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Motor Habituation in the DHT Model: Bin Analysis of Daytime and Nocturnal Locomotor Activity

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PRANZATELLI, M. R. AND S. R. SNODGRASS. *Motor habituation in the DHT model: Bin analysis of daytime and nocturnal locomotor activity*. PHARMACOL BIOCHEM BEHAV 24(6) 1679–1686, 1986.—We evaluated the usefulness of locomotor bin analysis as a measure of motor habituation, and the effects on habituation of serotonergic manipulations. Spontaneous and L-5-hydroxytryptophan (5-HTP)-evoked locomotor activity (LMA) was measured by photocells and computer-tabulated at 10 minute intervals (bins) during the day and at night in 150 adult rats treated intracisternally with 5,7-dihydroxytryptamine (DHT) or vehicle. Bins were analyzed by visual inspection, which differentiated decremental, incremental, continuous, and discontinuous patterns, and by calculating the ratio of the first to last bin of an hour. In controls, bin ratios were high due to rapid decline (decremental bin pattern) of daytime LMA. After DHT lesions, in contrast, ratios were low for one week. This was due to a failure of normal motor habituation, as reflected by an increase in continuous, discontinuous, and incremental bin patterns. 5-HTP evoked similar dose-related bin abnormalities in DHT-treated rats, after spontaneous patterns had returned to normal, and to a lesser extent in controls. However, no consistent drug or lesion effects on nocturnal LMA were seen. In comparison to daytime LMA, nocturnal LMA showed less habituation, and bin patterns were predominantly of the discontinuous type and more varied. These data suggest that bin analysis contributes useful information on motor habituation and drug and lesion effects and is easily incorporated into automated recording of LMA.

Locomotor activity Bin analysis Serotonergic syndrome DHT model Motor habituation
Nocturnal locomotion 5-Hydroxytryptophan 5,7-Dihydroxytryptamine

HABITUATION is the decline in behavioral frequency or magnitude which occurs with repeated stimulus presentation. It is seen with evoked or spontaneous behavior [8]. Drugs [5–8], brain lesions [19,30], or developmental factors [31] may impair habituation in the rat. Habituation is heterogeneous and may be subserved by multiple pharmacologic mechanisms and neurotransmitters [15,30]. Serotonergic (5-HT) manipulations alter habituation to startle [6,13] and tests of exploratory behavior [5]. Therefore, we wished to determine if altering 5-HT neurotransmission by giving L-5-hydroxytryptophan (5-HTP) with or without destruction of 5-HT terminals with 5,7-dihydroxytryptamine (DHT model) [26, 33–34] also modifies habituation of locomotor activity (LMA).

Studies of brain-behavior relationships often use LMA data, partly because collection of such data is readily automated [21–22, 28]. However, motor activity is highly situation specific and apparatus-dependent, and subject to maturational and physiologic changes [4,24]. Data on the effects of drugs and lesions on LMA are more often discrepant than for spontaneous LMA [9]. Most workers measure only total activity counts per testing session. We incorporated the analysis of epochs or bins of activity into our studies of LMA to evaluate the usefulness of bin analysis as a measure of motor habituation. We find that the rate of decline of LMA within a session (motor habituation) can be a more sensitive indicator of drug and lesion effects than is total LMA.

Nocturnal LMA is less often studied than daytime activity, despite the greater activity of rodents at night. Nocturnal studies may be important to understanding drug and lesion effects. The locomotor hyperactivity induced by lesions of the median raphe nucleus is predominantly nocturnal [3,13]. Therefore, we compared spontaneous and 5-HTP-evoked LMA in the daytime and at night in DHT-lesioned and unlesioned rats.

METHOD

Animals and Drugs

Male 80–100 g Sprague-Dawley rats were obtained from

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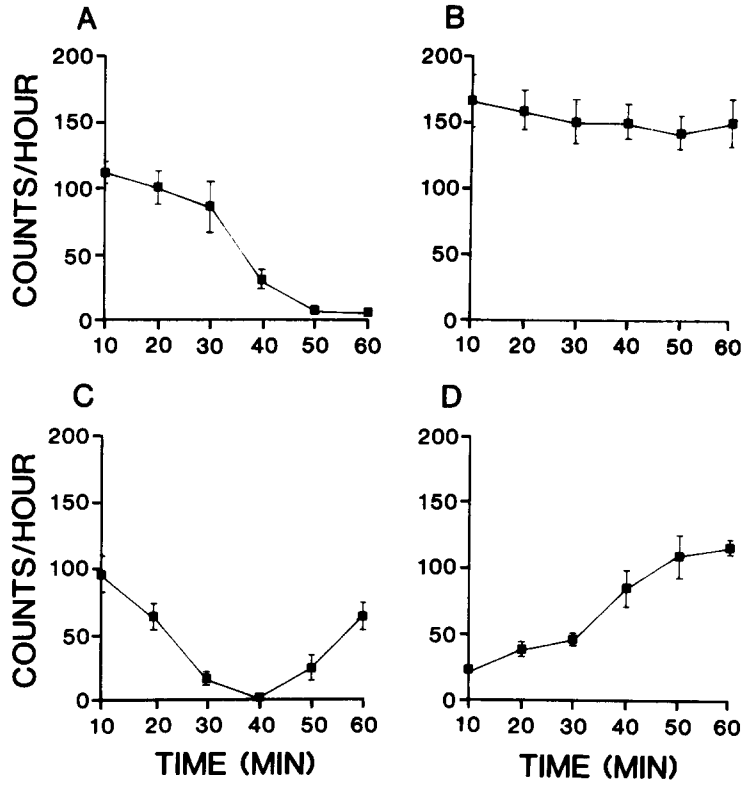

FIG. 1. Patterns of LMA during the first week after DHT lesions (N=40) revealed by analysis of ten minute epochs or "bins": (A) decremental, (B) continuous, (C) discontinuous, (D) incremental.

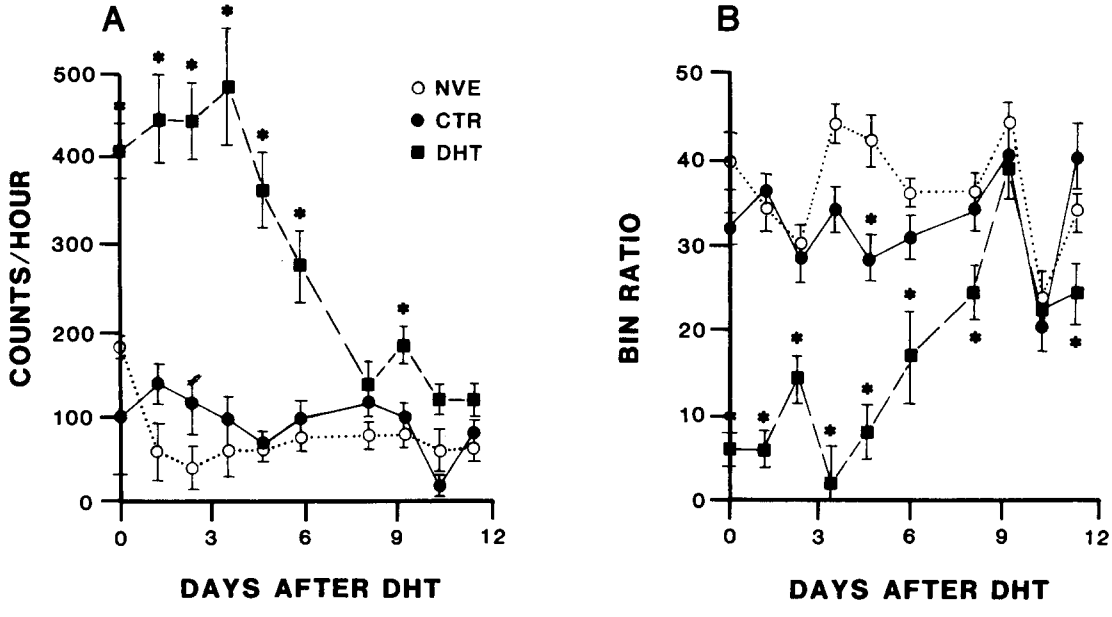

FIG. 2. Spontaneous daytime LMA in naive (NVE) (N=12), saline (CTR) (N=24), and DHT-treated rats (N=48). Testing began the day after the first DHT injection. (A) Total hourly counts. (B) Ratio bin 1:6. Significant differences ($p<0.05$) between DHT and CTR and between CTR and NVE rats are indicated (*).

Bantin and Kingman (Fremont, CA) and housed four to an 18×34×51 cm plastic-walled cage with free access to food and water, a 12-hour light-dark cycle (lights on 600–1800 hr), and constant temperature (23°C). All drugs were freshly prepared before use. Drug dosages (as salts) were calculated according to body weight determined on the day of testing and were administered in a one milliliter volume when possible. 5,7-Dihydroxytryptamine creatinine sulfate (Sigma), ascorbic acid (Sigma), desipramine HCl (donated, Merrell Dow) were dissolved in saline, and L-5-hydroxytryptophan (Calbiochem, San Diego, CA) was acidified with HCl. Phenobarbital (130 mg/ml, Elkins Sinn) was used in the manufacturer's vehicle.

Lesioning

Under ether anesthesia, rats received two intracisternal injections spaced 3–5 days apart of DHT (200 micrograms free base in 25 microliters 0.9% 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 abate immediate convulsions) by intraperitoneal injection [33]. This procedure consistently produces large and selective 5-HT depletions in multiple brain regions [25–26].

Measuring Locomotor Activity

Daytime studies. Different groups of rats were used for studies of daytime and nocturnal locomotor activity. LMA was measured at various intervals before and after rats were treated with intraperitoneal saline (naive) or intracisternal saline (control) or DHT (lesioned). Rats were transferred in their "home" cages from the animal facility to acclimatize to the test room conditions and placed in plastic cages (20×22.5×45 cm) lined with deotized cage board (Shepherd, Kalamazoo, MI) without food and water. Immediately after placement, LMA was measured for one hour simultaneously in 16 identical activity cages each fitted with a single photocell situated approximately three centimeters above the cage floor across the width of the cage. Proper functioning of the cages was tested at intervals through the study. Beam interruptions (counts) were recorded automatically and computer-tabulated as "bins" of ten minute duration and hourly totals. Studies were made between 1300–1600 hr, when baseline LMA in the rat is stable [34], under uniform fluorescent lighting with reasonable exclusion of external noise. This distribution of LMA within the hour was summarized for all drugs by the ratio of activity during the first and last ten minutes (bins) of the hour. In computing bin ratios, the common occurrence of an activity count of zero in the sixth bin was regarded as one to prevent division by zero. Periodic visual inspection of the rats and attention to on-line bin scores identified rats whose stereotypic-myoclonic behaviors interrupted the photocell beam and caused spuriously high counts. These rats were excluded from analysis.

All studies of 5-HTP dose-response were performed two weeks after intracisternal treatments. Control and DHT rats were injected intraperitoneally with 5-HTP (5, 10, 20, 30 mg/kg) or saline and immediately placed in photocell cages for recording of LMA.

Nocturnal studies. All-night (2200–0700 hr) recordings were conducted using the same equipment as described above. First, spontaneous LMA was measured in DHT-lesioned rats or their controls. One week later, these rats were injected with a single dose of 5-HTP (5, 10, or 20 mg/kg) or saline, and locomotor recording was begun immediately. Moist food was placed in the corner of the cage.

Statistics

The general linear models (GLM) procedure of the Statistical Analysis System (SAS) [27] was chosen for all statistical analysis, which was implemented on an IBM 3081 computer at the University of Southern California. Multivariate analysis of variance (MANOVA) was used to determine the effect of several independent variables (drug, dose, hour, intracisternal treatment (DHT vs. vehicle)) on dependent variables (total LMA, bin ratios, bin pattern). For all significant "main effects" (F statistic allowed rejection of the null hypothesis) [1], the Student-Newman-Keuls (SNK test) multiple range test of the means was used to clarify the nature of differences between individual groups, such as determining dose threshold effects. The probability of arriving at an F value greater than that observed if the null hypothesis were true was denoted by the significance probability $p<0.05$. Outliers (less than 5% of sample) were identified by inspection of the high and low values of the mean in the printed computer output [1]. All data are presented as means with standard errors (S.E.M.).

RESULTS

Spontaneous Daytime LMA

Visual inspection of LMA data by "bins" identified decremental, incremental, continuous, and discontinuous locomotor patterns (Fig. 1). The discontinuous pattern consisted primarily of the pattern shown in Fig. 1C, but also included its inversion (a pattern with activity only at 20–40 minutes). Bin ratios (ratio of one ten minute epoch to another) reflected these patterns: ratios>1 (decremental), ratios=1 (continuous or discontinuous), ratios<1 (incremental). They contributed most to analysis of LMA in the absence of changes in total hourly counts. We tested other ratios besides bin 1:6, such as the first to last thirty minutes, bin 1+2:5+6, and time of 50% change in response. Use of the ratio of bin 1+2:5+6 reduced variability but the habituation effect was also smaller. Of these methods, the 1:6 ratio was the most sensitive indicator of a change in motor habituation and was used in this study.

During the first week after lesioning, the bin pattern of LMA in DHT-treated rats was heterogeneous: decremental (62%), continuous (23%), discontinuous (12%), and incremental (8%). A particular pattern was often characteristic for a given rat. The response of controls was predominantly decremental (92%), and naive rats entirely so. For six days, bin ratios in the DHT group were decreased compared to controls (Fig. 2B), $F(7,38)=6.20$, $p<0.0003$, and total counts were elevated (Fig. 2A), $F(7,38)=10.28$, $p<0.0001$. Both recovered spontaneously. LMA declined significantly in all groups by 40 minutes, $F(10,63)=6.20$, $p<0.0003$. The rate of decline, measured by bin ratios (Fig. 3), differed significantly between groups, $F(7,63)=5.25$, $p<0.0002$: DHT and naive rats in all but the initial bin, DHT and control rats except at 40 minutes; and control and naive rats only at 10 and 40 minutes (SNK test, $p<0.05$). Small effects of intracisternal vehicle injections on bin scores were not seen in naive rats (Fig. 3). Standard deviations for LMA after DHT-lesioning were large compared to intact rats.

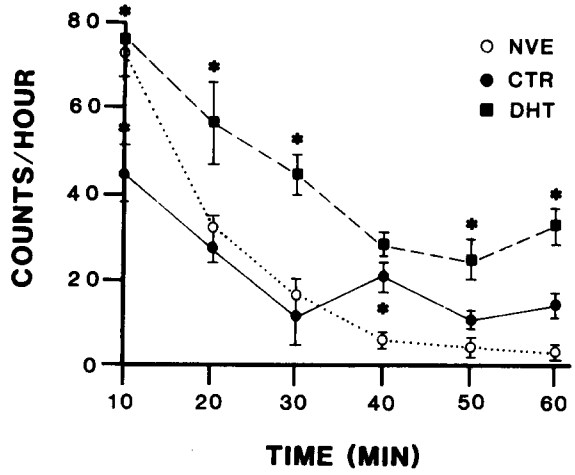

FIG. 3. Rate of decline of mean LMA during an hour long daytime recording in the same naive (NVE), saline (CTR) and DHT-treated rats shown in Fig. 2 (day three). Significant differences ($p<0.05$) between DHT and CTR and between CTR and NVE rats are indicated (*).

5-HTP Evoked Daytime LMA

Dose-response to 5-HTP was measured two weeks after intracisternal injections when total LMA and bin scores had returned to control levels. Analysis of bin scores substantiated weak drug effects evident from total counts. In total counts, significant differences occurred between DHT and control groups (Fig. 4A) at 5, 10, and 30 mg/kg 5-HTP, $F(5,27)=3.61$, $p<0.01$, $F(5,25)=2.04$, $p<0.04$, $F(5,25)=2.91$, $p<0.03$, but not within groups. Bin ratios differed between groups (Fig. 4B) at 10 and 20 mg/kg 5-HTP, $F(5,30)=3.40$, $p<0.015$ and $F(6,30)=3.29$, $p<0.02$. Low doses of 5-HTP significantly decreased bin ratios only in DHT-treated rats. LMA was distributed abnormally during the hour. 5-HTP reversibly shifted the pattern of LMA in DHT-lesioned rats (Table 1) from decremental to continuous and discontinuous, $F(6,42)=4.51$, $p<0.001$, at a dose threshold of 10 mg/kg (SNK test, $p<0.05$). The change to the continuous pattern in DHT-lesioned rats contributed most to the significant increase in total counts. However, the most prominent locomotor pattern in control, unlike DHT-lesioned, rats remained decremental. In the DHT group, 5-HTP transiently reestablished the bin pattern which had characterized the early effects of DHT.

Nocturnal Locomotor Activity

Over the first hour, total counts of nocturnal LMA declined significantly after saline injection (Fig. 5) in both controls and DHT-treated rats, $F(5,140)=47.33$, $p<0.001$. The decline was significant until 20 minutes, $F(1,28)=5.28$, $p<0.002$. Unlike daytime studies, there was no significant difference between groups, $F(1,24)=1.07$, $p<0.31$.

Nocturnal LMA was greater than daytime LMA, as expected. Over the night (Fig. 6), LMA declined significantly but remained higher than daytime levels (not shown). Differences between control and DHT groups were not statistically significant. However, in DHT-lesioned rats, the range of LMA during most of the night was reduced and a nadir between 0200 and 0400 hours in control rats was not seen (Fig. 6A).

The nocturnal bin pattern differed significantly from the daytime pattern. Intermittent bursts of activity for 10–30 minutes with longer quiescent periods occurred in unlesioned and DHT-lesioned rats. Compared to daytime studies, the distribution of nocturnal activity was heterogeneous: approximately half of the rats had a discontinuous pattern, and the other patterns were represented almost

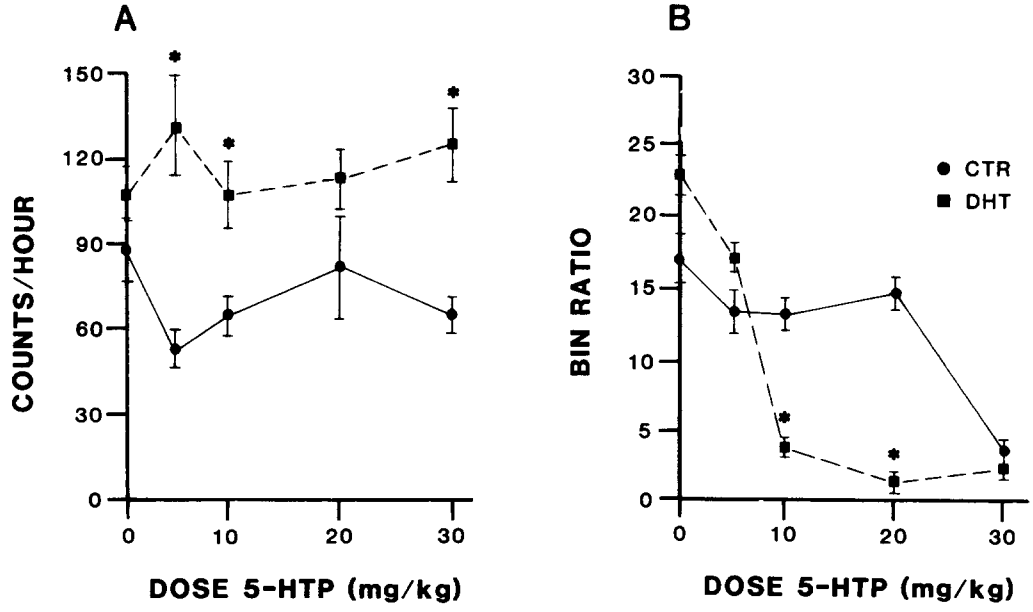

FIG. 4. (A) Mean daytime locomotor response (total counts) to increasing doses of 5-HTP in saline (CTR) (N=10) and DHT-treated rats (N=16–21). Significant between-group differences ($p<0.05$) are indicated (*). (B) Ratio bin 1:6.

TABLE 1

PERCENTAGE OF RATS EXHIBITING EACH BIN PATTERN OF LMA IN RESPONSE TO 5-HTP

	Control				DHT			
Dose (mg/kg)	Inc	Dec	Cont	Disc	Inc	Dec	Cont	Disc
Daytime								
0	0	92	9	0	8	83	8	8
5	0	91	9	0	11	73	18	0
10	8	75	17	0	0	22	67	11
20	0	56	33	11	0	22	56	22
30	11	45	11	33	8	25	67	0
Nocturnal								
0	10	21	16	53	14	20	20	46
5	4	17	21	58	3	30	3	64
10	14	17	17	52	9	23	11	57
20	15	23	6	56	11	6	23	60

Abbreviations: Inc=incremental, Dec*=decremental, Cont=continuous, Disc=discontinuous. N=9–12 rats also shown in Fig. 4 (Daytime) and Fig. 6(B) and 6(C) (Nocturnal). Dose 0 is the sum of saline-treated groups, which were not statistically different. One hour daytime studies are compared to the first hour of nocturnal recording after 5-HTP or saline injection.

equally (Table 1). Patterns did not change significantly over the night. 5-HTP did not significantly modify the basal pattern of locomotor activity in controls (Fig. 6B) or DHT-treated rats (Fig. 6C), whether the data was analyzed for the first hour after injection (to make it more comparable to daytime studies) or for all nine hours of the night.

DISCUSSION

Motor Habituation

We found significant lesion and drug effects on the habituation of LMA in our DHT-treated rats. Locomotor hyperactivity due to DHT or 5-HTP was associated with failure of motor habituation. The impairment of habituation we observed was short-term, seen within a test session [8,30], in contrast to long-term habituation, which can be observed between sessions [36]. Impairment of habituation frequently results in a continuous level of activity for the entire experimental period [7–8]. Such a pattern, which follows lesions of the median raphe nucleus, resembles that seen in some human disorders: the animals spend time moving about, less time exploring or working for a reward, and their behavior does not habituate normally [3,36]. The median raphe nucleus appears to be involved in the regulation of activity level and the reaction to novel, aversive, and other environmental stimuli [11, 13, 18, 32]. Hippocampal lesions are especially likely to reduce habituation [19–20]. A reduction in hippocampal 5-HT has been proposed to explain increased LMA induced by median raphe lesions [16–17, 35].

The rate of decline of LMA over the testing session we found after intracisternal DHT is similar to that reported after intracerebroventricular injection (using similar recording methods) [23]. The heterogeneity of bin patterns (decremental, incremental, continuous, discontinuous) in DHT-treated rats may reflect variable destruction of 5-HT neurons

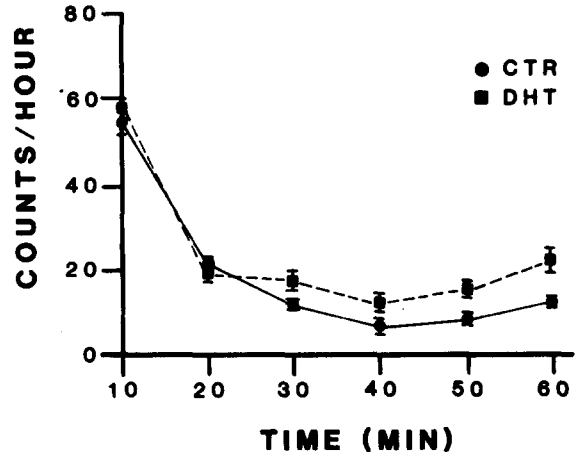

FIG. 5. Rate of decline of mean LMA during the first hour of nocturnal recording in the same saline (CTR) and DHT-treated rats (each N=8).

in critical brain regions. Spontaneous resolution of this pattern during the first two weeks of recovery after DHT possibly involves several mechanisms: recovery of non-lethally injured neurons, pre- and post-synaptic alterations which restore normal motor inhibition by serotonergic and other neurotransmitter systems, or development of additional compensatory mechanisms. 5-HTP transiently reestablished this pattern of impaired habituation in DHT-treated rats when spontaneous LMA had returned to control levels. Variable effects of 5-HTP on LMA in unlesioned [12,29] and DHT-lesioned rats [34] have been reported when only total activity counts were recorded. The effect of 5-HTP on

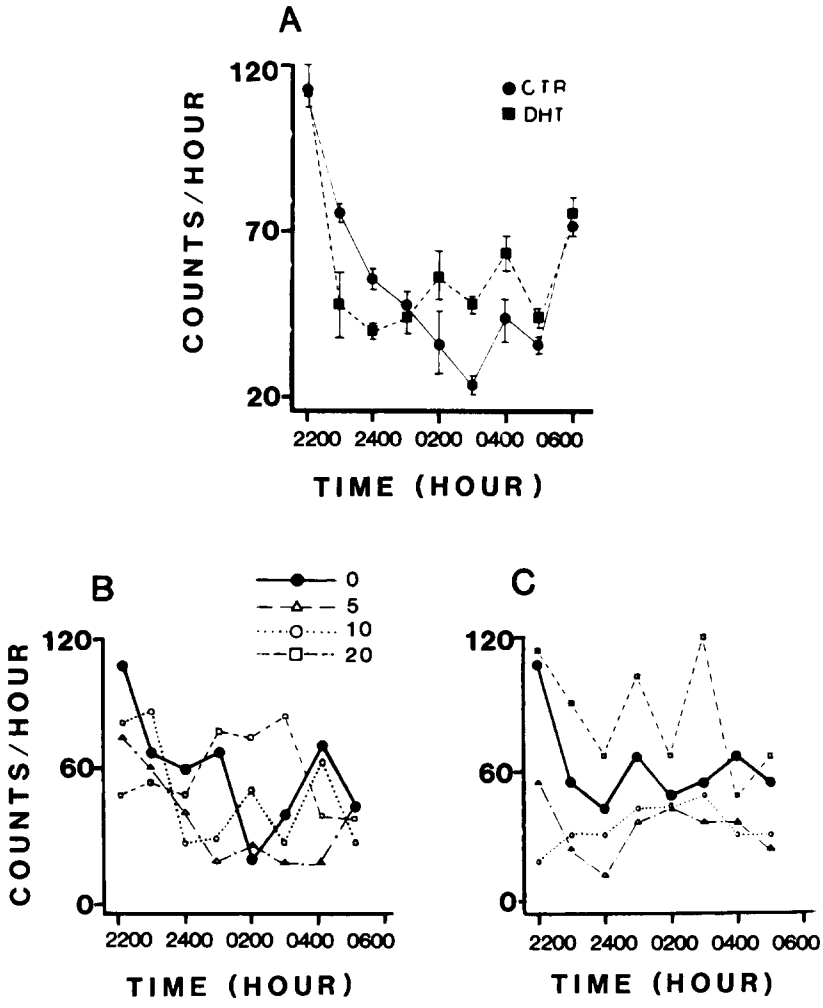

FIG. 6. (A) Spontaneous nocturnal locomotor activity in the same rats shown in Fig. 5. (B) Nocturnal response of controls and (C) DHT-lesioned rats to 0, 5, 10 or 20 mg/kg 5-HTP injected immediately before the recording session at 2200. The solid line identifies the saline-treated group.

habituation may be specific since thresholds differed in unlesioned and lesioned rats. The mechanism of the effect (loss of specificity, sensory thresholds, changed baseline response level, memory impairment) is unclear, and secondary effects (autonomic, generalized slowing of activity) cannot be excluded [8]. Bin analysis of the effects of other drugs which evoke 5-HT mediated behavior [14] will be necessary to determine the specificity of 5-HTP in changing bin patterns.

Our studies suggest that bin analysis is a useful measure of locomotor habituation. Routine use of bin analysis together with total locomotor counts provides more information about motor activity and may help identify environmental and brain factors which regulate LMA. The situation specificity of LMA has been related to various methodologic considerations, such as apparatus, testing paradigms, method and nature of lesioning [12, 22, 28, 36]. For example, mesencephalic (electrolytic) raphe lesions increase open field [18, 32, 36] but not home cage [32] motor activity. Habituation of LMA has been calculated in several ways, including regression over the entire observation period and the use of epochs of various lengths (1, 10, 30 minutes) [2, 23, 31]. Several of these methods provide comparable information. Bin ratios revealed most trends found by more elaborate analysis of bin patterns. Since lesioning tends to increase the variance of LMA in our studies and in others [9], bin analysis is best suited to large studies where outliers are readily identified and can be excluded.

Time of Day Effects on LMA

The lack of significant drug and lesion effects on motor activity in our nocturnal but not daytime studies is perhaps counter-intuitive, since rodents are nocturnal animals. However, such situation specificity has been reported after various 5-HT lesions. Two weeks after injection of DHT in the fornix-fimbria, nocturnal activity in photocell cages increased 150–170% of controls [36]. Nocturnal LMA (crossovers) increased two- to three-fold after median (but not dorsal or lateral) raphe lesions [13]. Neither of these lesions was associated with significant daytime locomotor activity. We

found no reports of nocturnal LMA after intracisternal DHT with which to compare our results. If lesions of the mesencephalic raphe nucleus are an important mechanism of nocturnal locomotor hyperactivity, one might predict that intracisternal DHT would not have the same effect, since it does not significantly deplete 5-HT in the midbrain [25–26].

Lack of significant nocturnal hyperactivity after DHT or 5-HTP may relate to physiologic or pharmacologic differences in the regulation of nocturnal and daytime LMA. There are other explanations. A ceiling effect is possible, since LMA was already maximally increased at night in both groups. Our nocturnal and daytime studies are not strictly comparable since animals were fed during the prolonged nocturnal recording but not the hour long daytime recording. Analysis of nocturnal LMA is more complex due to the greater activity, variability in bin patterns, and the similarity of drug- and lesion-induced bin patterns to spontaneous nocturnal patterns. More sophisticated statistical analysis involving spectral array may ultimately be required to maximize information for nocturnal drug and lesion studies, however, there were no major effects. The time of night we chose to administer 5-HTP may have also been an important variable, since increased LMA has been found in some studies only in the second half of the night period [13,36]. Diurnal variations in the concentration of 5-HT in brain are small, but 20-fold changes have been reported in CSF, peaking several hours after lights-off [10]. The influence of 5-HT released physiologically by various regions such as the mammalian pineal [10] on nocturnal patterns of LMA has not been studied. However, pharmacologic alteration of 5-HT levels by 5-HTP may supercede the effects of physiologic release.

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