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Tonic Convulsive Thresholds and Responses During the Postnatal Development of Rats Administered 6-Hydroxydopamine or 5,7-Dihydroxytryptamine within Three Days Following Birth[1]

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WALLER, S. B. AND G. G. BUTERBAUGH. *Tonic convulsive thresholds and responses during the postnatal development of rats administered 6-hydroxydopamine or 5,7-dihydroxytryptamine within three days following birth.* PHARMACOL BIOCHEM BEHAV **19**(6) 973–978, 1983.—The maturation of the electroshock tonic convulsive pattern and threshold was investigated in rats between the ages of 4 and 30 days following intracisternal injections of 6-hydroxydopamine (6-OHDA) on postnatal days 1 and 2; or 5,7-dihydroxytryptamine (5,7-DHT) after desipramine on postnatal day 3. In 6-OHDA treated rats decreases in brain norepinephrine (mean values of 55% of control) and dopamine (mean values of 17% of control) were associated with a large reduction in the convulsive threshold and intensification of the pattern on postnatal day 4. Whereas the reduction in catecholamine concentrations and the intensification of the pattern were still evident on postnatal day 30, the last day of testing, the threshold effect was not evident by postnatal day 15. Although 5,7-DHT reduced brain serotonin concentrations (mean values of 59% of control) as early as postnatal day 4, the pattern was not intensified until postnatal day 8, and the threshold was not reduced until postnatal day 21. These effects were still evident on postnatal day 30. The results demonstrate a sequential maturation of monoaminergic regulation in seizure susceptibility and severity, with an apparent transition from catecholaminergic to serotonergic regulation of the tonic threshold during the third postnatal week.

Monoamines Electroshock Convulsions Development Catecholamines Serotonin

IN adult rats, pharmacological reduction in the brain levels of catecholamines and serotonin have been repeatedly associated with decreased convulsive thresholds and/or intensified convulsive response patterns [1, 3, 4, 5, 11, 12, 16, 17, 18, 23, 24, 25, 37, 41, 45]. Since some of these studies suggest a greater role for catecholamines in these effects [3, 16, 17, 18, 41], and others indicate a greater serotonergic involvement [4, 5, 23, 24], the relative importance of either system in adult convulsive phenomena is not clear.

In neonatal rats, similar studies have demonstrated a clearer separation of catecholaminergic and serotonergic involvement in the regulation of tonic convulsive thresholds and responses, especially during early postnatal development. In 7–8 day old rats, the electroshock threshold for inducing tonic convulsions is 3–4 times higher than in the adult rats, and the resulting convulsive responses are immature. At this age, decreases in the concentrations of brain catecholamines, but not serotonin, are associated with a convulsive response characteristic of a later developmental age and a markedly decreased tonic threshold [28]. In 30 day old rats, the tonic threshold and response pattern resemble those in adult rats. At this age, reduction in brain concentrations of serotonin, but not catecholamines, is associated with a decreased tonic threshold [29]. At the intermediate age of 15 days, decreases in both catecholamines as well as serotonin are required to obtain a decreased tonic threshold [29]. These results suggest a developmental transition from catecholaminergic to serotonergic dominance in the regulation of convulsive phenomena during postnatal maturation.

In previous studies, neonatal rats receiving central

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monoamine level reducing agents or neurotoxin treatments, were observed at only one of three postnatal ages, 7–8, 15 or 30 days. In the present study, 6-hydroxydopamine (6-OHDA) or 5,7-dihydroxytryptamine (5,7-DHT) were administered within the first three postnatal days to cause permanent disruption of catecholaminergic neurons [2] or serotonergic neurons [10], respectively. This allowed the repeated assessment of convulsive thresholds and responses in the neurotoxin treated rats during the first postnatal month. The intent was to determine how disruption of monoaminergic neuronal systems soon after birth would alter the neonatal maturation of convulsive phenomena, and if the alterations would be consistent with a developmental transition from catecholaminergic to serotonergic dominance which was suggested previously [28,29].

A preliminary report of this work has been published [44].

METHOD

Animals and Animal Care

Pregnant, Sprague-Dawley rats were housed in large individual cages in an environment of controlled temperature (25–27°C) and alternating 12 hour light (0600–1800 hr) and dark cycles from day 13 or 14 of gestation. Litter sizes were adjusted within two days following birth to 10 or fewer pups. Pups remained with their mothers until 24 days following birth when they were weaned and placed into groups of 10 per cage. Dams and pups were allowed free access to food and water at all times.

Drug Treatments

6-OHDA hydrobromide or 5,7-DHT creatinine sulfate (Sigma Chemical Co., St. Louis, MO) was dissolved in 0.9% NaCl containing 0.4 mg/ml ascorbic acid as an antioxidant. The neurotoxins were administered by intracisternal injection [14] to pups anesthetized with diethyl ether. The intracisternal injection volume was 10 μl administered over 65 seconds. Pups were injected with 6-OHDA on two successive days: 100 μg (free base) on postnatal day one and 50 μg (free base) on postnatal day two. A separate group of pups were injected with 5,7-DHT (100 μg free base) on postnatal day three, one hour after desipramine (25 mg/kg; IP) to protect catecholamine neurons from the neurotoxin [10]. Control groups received intracisternal injections of vehicle according to 6-OHDA or 5,7-DHT (including desipramine) treatment regimens. Brain and body weights were not significantly altered by any of these treatments throughout the testing period. (Data not shown.) It should be noted that the control values reported in the present study were obtained from pups that received intracisternal injections of vehicle according to the 6-OHDA treatment regimen. However, they are almost identical to values obtained from pups that received intracisternal injections of vehicle according to the 5,7-DHT treatment regimen, differing by less than 7%.

Electroshock Procedures

Animals injected with neurotoxin or vehicle were tested on postnatal days 4, 8, 12, 15, 17, 21 and 30, always between 0800 and 1100 hours. Electroshock was administered to individual rats from each treatment group, alternated with an animal from the control groups, to reduce the possible effects of diurnal variation in seizure threshold. Single shocks of 60 Hz alternating current, 200 msec duration, were administered with an electroshock apparatus (Wahlquist Instruments, Salt Lake City, UT) using electrodes placed on the eyelids (before age 15) or corneas. Isotonic saline was applied to the electrodes and eyelids or corneas to insure good contact. Rats were restrained by gloved hand and released immediately after stimulation to permit observation of the convulsive response. In a separate series of experiments, it was determined that repeated electroshock administration to control or neurotoxin-treated animals beginning on postnatal day 4 did not result in any significant changes in the tested parameters when compared to similarly treated groups of animals first administered electroshock at a later postnatal age (data not shown).

To determine convulsive thresholds, four to six current intensities of electroshock were administered, with nine to 15 animals per intensity. For each intensity, approximately equal numbers of male and female pups were taken from at least three similarly treated litters. The tonic convulsive threshold (median convulsant current; CC_{50}) was defined as the current intensity required to produce tonic forelimb extension (accompanied by tonic hindlimb flexion or extension) in 50% of the animals capable of responding with a tonic convulsion. The convulsive response pattern was determined in a separate group of pups using current intensities 100 mA above the previous day's CC_{50}. Current intensities above 300 mA were not used because the repeated application of higher intensities can produce tissue damage at the electrode contact areas. The exceptions were groups of pups shocked on day four and not used in further experiments.

Monoamine Analysis

Unshocked animals from control and neurotoxin groups were decapitated between 0800–1100 hours and brains rapidly removed and frozen and stored in liquid nitrogen for a maximum of 10 days before analysis. At least four brains from each group at each testing age were assayed fluorometrically for norepinephrine, dopamine and serotonin [15].

Statistical Methods

CC_{50} values with 95% confidence intervals were calculated by probit analysis [27]. A difference between CC_{50} values in control and treated groups was considered significant if the 95% confidence interval for potency ratios did not include one. All other comparisons were made by one-way analysis of variance and Duncan's new multiple range test [40]. The criterion for significance statements was $p<0.05$.

RESULTS

Convulsive Thresholds and Responses and Brain Monoamine Concentrations in Control Pups

The maturation of the tonic convulsive threshold and of whole brain concentrations of norepinephrine, dopamine and serotonin during the first postnatal month in control pups are illustrated together in Fig. 1. On postnatal day four, the threshold could not be determined because it was above the 500 mA limit of the electroshock apparatus [28]. Between days eight and 15, the tonic threshold declined slowly from 152 mA to 115 mA, declined to 44 mA by day 21, and was 35 mA on day 30. The norepinephrine concentration increased steadily from day four through day 30 with the 30 day concentration four times that at day four. The dopamine concentration showed little change with age through day 15, followed by a relatively rapid increase to 2.5 times the day four concentration by day 30. The serotonin concentration also increased most rapidly after day 15, reaching 1.5 times that

TABLE 1

MODIFICATION OF THE DEVELOPING CONVULSIVE RESPONSE PATTERN TO MAXIMAL ELECTROSHOCK BY EARLY POSTNATAL ADMINISTRATION OF 6-HYDROXYDOPAMINE OR 5,7-DIHYDROXYTRYPTAMINE

Age at Testing (Days)	Treatment*	Hyperkinesia	Clonic Convulsions	Tonic Forelimb Extension	Tonic Hindlimb Extension
4	Control	78†	22	—‡	—
	6-OHDA	—	50	50	—
	5,7-DHT	50	50	—	—
8	Control	—	78	22	—
	6-OHDA	—	5	50	45
	5,7-DHT	—	35	55	10
12	Control	—	—	100	—
	6-OHDA	—	—	—	100
	5,7-DHT	—	—	56	44
15	Control	—	—	100	—
	6-OHDA	—	—	—	100
	5,7-DHT	—	—	30	70
17	Control	—	—	45	55
	6-OHDA	—	—	—	100
	5,7-DHT	—	—	10	90
21	Control	—	—	20	80
	6-OHDA	—	—	—	100
	5,7-DHT	—	—	—	100
30	Control	—	—	20	80
	6-OHDA	—	—	—	100
	5,7-DHT	—	—	—	100

*6-OHDA was administered intracisternally on days 1 (100 μg) and 2 (50 μg); 5,7-DHT was administered intracisternally on day 3 (100 μg) one hr after desipramine (25 mg/kg, IP); control animals were administered neurotoxin vehicles according to neurotoxin treatment regimens.

†The motor convulsive responses are summarized as the percentage of rats with a given response at each age. N=30 to 60 animals per treatment per age.

‡Indicates responses not observed in any animals.

at day four by day 30. These control values are similar to those reported earlier for tonic thresholds [28,43] and for monoamine concentrations [2, 7, 8, 35]. The development of the predominant response to suprathreshold stimulation in control pups occurred in four sequential stages (Table 1): hyperkinesia on day four; clonic limb convulsions on day eight; tonic forelimb extension on days 12 and 15 and tonic hindlimb extension on days 17, 21 and 30. These are similar to previous descriptions [28, 32, 33].

Brain Monoamine Concentrations in Neurotoxin Treated Pups

Monoamine concentrations in neurotoxin treated pups, although selectively reduced, increased with age in a manner similar to that in the control pups. Pups treated with 6-OHDA had continued, significantly reduced norepinephrine and dopamine concentrations from day four through 30 (mean values of 55% and 77% of controls, respectively), with no significant change in serotonin (Fig. 2, top). Pups treated with 5,7-DHT had significantly reduced concentrations of serotonin during the same time period (mean values of 59% of control), with no significant change in catecholamines (Fig. 2, bottom).

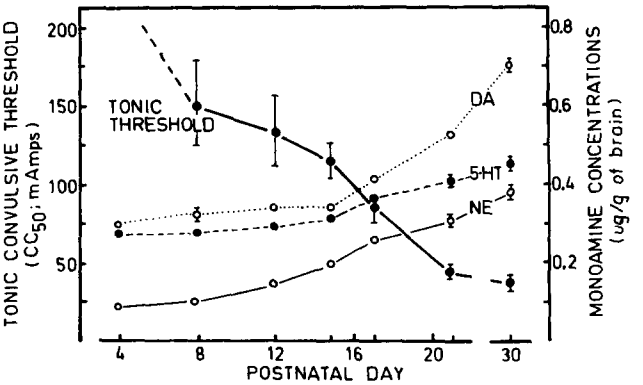

FIG. 1. Maturation of tonic threshold and whole brain concentration of norepinephrine (NE), dopamine (DA), and serotonin (5-HT) during the first postnatal month. Tonic thresholds (left axis) are expressed as CC_{50} in mAmps with 95% confidence intervals (vertical brackets). Whole brain monoamines concentrations (right axis) are expressed in terms of μg monoamine per g of brain with each point being the mean of at least 7 separate brain determinations with S.E.M. indicated by the vertical brackets. In some cases the S.E.M. was too small to be accurately represented on the figure and is omitted.

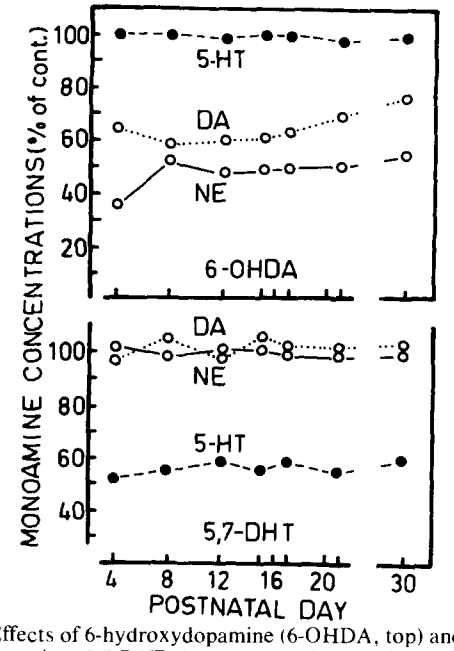

FIG. 2. Effects of 6-hydroxydopamine (6-OHDA, top) and 5,7-dihydroxytryptamine (5,7-DHT, bottom) on whole brain concentrations of norepinephrine (NE; —), dopamine (DA; · · · · ·) and serotonin (5-HT; ----). 6-OHDA was administered intracisternally on days 1 (100 μg) and 2 (50 μg); 5,7-DHT was administered intracisternally on day 3 (100 μg) one hr after desipramine (25 mg/kg, IP). Monoamine values are expressed as percentages of the age-matched control concentration reported in Fig. 1. All S.E.M. are less than 7%. 6-OHDA treatment resulted in significantly lower whole brain concentration of NE and DA, but not 5-HT, at all test ages; 5,7-DHT treatment resulted in significantly lower whole brain concentration of 5-HT, but not DA or NE at all test ages.

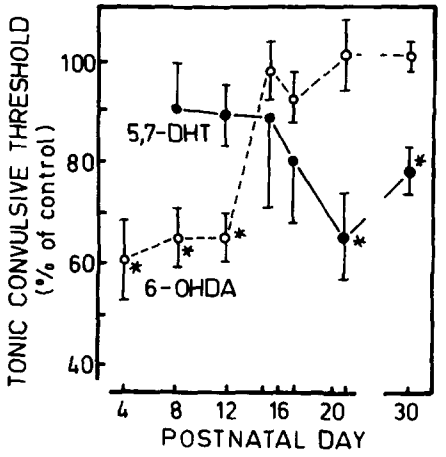

FIG. 4. Effect of 6-hydroxydopamine (6-OHDA) and 5,7-dihydroxytryptamine (5,7-DHT) on the developing tonic convulsive threshold. 6-OHDA was administered intracisternally on days 1 (100 μg) and 2 (50 μg); 5,7-DHT was administered intracisternally on day 3 (100 μg) one hr after desipramine (25 mg/kg, IP). Tonic convulsive thresholds are expressed as percentages of the age-matched control thresholds (reported in Fig. 1) with 95% confidence intervals (vertical brackets). *Indicates significantly different from age-matched control tonic threshold ($p<0.05$).

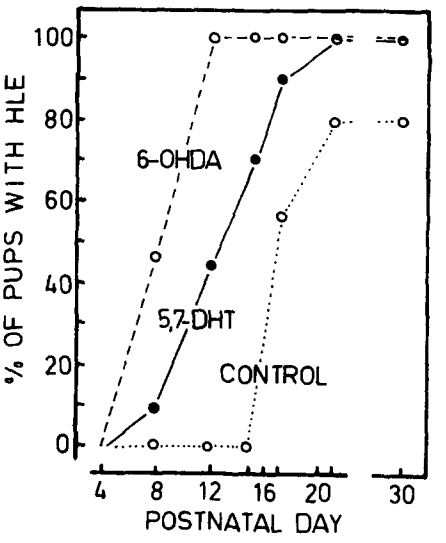

FIG. 3. Effect of 6-hydroxydopamine (6-OHDA) and 5,7-dihydroxytryptamine (5,7-DHT) on the maturation of the tonic hindlimb extension response pattern (HLE). 6-OHDA was administered intracisternally on days 1 (100 μg) and 2 (50 μg); 5,7-DHT was administered intracisternally on day 3 (100 μg) one hr after desipramine (25 mg/kg, IP); control was administered intracisternally neurotoxin vehicle according to 6-OHDA (see the Method section). Responses are summarized as percentage of rats with HLE at a given age (N=30 to 60 rats per treatment per age).

Tonic Convulsive Responses in Neurotoxin Treated Pups

At each age tested, neurotoxin treated pups responded to electroshock with an increased frequency and/or intensity of convulsive response pattern characteristic of a later age in the control pups (Table 1). This effect was the most pronounced in the 6-OHDA treated pups. For example, on day four, when the predominant response in control pups was hyperkinesia (78%), 50% of the 6-OHDA treated pups showed tonic forelimb extension, a response that did not become predominant in control pups until day 12. On day 12, 100% of the 6-OHDA and 44% of the 5,7-DHT treated pups responded with tonic hindlimb extension, a response not observed in control pups until five days later on day 17. The earlier appearance of the tonic hindlimb extension response pattern in neurotoxin treated pups is illustrated in Fig. 3. The percentage of tonic hindlimb extension was maximum by day 12 in 6-OHDA treated pups (100%) and by day 21 in control (80%) and 5,7-DHT treated pups (100%).

Tonic Convulsive Thresholds in Neurotoxin Treated Pups

Age-related changes in the tonic convulsive threshold in neurotoxin treated pups are illustrated in Fig. 4, expressed as a percent of the threshold obtained in age-matched control pups. Although the tonic convulsive threshold could not be determined in control rats at 4 days of age, the increased frequency and intensity of the convulsive response in 6-OHDA treated pups on day four allowed the determination of a threshold of 304 mA (shown in Fig. 4 as 61% of the 500 mA limit of the electroshock apparatus). Thresholds determined on days eight and 12 remained significantly decreased (67% of control). By day 15 the threshold in 6-OHDA treated pups was no longer different from the control threshold (96%) and continued to be not different from control through

day 30. In contrast, the threshold in 5,7-DHT treated pups could not be determined until day eight when the pups began to respond with tonic forelimb extension. On day eight, the threshold was 87% of control and decreased only slightly and nonsignificantly through day 17 to 80% of control. By day 21, the threshold had significantly decreased to 60% of control and remained significantly decreased on day 30.

DISCUSSION

We have previously found that in neonatal rats, the sensitivity of convulsive thresholds and responses to selective decreases in brain monoamines is age dependent [28,29]. These studies using 7–8, 15 or 30 day old rats also suggest a developmental transition from catecholaminergic to serotonergic dominance in the regulation of the tonic convulsive threshold during the first postnatal month. The present investigation examined this in more detail by following the continuous maturation of the tonic convulsive threshold and response pattern between the ages of 4 and 30 days in pups administered selective neurotoxins within three days following birth to cause a moderate reduction of central catecholamines and serotonin. Only a moderate reduction was effected, to minimize changes in behavior or growth which could interfere with the interpretation of the effects on maturation of convulsive phenomena. The results support an apparent transition during the third postnatal week from catecholaminergic to serotonergic regulation of the tonic threshold. By day 15, the decreased threshold in 6-OHDA treated pups was no longer observed despite persisting catecholamine depletion. In contrast, although 5,7-DHT selectively reduced brain serotonin concentrations as early as day 4, a decreased threshold was not observed in the pups until day 21.

Reduction of brain monoamine concentrations also was associated with an intensification and increased frequency of the maximal convulsive response pattern during the first postnatal month. However, this effect was clearly dissociated from the effect of monoamine concentration reduction on the threshold. Although the effects of 6-OHDA treatment were more pronounced at the earlier ages compared to the effects of 5,7-DHT treatment, the changes in the convulsive pattern were observed in both neurotoxin treatment groups throughout the testing period, whereas the effect of neurotoxin treatments on the threshold were clearly age-dependent. Because these effects on the convulsive pattern were so persistent, there was no evidence supporting a developmental transition from catecholaminergic to serotonergic regulation of the response pattern.

These age-associated effects undoubtedly reflect the maturation of neurotransmitter functions and interactions involved in seizure control. The apparent transition from catecholaminergic to serotonergic regulation of the threshold agrees with information on the functional maturation of these systems in the rat [26]. Early catecholaminergic and later serotonergic maturation have been demonstrated using morphological and neurochemical markers [13, 21, 22, 30, 31, 35, 42]. Moreover, amphetamine increases stabilimeter cage activity in rats throughout the first postnatal month [6] suggesting catecholaminergic function early in postnatal life. In contrast, inhibition of serotonin synthesis does not increase stabilimeter cage activity until after postnatal day 15, and potentiates amphetamine-induced activity only after day 20 [30]. These results suggest that central serotonergic systems, including their interactions with other transmitter systems, undergo functional maturation during or after the third postnatal week. Thus, the changes in the threshold and response observed as early as postnatal day four in the pups that received the 6-OHDA treatment are consistent with the early functional maturity of catecholaminergic systems. The more gradual intensification of the response pattern and the later reduction of the threshold in pups that received the 5,7-DHT treatment are consistent with the delayed maturation of serotonergic systems.

There are other possible explanations which may account for the lack of persistence of the decreased threshold in 6-OHDA treated pups beyond the second postnatal week, in spite of continued catecholamine depletion. One may relate to our administration of 6-OHDA early in postnatal development to effect only a moderate disruption of the catecholaminergic system. Norepinephrine-mediated behaviors are relatively well developed in rats at birth while dopamine-mediated behaviors are not fully developed until after the third postnatal week [21]. Pronounced antagonistic effects of norepinephrine and dopamine on behavior have been reported [39]. Perhaps, the return of the threshold to control levels in 6-OHDA treated pups may reflect the later functional maturation of dopaminergic neurons left intact or spared by the early postnatal 6-OHDA treatments. In addition, this sparing effect of our early postnatal administration of 6-OHDA need not be restricted to the dopaminergic neuronal systems. Schmidt and Bhatnagar [38] present evidence that noradrenergic neuronal systems may differ in their resistance and survivability to 6-OHDA treatment during postnatal development. Thus, the return of the tonic threshold to control levels in 6-OHDA treated pups may reflect the functional maturation of noradrenergic neurons that were not affected by 6-OHDA administered on postnatal days 1 and 2. Additional study of the importance of the time of 6-OHDA administration to convulsive phenomena during postnatal development may provide insight into functional maturation of catecholaminergic systems.

Also, the second and third postnatal weeks also represent a time of intense and rapid morphological and functional maturation of other transmitter systems, including GABAergic and cholinergic systems [9, 19, 20, 26, 34]. There is considerable evidence for interactions and interdependence among neurotransmitter systems as reviewed by Pradhan and Bose [36]. The present results, including the apparent transition from catecholaminergic to serotonergic dominance of the tonic threshold, may reflect the developing influence of interactions with other neurotransmitter systems.

All things considered, it is evident that the third postnatal week in rats is a period of rapid maturation of neurotransmitter systems and convulsive phenomena. This age period may be especially vulnerable to abnormalities which may result in inefficient modulation of seizure susceptibility and severity, perhaps lasting into adulthood.

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