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Behaviors Induced by 5-Hydroxytryptophan in Neonatal, Preweaning, Postweaning, and Adult Sprague-Dawley Rats

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MOKLER, D. J., S. A. SULLIVAN AND B. J. WINTERSON. *Behaviors induced by 5-hydroxytryptophan in neonatal, preweaning, postweaning, and adult Sprague-Dawley rats.* PHARMACOL BIOCHEM BEHAV 42(3) 413–419, 1992.– The behaviors induced by the 5-hydroxytryptamine (5-HT) precursor 5-hydroxytryptophan (5-HTP) has been called the "5-HT (serotonin) syndrome." These behaviors and others identified in rat pups were observed following administration of 5-HTP (300 mg/kg, SC) on postnatal (PN) days 3, 14, and 28 and in adult rats. Certain 5-HT syndrome behaviors and other uniquely neonatal behaviors were present in PN3 pups treated with vehicle. 5-HTP-treated PN3 pups showed increased head-shakes, rollovers, vocalizations, and forepaw treading and decreased hindlimb abduction. No 5-HT syndrome or neonatal behaviors were present at PN14 or PN28 or in adults treated with vehicle. 5-HTP administered at PN14 stimulated circling, forepaw treading, and resting tremor; at PN28, stimulated head-shakes and resting tremor; and in adults produced only head-shakes. To determine if prior exposure to 5-HTP affected the sensitivity of 5-HT receptor subtypes, the 5-HT_{1A} agonist (±)-8-hydroxy-dipropylaminotetralin (8-OH-DPAT) and the 5-$HT_{2/1C}$ agonist (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) were administered to all rats as adults. 8-OH-DPAT (1 mg/kg, SC) produced flattened body posture unaffected by prior exposure to 5-HTP. Head-shakes induced by DOI (5mg/kg, IP) were decreased by prior exposure to 5-HTP at PN3 and adult, but increased by preexposure at PN28. Thus, serotonergic neural systems are implicated in some behaviors of neonates. The developmental patterns suggest changes in the sensitivity to these systems. Further, lasting changes in 5-$HT_{2/1C}$ receptor sensitivity occur due to exposure to 5-HTP.

5-Hydroxytryptamine 5-Hydroxytryptophan 5-HT syndrome Development DOI 8-OH-DPAT Behavior

ADMINISTRATION of the 5-hydroxytryptamine (5-HT) precursor 5-hydroxytryptophan (5-HTP) to rats induces a characteristic set of behaviors that has been termed the "5-HT syndrome" (2,5,11,13–15). These behaviors include head-shakes, forepaw treading, hindlimb abduction, wet-dog shakes, and abnormal body posture. Many of these behaviors resemble behaviors in rat pups during nursing [(17), Mokler et al., unpublished observations]. Spear and colleagues have shown that 5-HT is involved in nursing behavior in rat pups (12, 17,19). They also noted behaviors in neonatal [postnatal day (PN) 3–4] and preweanling (PN17–18) pups in response to selective 5-HT agonists (4,12). These behaviors included mouthing and probing at both ages and behavioral activation in neonates and grooming in preweanling rats. Jacobs (10) and Jackson and Kitchen (9) also examined behaviors in rat pups following 5-HT agonists. Both studies demonstrated changes in certain behaviors but concluded that the syndrome is incomplete in pups.

Since a number of the behaviors that are seen in the 5-HT syndrome are similar to behaviors in nursing pups, the purpose of the present experiment was to observe behavior in rat pups at different developmental stages both with and without the activation of brain 5-HT systems by administration of the 5-HT precursor 5-HTP. Furthermore, we wanted to determine if prior exposure to 5-HTP would alter the later adult responses to the 5-HT_{1A} agonist (±)-8-hydroxy-dipropylaminotetralin (8-OH-DPAT) or the 5-$HT_{2/1C}$ agonist (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI).

METHOD

Pregnant Sprague-Dawley rats (Charles River Labs, Wilmington, MA) arrived on day 14 of pregnancy. All pups were born within a 24-h period on day 21 of pregnancy. Litters ranged from 8–10 pups and were not culled to avoid stressing or contacting the pups. Date of birth was termed postnatal

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day 0 (PN0). On PN3, two animals were selected from each litter, one for inclusion in a group receiving 5-HTP and another in the group receiving vehicle. Thus, each group consisted of six animals from different litters. After weighing, animals in one group were injected with 300 mg/kg 5-HTP (15 ml/kg, SC). Animals in a second group were injected with vehicle. Animals were then placed in clean Petri dishes on a counter in a darkened room with ambient light from a small window. Room temperature was maintained at 75°C. Behaviors were recorded for 2 h by an experienced observer, as well as on videotape. The behaviors selected for rating were determined by a review of the literature on the 5-HT syndrome, as well as preliminary experiments (Table 1). At the end of the observation period, animals were marked with ear punches and returned to their home cages.

Similarly, on PN14 and PN28 two animals from each litter were selected. These were not animals that had been used in previous experimental groups. Animals were weighed and placed in clean cages without litter. They were then injected with either 300 mg/kg 5-HTP SC or vehicle. Behaviors were again rated for 2 h and videotaped. Animals were marked by ear punches and returned to their home cage. Observations were confirmed by another observer who viewed the videotapes.

At 8 weeks of age, all animals were injected with 8-OH-DPAT (1 mg/kg, SC) to determine the effects of prior exposure to 5-HTP on behaviors stimulated via 5-HT_{1A} receptors. Rats were monitored for 1 h postinjection. Two weeks later, animals were injected with (±)-DOI (5 mg/kg, IP) and monitored for 1 h.

Adult animals (8 weeks of age) were also injected with vehicle or 300 mg/kg 5-HTP and observed for 2 h. Two weeks later, adult animals were injected with 8-OH-DPAT and observed for 1 h. Four weeks after 8-OH-DPAT, animals were injected with DOI and observed for 1 h.

(±)-DOI HCl and 8-OH-DPAT HBr were purchased from Research Biochemicals Inc. (Natick, MA). Solutions were made up daily in distilled water. 5-HTP was purchased from Research Biochemicals Inc. and was suspended in distilled water and five drops Tween-80 (Sigma Chemical Co., St. Louis, MO) per 10 ml. All solutions were made up just prior to injection.

TABLE 1

DESCRIPTION OF ANIMAL BEHAVIORS

Flattened Body Posture	Animal lying on belly
Circling	Animal moves in a clockwise direction at a steady pace
Wet-dog shakes	Animal shakes body abruptly
Resting tremor	Body tremor at rest
Head weave	Head moves from side to side or in an up-and-down "nodding" movement
Vocalizations	Brief high-pitched squeaks
Rollover	Animal abruptly assumes a supine posture and rolls from side to side
Straub tail	Tail is extended
Hindlimb abduction	Hindlimbs are extended
Forepaw tread	Both forepaws move in an alternating motion
Head-shakes	Head shakes abruptly
Other	Grooming behaviors, cage exploration

Individual behaviors were tallied as the presence or absence of behaviors or the total number of behaviors per 5-min period for 2 h following 5-HTP administration (head-shakes, hindlimb abduction, forepaw treading, rollovers). DOI- and 8-OH-DPAT-induced behaviors were monitored for 1 h. For analysis, scores were totaled across the entire observation period. The flattened body posture induced by administration of 8-OH-DPAT was quantified by the total time the animal remained in this posture during the 1 h following administration. Statistical analysis for the analysis of developmental behaviors was done using a two-way analysis of variance (ANOVA) with age and drug treatment as factors. Posthoc testing was done using the least significant differences test (8). Statistical significance was set at $p < 0.05$ for all analyses.

RESULTS

Nearly all behaviors were already present in the PN3 rats treated with vehicle (Fig. 1); the only exception was rollovers. Although not observed in the experimental situation, rollovers were commonly observed in the home cages in the presence of the dam. These behaviors were differently affected by treatment with 5-HTP in neonatal rats: head-shakes, forepaw treading, and vocalizations were increased, hindlimb abduction was decreased, and Straub tail, resting tremor, and circling were unchanged. Rollovers were induced by administration of 5-HTP (Fig. 1E).

By PN14, the neonatal behaviors had disappeared and similarly were not seen at PN28 or in adults. 5-HTP administration continued to produce a number of behaviors that had been seen in PN3 animals. Forepaw treading and resting tremor were both observed but at lower levels than in PN3 pups receiving 5-HTP or vehicle. Many behaviors were absent in PN14 pups treated with 5-HTP. Head-shakes, hindlimb abduction, rollovers, Straub tail, and vocalizations were not seen. Circling behavior was dramatically increased after administration of 5-HTP in PN14 pups (Fig. 1F).

Head-shakes and resting tremor were increased in PN28 rats following 5-HTP relative to PN14 rats. These behaviors were absent in PN14 rats. Other behaviors were decreased in PN28 animals compared with PN14 or PN3; these included hindlimb abduction, rollovers, circling, forepaw treading, Straub tail, and vocalizations. Finally, adult rats displayed only head-shakes following administration of 5-HTP.

The effects of 5-HTP on the total behaviors (as rated by total all observations in each animal) are shown in Fig. 2. PN3 pups that received only vehicle showed the highest number of behaviors of control animals receiving vehicle injections. This is artificially high due to the inclusion of selective neonatal behaviors. In animals treated with 5-HTP, neonates also had the highest level of behaviors, which were significantly higher than vehicle-treated pups or adults treated with 5-HTP. In contrast, PN14 pups treated with 5-HTP showed significantly fewer behaviors than adults treated with 5-HTP. The number of behaviors in PN14 pups treated with 5-HTP was still, however, higher than animals treated with vehicle at PN14. At PN28, pups treated with 5-HTP did not differ significantly from adult animals in total behaviors.

Administration of 8-OH-DPAT to adult rats previously exposed to 5-HTP during development produced a number of behaviors seen as part of the 5-HT syndrome (Table 2, Fig. 3). The behaviors did not differ significantly with the exception of abnormal body posture. With abnormal body posture, animals were less sensitive to 8-OH-DPAT if 5-HTP was ad-

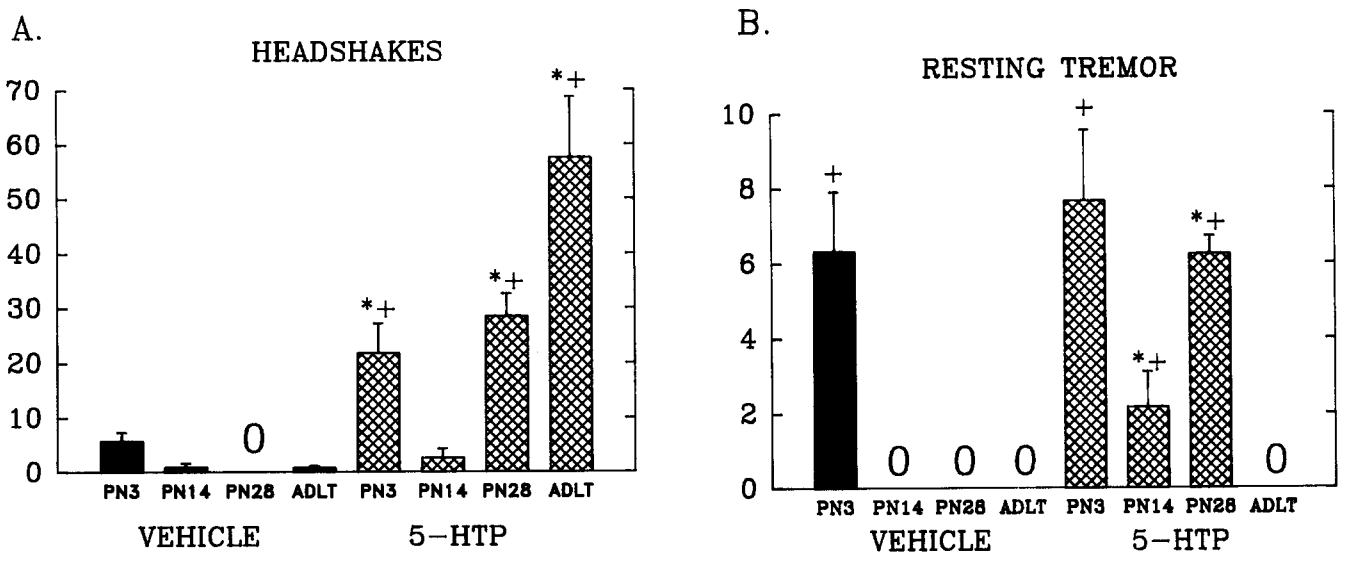

FIG. 1. Behaviors in animals treated with vehicle or 300 mg/kg 5-HTP (SC) at different ages (PN, postnatal day). Values represent mean ± SEM (n = 6–7). *Significantly different from vehicle-treated animals, $^{+}$significantly different from adult animals, $p < 0.05$, two-way ANOVA, least significant difference test. A, head-shakes; B, resting tremor; C, hindlimb abduction; D, Straub tail; E, rollovers; F, circling; G, vocalizations; H, forepaw tread.

ministered at PN28 as there was an increase in 8-OH-DPAT-induced abnormal body posture in rats treated with vehicle at PN28.

DOI administration to animals previously injected with vehicle only showed head-shakes, which did not differ between groups. Those rats previously exposed to 5-HTP showed a varied response to DOI (Fig. 4). PN3 animals that had received 5-HTP showed a small decrease in head-shakes following DOI, whereas animals treated on PN28 with 5-HTP showed increased head-shakes following DOI. Adult animals that had been treated with 5-HTP did not show head-shakes following DOI, in contrast with adult animals treated with vehicle that showed similar numbers of head-shakes as animals treated with vehicle during development.

DISCUSSION

The syndrome elicited by administration of 5-HTP to rats at different developmental stages resembles the syndrome elicited in adult rats following 5-HTP (10,11,15). In addition, some uniquely neonatal behaviors were enhanced by 5-HTP. Behaviors associated with the "serotonin syndrome" are seen in animals on PN3 after administration of vehicle. These behaviors have also been seen in nursing rat pups. In addition, we noted the presence of two characteristic behaviors not present in older pups or adults. The behavior that we termed "rollovers" was induced by 5-HTP; however, these rollovers are also seen in nursing pups, allowing pups to orient toward the mother's teats (unpublished observations). These rollovers may be developmentally related to circling observed in older pups (PN14) in that both represent organized seeking/exploratory behaviors. Indeed, others have observed increased behavioral activation in rat pups following 5-HT agonists (9, 12,18,19).

High-pitched vocalizations in the audible range were also observed in PN3 pups and enhanced by the administration of 5-HTP. The significance of these vocalizations is unknown although 8-OH-DPAT (6) or decreases in 5-HT levels by MDMA decreases ultrasonic vocalizations in rat pups (21).

Some behaviors were inhibited by administration of 5-HTP. Hindlimb abduction was decreased in PN3 animals treated with 5-HTP. This reduction may be related to a tendency toward whole body flexion (rollover) in the neonate. However, hindlimb abduction is a major behavior noted in the 5-HT syndrome in adult rats. In the neonate, the increase in flexor postures (e.g., rollovers) may override a tendency toward hindlimb abduction. Also of interest is the lack of hindlimb abduction in PN14 and PN28 pups and adults in this study. This suggests that neonates are more sensitive to the effects of 5-HTP than older rats.

Ristine and Spear (18,19) also examined behaviors at PN3–4 using the mixed 5-HT agonist quipazine. They suggested that some behaviors seen in neonates are similar to behaviors in adults following quipazine administration. The behaviors seen in neonates included mouthing, forward locomotion, hyperactivity, forelimb paddling, hindlimb treading, and wall climbing. A behavior termed unusual position of the limbs (UPL) was also increased by quipazine. This behavior may be related to the limb posture in rollovers observed in the present experiment. Two of the behaviors observed by Ristine and Spear (mouthing, UPL) were blocked by the nonselective 5-HT antagonist metergoline, but not the dopamine antagonist haloperidol, nor the α-adrenergic antagonist phentolamine (18). Arnt et al. (1) showed that the ability of a large number of drugs of different classes to antagonize head-shakes induced by 5-HTP in combination with the 5-HT uptake inhibitor citalopram correlated with their affinity for 5-HT_2 receptors. These findings suggest that the behaviors induced by 5-HTP are related to 5-HT stimulation.

Some behaviors (resting tremor and head-shakes) were seen or induced in PN3 and PN28 pups but not PN14 pups. These findings suggest a relative insensitivity of the response to

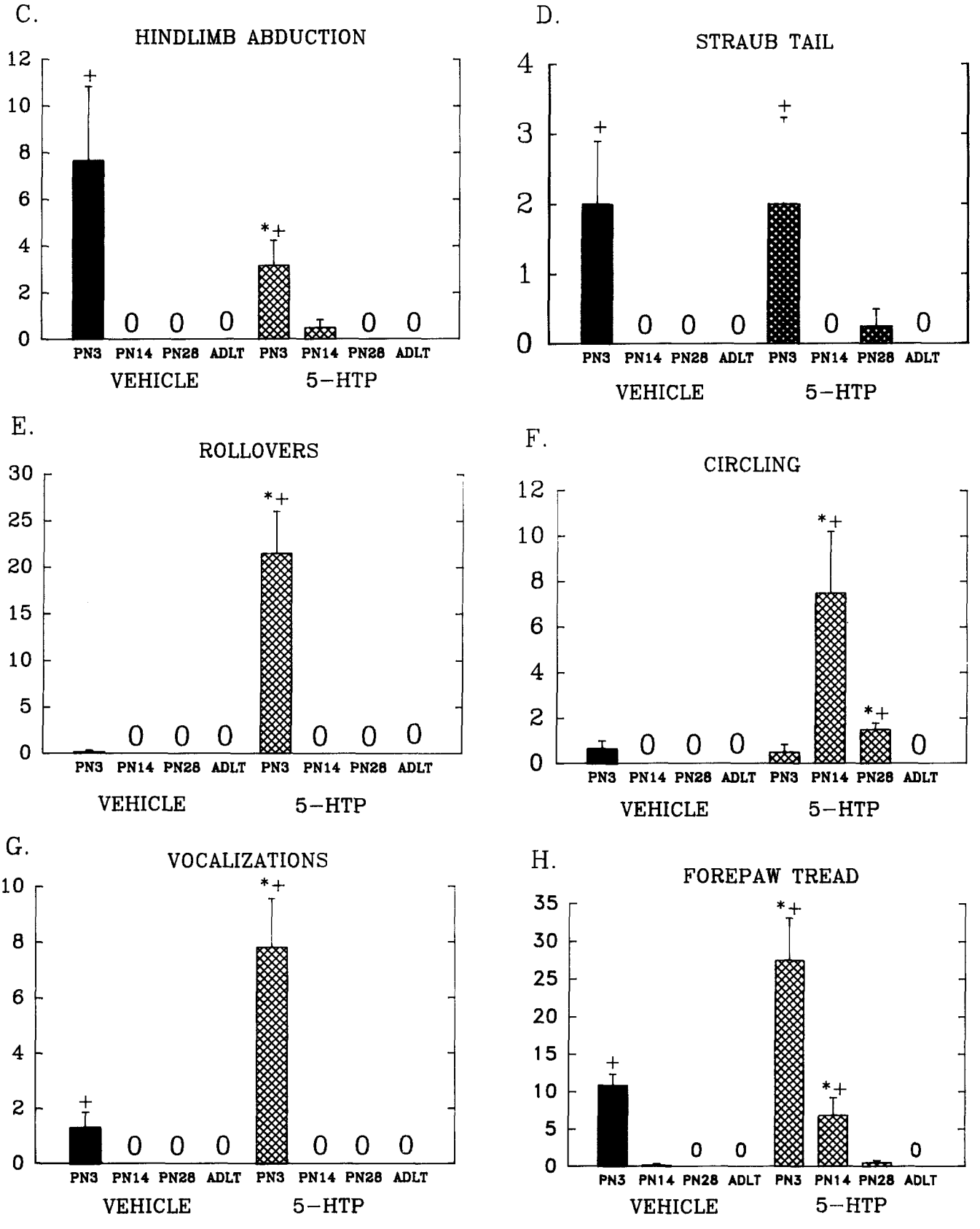

FIG 1. Continued.

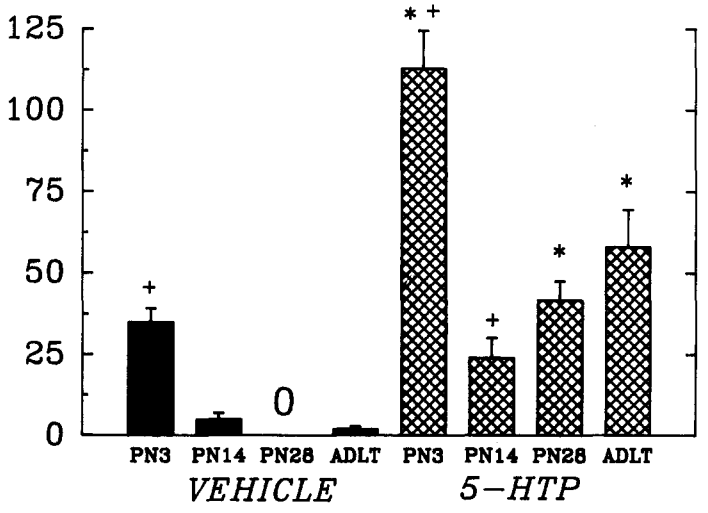

FIG. 2. Total behaviors in animals treated with vehicle or 300 mg/kg 5-HTP (SC) at different ages (PN, postnatal day). Values represent mean ± SEM (n = 6–7). *Significantly different from vehicle-treated animals, $^{+}$significantly different from adult animals, $p < 0.05$, two-way ANOVA, least significant difference test.

5-HTP in PN14 pups. This change may reflect changes in receptor number or sensitivity. It also may suggest changes in postsynaptic second messenger mechanisms. Hernandez (7) showed that [^{3}H]5-HT binding, indicative of 5-HT_1 sites, is low until PN6 and increases to adult levels by PN18 in the cortex of rats. Spinal cord 5-HT binding showed a similar increase from PN5–PN30. Activation of adenylate cyclase in cortex linked to 5-HT_{1A} receptors showed a similar ontogeny increasing from birth to PN15 (23). Coupet and Tricoli (3) recently reported that the DOI stimulation of phosphoinositol turnover in the cortex was maximal at PN9. However, presynaptic levels of 5-HT and tryptophan-5-hydroxylase activity did not reach adult levels until PN21 (23).Therefore, the 5-HT receptors and second messenger systems may mature prior to the maturation of the presynaptic availability of 5-HT. Thus, administration of the precursor 5-HTP would result in a reduced response at the time when there is a mismatch between presynaptic and postsynaptic elements.

The present results could also be explained by changes in the distribution of 5-HTP following injection in rats during development.Thus, the variability in the presence or absence of behaviors in pups may be due to alterations in the pharmacokinetics of the uptake and distribution of 5-HTP in rats at different developmental stages. However, the pattern of changes in the different responses to 5-HTP would not support this explanation. For example, resting tremor shows the highest response at PN3, decreases at PN14, increases again at PN28, and disappears in adults. On the other hand, head-shakes are maximal in adult rats and variable in PN3, PN14, and PN28 pups. The pattern of differences do not suggest pharmacokinetics as the sole explanation for the differences in response to 5-HTP.

Prior exposure to 5-HTP failed to affect the response to 8-OH-DPAT in adult rats. This suggests that 5-HT_{1A} receptor systems are not affected long term by 5-HTP administration. In contrast, the frequency of DOI-induced head-shakes was affected by prior exposure to 5-HTP. The decreased adult response to DOI when 5-HTP was administered at PN3 may be explained by a subsensitivity of the 5-$HT_{2/1C}$ receptor mechanisms, whereas the response to DOI in adult animals treated at PN28 with 5-HTP suggests a supersensitivity of these systems. The cellular correlates of these changes may include alterations in the 5-HT_2 or 5-HT_{1C} receptor numbers either primary to the exposure to 5-HTP or secondary to long-term changes in the synthesis or release of 5-HT. The present experiment also showed that adult animals exposed to 5-HTP have

TABLE 2

EFFECTS OF 8-OH-DPAT ON BEHAVIOR IN RATS TREATED WITH 5-HTP DURING DEVELOPMENT

	3 Days		14 Days		28 Days		Adult	
Behavior	SAL	5-HTP	SAL	5-HTP	SAL	5-HTP	SAL	5-HTP
Head-shakes	2.3 ± 0.9	4.2 ± 2.2	3.2 ± 1.6	4.0 ± 1.1	3.5 ± 2.0	1.6 ± 1.2	1.5 ± 1.3	0.7 ± 0.7
Hindlimb abduction	0.3 ± 0.3	15.8 ± 11.1	7.3 ± 5.6	4.2 ± 3.6	0.3 ± 0.3	1.0 ± 1.0	2.7 ± 2.7	12.7 ± 2.9
Straub tail	14.3 ± 11.0	2.2 ± 2.2	5.8 ± 3.1	3.7 ± 3.6	5.3 ± 4.6	5.4 ± 4.8	0	0
Circling	8.7 ± 3.9	0	0	2.2 ± 1.5	0	1.6 ± 1.1	0	0
Head weaving	0	0	0	0	0.8 ± 0.8	1.2 ± 1.2	0	0

SAL, saline.

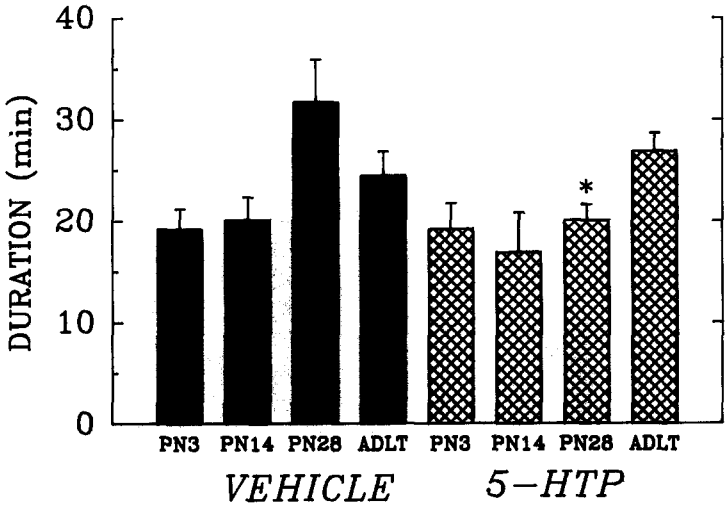

FIG. 3. Duration of abnormal body posture following administration of 8-OH-DPAT (1 mg/kg, SC) in adult animals previously treated with vehicle or 300 mg/kg 5-HTP (SC) at different ages (PN, postnatal day). Values represent mean ± SEM (n = 6–7). *Significantly different from vehicle-treated animals, $p < 0.05$, two-way ANOVA, least significant difference test.

reduced numbers of head-shakes following administration of DOI. Thus, there continues to be a potential for plasticity within the 5-$HT_{2/1C}$ system in adulthood.

Previous studies have shown that coadministration of 8-OH-DPAT reduces head-shakes induced by quipazine (22). The DOI-induced head-shakes in the present study were uninfluenced by administration of 8-OH-DPAT 4 weeks earlier since control animals (which received 8-OH-DPAT) showed a normal response to DOI. Other investigators have reported changes in the behavioral response to 5-HT agonists by prior alterations in 5-HT systems. Pranzatelli et al. (16) demonstrated that adult rats that had received intracisternal or intraperitoneal administration of the neurotoxin 5,7-DHT had increased sensitivity to the effects of DOI, 8-OH-DPAT, and 5-HTP. Chronic administration of antidepressants or 5-HT_{1A} agonists diminishes the head-shake response to 5-HT and 5-HT_2 agonists (13). Similar regimens produced a downregulation of 5-HT_2 receptors. The present findings suggest a long-term supersensitivity to the effects of DOI in animals treated at PN28 with 5-HTP and a subsensitivity in adults treated with 5-HTP.

In summary, the present study has shown that the 5-HT

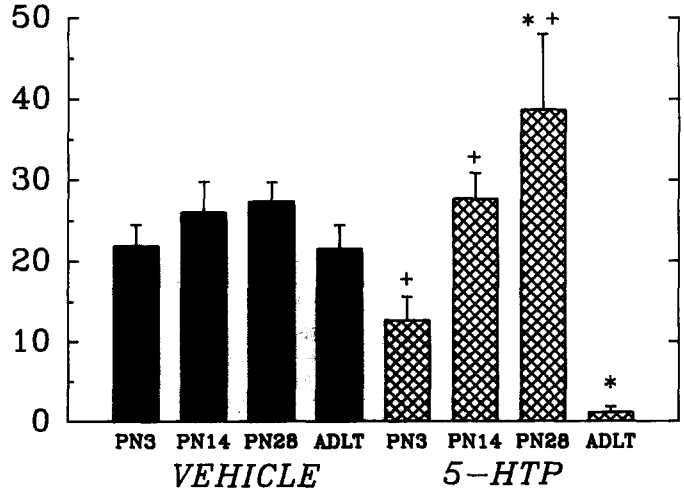

FIG. 4. Head-shakes following administration of DOI (5 mg/kg, IP) in adult animals previously treated with vehicle or 300 mg/kg 5-HTP (SC) at different ages (PN, postnatal day). Values represent mean ± SEM (n = 6–7). *Significantly different from vehicle-treated animals, $^+$significantly different from adult animals, $p < 0.05$, two-way ANOVA, least significant difference test.

syndrome has many behaviors in common with behaviors seen in neonatal rats. The presence or absence of the behaviors associated with the 5-HT syndrome varies as to the age of the animal. This may reflect the status of the development of the 5-HT system in the brain.

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