg of 33, 0, 33, and 34, respectively

Agonist Effects on Habituation

The continuous pattern of RU24969-stimulated LMA indicated a failure of motor habituation (Fig 3) Bin ratios were significantly reduced by RU24969 and by DOI for different reasons RU24969 increased and equalized bin counts and DOI reduced counts in the first bin

Effects of Chronic Drug Treatments

Differences between pre- and post-treatment LMA (three days before and after study) and intragroup differences for saline treatments (unlesioned and DHT-lesioned rats) were not significant (Figs 1 and 2) In the few instances of large discrepancies, there was also greater variability in the post-treatment measurement and no consistent direction of change among 5-HT_2 antagonists The effects of 5-HT_2 antagonists on bin patterns remitted by the next testing session Ninety-two percent of unlesioned and 69% of DHT-lesioned rats treated with pirenperone alone showed a decremental pattern of spontaneous post-treatment LMA Thirty percent of the DHT group had a continuous pattern Of rats which had been treated with both pirenperone and 5-HTP, the bin pattern of 82% of unlesioned and 80% of DHT-lesioned rats was decremental, and 10% of each group was continuous (not shown)

DISCUSSION

5-HT Receptors and Locomotor Activity

Our data support a different role for 5-HT_1 and 5-HT_2 receptors in LMA in the DHT model In naive rats, recent evidence suggests that stimulation of 5-HT_1 or 5-HT_2 receptors facilitates or inhibits, respectively, DA-dependent LMA [15,19] The effect of RU24969 to increase LMA in naive rats has been attributed to activity at the 5-HT_{1B} receptor [19, 28, 29], but the putative 5-HT_{1B} agonist m-chlorophenylpiperazine (m-CPP) decreases locomotor activity in the rat [35] This discrepancy may relate to the low selectivity of m-CPP for 5-HT_1 vs 5-HT_2 sites [26], or the greater degree of selectivity of RU24969 for 5-HT_{1B} vs 5-HT_{1A} sites [27,36] In rats with DHT lesions, RU24969 increased LMA In contrast, the suppressive effects of DOI were reversed by ritanserin at a dose which did not itself reduce LMA and may therefore represent a 5-HT_2 agonist effect

5-HTP had a different effect on LMA than either 5-HT_1 or 5-HT_2 agonists given alone in rats with DHT lesions We previously found time- and dose-related biphasic responses to 5-HTP in rats with DHT lesions LMA is suppressed transiently, especially with high 5-HTP doses, then rebounds [31,32] The early suppression is similar to the effect of DOI, whereas the subsequent increase resembles RU24969-induced LMA However, 5-HT agonists given alone had monophasic effects on LMA There are several possible explanations for the biphasic effect of 5-HTP A pharmacologic dose of 5-HTP, when decarboxylated to 5-HT, presumably stimulates both 5-HT_1 and 5-HT_2 receptors, allowing for both behavioral outcomes Blockade of low dose 5-HTP-induced behavioral depression in rats also was reported with LY53857, a selective 5-HT_2 receptor antagonist of the ergot alkaloid class, and with mianserin [20] The locomotor response may vary depending on whether 5-HT_1 receptors alone, as with RU24969, or both 5-HT_1 and 5-HT_2 receptors are stimulated simultaneously in association with a myoclonic response [34], as with 5-HTP but not RU24969 The 5-HT_2 agonist effect may have been merely of greater magnitude but briefer

Alternatively, 5-HT_1 and 5-HT_2 receptors may be functionally linked 5-HT_2 inhibition of 5-HT_{1B} sites may explain the report that ritanserin increases RU24969-induced locomotor hyperactivity in naive rats [15] In our rats with DHT lesions, it did not increase the response to RU24969 Our studies cannot differentiate between loss of a 5-HT permissive effect or a post-synaptic 5-HT receptor change as a

result of DHT to explain this discrepancy Functional linkage of 5-HT_1 and 5-HT_2 sites may also explain why in the present study, simultaneous use of 5-HTP and a 5-HT_2 antagonist to simulate the effects of 5-HT_1 agonists did not increase LMA 5-HT would have been expected to act as a 5-HT_1 agonist under these circumstances if stimulation of LMA by 5-HTP involves only a serotonergic mechanism [34] and 5-HT_1 and 5-HT_2 sites were not functionally linked [30]

Our studies differentiate between effects of neuroleptic and non-neuroleptic 5-HT_2 antagonists Neuroleptic-reversed 5-HTP stimulation was probably due to an antidopaminergic mechanism, since the rank order of inhibition by 5-HT_2 antagonists of LMA induced by 5-HTP in DHT-treated rats correlated better with their antidopaminergic properties (100-fold range) than with in vitro 5-HT_2 (20-fold range) or alpha$_1$-adrenergic properties [24] The complex relationship between DA and 5-HT in serotonergic syndromes [2,5] warrants further study, since 5-HT has a generally inhibitory effect on DA-dependent LMA [8, 13, 23], and the effect of 5-HTP on LMA has been attributed to central and peripheral serotonergic as well as catecholaminergic neurotransmission [3, 10, 22]

The approximately 200-fold difference we found in the threshold for reduction of LMA in vivo by 5-HT_2 antagonists which are essentially equipotent at the 5-HT_2 binding site [25] could suggest effects at peripheral 5-HT_2 receptors [12,21] However, the reduction of LMA induced by 5-HT_2 antagonists is most likely central, since only central 5-HT receptors are involved in DHT lesions [40], and the order of potency of locomotor effects correlated with lipophilicity and hence central activity [6] The role of peripheral 5-HT_2 receptors in LMA has not been investigated, although peripheral influences on sensorimotor responsiveness are known [3,22] The lack of well defined dose-response in many of the curves for 5-HT_2 antagonists with weak central activity may suggest influence of effects of stimulation of other types of receptors with increasing dose [25]

Effects of 5-HT_2 Antagonists on Motor Habituation

We have previously shown that analysis of sequential epochs or "bins" of activity is a useful index of motor habituation in studies of locomotor activity [31] The most characteristic effect of low dose 5-HTP on bin patterns in DHT-treated rats was continuous and incremental activity at the expense of the normal decrement of LMA (habituation) In our current study, 5-HT_2 antagonists significantly altered these bin patterns and hence motor habituation only at neuroleptic doses, which definitionally produced the "no activity" pattern Both RU24969 and DOI altered habituation A selective effect of RU24969 on motor habituation is suggested by fact that 8-OH-DPAT also increased LMA but did not impair habituation The effect of DOI may be selective for 5-HT_2 receptors since it was reversed by ritanserin These data suggest that multiple 5-HT receptors differentially modulate motor habituation, that 5-HT_{1B} sites play a major role, and that bin analysis provides useful qualitative information about these relationships not provided by total counts alone Further studies with other putative selective agonists at multiple doses will be necessary to confirm this hypothesis

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