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Convulsive Thresholds and Severity and the Anticonvulsant Effect of Phenobarbital and Phenytoin in Adult Rats Administered 6-Hydroxydopamine or 5,7-Dihydroxytryptamine During Postnatal Development

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WALLER, S. B. AND G. G. BUTERBAUGH. *Convulsive thresholds and severity and the anticonvulsant effect of phenobarbital and phenytoin in adult rats administered 6-hydroxydopamine or 5,7-dihydroxytryptamine during postnatal development.* PHARMACOL BIOCHEM BEHAV **23**(3) 473–478, 1985.—Rats were administered intracisternal 6-hydroxydopamine (6-OHDA) or 5,7-dihydroxytryptamine (5,7-DHT) within the first three postnatal days, at several ages centered on the third postnatal week or on postnatal day 180. When the rats were 210-days-old, maximal electroshock convulsive thresholds and responses and the anticonvulsant effect of phenobarbital and phenytoin were determined. All 5,7-DHT treatments resulted in an approximate 21% decrease in the tonic convulsive threshold and increased the incidence of tonic hindlimb extension (HLE). Only the 5,7-DHT treatment at 180 days was associated with a more severe HLE response (shortened onset and prolonged duration). All neonatal 6-OHDA treatments were associated with no change in the tonic threshold, but increased the incidence and severity of HLE. The latter effect depended on the postnatal age of 6-OHDA-treatment: treatment at postnatal days 14 and 15 resulted in the greatest increase in severity (52% decrease in onset and 48% increase in duration). The 6-OHDA treatment to 180-day-old rats increased the incidence and duration of HLE but had no influence on the tonic threshold or onset of extension. The effectiveness of both phenobarbital and phenytoin to block HLE was variably decreased by all neurotoxin treatments. The results suggest that interference with the postnatal maturation of monoaminergic influences on seizure processes can have a long-lasting influence on the ability of the brain to limit the generation and spread of seizure activity and on the effectiveness of anticonvulsant drugs.

Monoamines Electroshock Convulsions Catecholamines Serotonin Phenobarbital Phenytoin Neonatal development

THERE is substantial evidence for the rapid and sequential maturation of convulsive thresholds and responses during the first three postnatal weeks in the rat [21, 26, 27, 38, 39, 40]. Rats less than one week old are resistant to electroshock-induced maximal convulsions as reflected by a highly elevated tonic convulsive threshold. Convulsive responses are also immature and do not develop into the adult response of tonic hindlimb extension until during the third postnatal week. Likewise, a rapid decline in the tonic convulsive threshold occurs immediately following the maturation of the tonic hindlimb response.

We have previously reported age-dependent effects of selective monoaminergic depletion on convulsive thresholds and responses in neonatal rats [21,22]. There is an apparent developmental transition from catecholaminergic to serotonergic dominance in the regulation of the tonic threshold during the third postnatal week [40]. This age period coincides with the functional maturation of central serotonergic systems [19, 23, 28, 35], although other neurotransmitter systems also undergo morphological and functional maturation during the second and third postnatal weeks [7, 13, 14, 16, 17, 19, 24]. The rapid maturation of convulsive phenomena and neurotransmitter systems during the third postnatal week in rats suggests that damage to these

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systems during this critical age period may result in long-lasting effects on seizure susceptibility and severity and in altered anticonvulsant drug effects.

In the present study, we investigated this possibility with regard to central monoaminergic systems. We administered 6-hydroxydopamine (6-OHDA) or 5,7-dihydroxytryptamine (5,7-DHT) to cause injury to catecholaminergic [1] or serotonergic [8] neurons, respectively, within the first three postnatal days and at several ages centered on the third postnatal week. We then determined the effect of these treatments on tonic convulsive thresholds and responses and on the anticonvulsive effects of phenobarbital and phenytoin in the rats when they reached an adult age (210-days-old) compared to rats treated with neurotoxins when 180-days-old.

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 to groups of 10 per cage. All animals 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 to rat pups anesthetized with diethyl ether. The injection volume was 10 μl administered over 65 seconds. Pups were injected with 6-OHDA on two successive days: 100 μg (free base) on treatment day one and 50 μg (free base) on treatment day two. Treatment of rat pups according to this 6-OHDA regimen was initiated on postnatal days 1, 12, 14, 16, or 18. Separate groups of pups were administered a single injection of 5,7-DHT (100 μg free base), one hour after desipramine (25 mg/kg, IP) to protect catecholamine neurons from the neurotoxin [8]. Treatment of the pups according to this 5,7-DHT regimen was initiated on postnatal days 3, 12, 14, 16 or 18. Naive, adult rats (180-days-old) were administered single intracisternal injections of either 6-OHDA (75 μg free base) or 5,7-DHT (70 μg free base one hour following desipramine, 25 mg/kg, IP) using ketamine anesthesia (100 mg/kg, IP). Adult brain and body weights were not significantly altered by any of these treatments (data not shown). Control values reported were obtained from animals that received intracisternal injections of vehicle according to the 6-OHDA treatment regimen initiated on postnatal day 1. Control values obtained from animals that received intracisternal injections of vehicle according to the other 6-OHDA or to the 5,7-DHT treatment regimens differed nonsignificantly by less than 7% from the reported control values. For simplicity of presentation, neurotoxin treatments are identified by the neurotoxin used and the first day of neurotoxin treatment. For example, 6-OHDA/D12 represents the group of 6-OHDA treated animals first treated with 6-OHDA on postnatal day 12.

Electroshock Procedures

Animals injected with neurotoxin or vehicle were tested on postnatal day 210, always between 0800 and 1100 hours. Electroshock was administered to individual rats from each treatment group, alternated with an animal from the control group, to reduce possible effects of diurnal variation on 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 corneas. Isotonic saline was applied to the electrodes and corneas to insure good contact. Rats were restrained by gloved hand and released immediately after stimulation to permit observation of the convulsive response.

To determine convulsive thresholds, four to six current intensities of electroshock were administered to nine to 15 animals per intensity. For each intensity, approximately equal numbers of male and female animals, selected randomly from each treatment or control group, were used. The tonic convulsive threshold (median convulsant current; CC50) was defined as the current intensity required to produce tonic forelimb extension (accompanied by tonic hindlimb flexion or extension) in 50% of the animals.

The convulsive response pattern was determined in a separate group of animals using a current intensity of 150 mA. The patterns were classified as one of four possible responses: hyperkinesia, clonus, tonic forelimb extension or tonic hindlimb extension. When tonic hindlimb extension was observed, the latency to onset of extension (interval between stimulation and complete hindlimb extension) and the duration of hindlimb extension (interval between complete extension and beginning of hindlimb relaxation), were timed, always by the same observer. Complete hindlimb extension was maximum extension of hindlimbs with extended hind paws.

Anticonvulsant Evaluation

The ability of phenobarbital sodium (Mallinckrodt, St. Louis, MO) and phenytoin (Sigma Chemical Co.) to prevent tonic hindlimb extension following maximal electroshock stimulation (150 mA) was determined using four or more doses, with eight or more animals per dose. The protective dose 50 (PD50) is usually defined as the dose required to prevent tonic hindlimb extension in 50 percent of the animals tested. However, in the present study, not all untreated animals responded with hindlimb extension. Therefore, the PD50 was defined as the dose required to reduce the predetermined, untreated control incidence of tonic hindlimb extension by 50%. Thus, in non-neurotoxin treated animals, 67% responded with hindlimb extension; the PD50 dose was the dose at which 33.5% of the treated animals responded with hindlimb extension. Likewise, in neurotoxin-treated groups, 93% responded with hindlimb extension; the PD50 dose was the dose at which 46.5% of the treated animals responded with hindlimb extension. Phenobarbital sodium, dissolved in 0.9% NaCl, or phenytoin, dissolved in slightly alkaline 0.9% NaCl, was injected IP one hour prior to electroshock. Equal numbers of male and female animals, selected randomly from each treatment group, were used. In a separate series of experiments we determined that the anticonvulsant drug vehicles afforded no protection from hindlimb extension.

Monoamine Analysis

Unshocked animals randomly selected from the control and neurotoxin groups at the time of electroshock testing

TABLE 1

MAXIMAL ELECTROSHOCK TONIC CONVULSIVE THRESHOLD AND PATTERN IN ADULT RATS ADMINISTERED 6-OHDA OR 5,7-DHT AT SEVERAL POSTNATAL AGES

Treatment Group†	Tonic Threshold	% Hindlimb Extension
Vehicle Control	54.3 (50–58)§	67
6-OHDA/1	58.2 (56–60)	92
6-OHDA/12	57.4 (53–60)	95
6-OHDA/14	57.3 (54–60)	92
6-OHDA/16	49.3 (47–53)	90
6-OHDA/18	52.1 (51–54)	94
6-OHDA/180	50.3 (47–55)	95
5,7-DHT/3	42.6 (36–49)*	96
5,7-DHT/12	44.3 (41–47)*	94
5,7-DHT/14	42.3 (39–46)*	90
5,7-DHT/16	38.5 (32–43)*	92
5,7-DHT/18	45.3 (41–46)*	92
5,7-DHT/180	53.3 (40–46)*	96

†Rats were first administered 6-OHDA or 5,7-DHT at various postnatal ages as described in the Method section.

‡All rats responding to MES with tonic convulsions had forelimb extension. §CC50 (95% confidence interval); mAmps. *Significant from control, $p<0.05$. The % of hindlimb extension in all neurotoxin treated groups was significant from control, $p<0.05$.

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 were assayed fluorometrically for norepinephrine, dopamine, and serotonin [11]. To test for possible regional differences in monoamine levels in the treated rats, the brains from five rats receiving the 6-OHDA/D1 or the 5,7-DHT/D3 treatment were dissected into cerebral cortex, cerebellum and brain stem-midbrain regions before freezing.

Statistical Methods

PD50 values for phenobarbital and phenytoin and CC50 values with 95% confidence intervals were calculated by probit analysis [18]. A difference in the values of PD50 or CC50 between control and treated groups was considered significant if the 95% confidence limits of potency ratios did not include one. All other comparisons were made by analysis of variance and Duncan's new multiple range test [22]. The criterion for significance statements was $p<0.05$.

RESULTS

Brain Monoamine Concentrations

Whole brain levels of monoamines in control adult rats were 0.43±0.02 (mean±S.E.M.; N=7–10) μg serotonin, 0.71±0.05 μg dopamine, and 0.38±0.01 μg norepinephrine per g brain. Animals treated with 6-OHDA had significantly reduced norepinephrine (51% of control; range of 48% to 53% among the six treatment groups) and dopamine (63% of control; range of 62% to 71%) concentrations, with no significant change in serotonin. Animals treated with 5,7-DHT had significantly reduced whole brain levels of serotonin (55% of control; range of 53% to 59%) with no significant changes in catecholamines. The S.E.M. for each of the neurotoxin-treated and control groups was less than 7% of the mean value. There were no significant differences in monoamine depletion among the various 6-OHDA-treatment groups or among the 5,7-DHT-treatment groups.

Regional analysis revealed a small but significant recovery of norepinephrine and dopamine levels in the brainstem-midbrain regions of rats receiving the 6-OHDA/D1 treatment. Norepinephrine levels were 67% of control compared to the 51% found for whole brain. Dopamine levels were 80% of control compared to 63% found for whole brain. Catecholamine depletions in the cortex and cerebellum, and serotonin depletions in all three regions, were similar to depletions found in whole brain.

Tonic Convulsive Threshold

Catecholamine reduction in 6-OHDA treated rats was not associated with significant changes in the tonic convulsive threshold compared to the control threshold current of 54.4 mA (Table 1). In contrast, an average reduction of 21% was found in the tonic convulsive thresholds of animals treated with 5,7-DHT compared to the tonic thresholds of control animals. Although the threshold in each of the 5,7-DHT treatment groups was significantly less than control, there were no significant differences in thresholds among the six 5,7-DHT treatment groups.

Maximal Electroshock Responses

All neurotoxin treated animals responded to maximal electroshock stimulation (150 mA) with an increased frequency of tonic hindlimb extension (Table 1). Although all animals tested displayed tonic forelimb extension, an average of 93% of neurotoxin-treated animals responded with the tonic hindlimb extension response compared to only 67% of the control, vehicle-treated animals.

Although there were no differences among the 6-OHDA and 5,7-DHT treatments in the increased frequency of tonic hindlimb extension, there were differences in the latency to onset and the duration of the hindlimb extension within and between the treatment groups (Fig. 1). In all cases, catecholamine reduction by 6-OHDA was associated with a faster onset of hindlimb extension and a prolonged duration of hindlimb extension compared to control. All changes in onset and duration were significantly different from control with the exception of the onset of extension in 6-OHDA/D180 treatment groups. The greatest difference between 6-OHDA treated rats and control animals was in rats first treated on postnatal day 14 (group 6-OHDA/D14). Compared to the control onset of 2.5 sec and duration of 9.3 sec, the 6-OHDA/D14 treatment decreased the onset by 52% to 1.2 sec and prolonged the duration almost two-fold to 13.8 sec.

In contrast, only in rats administered 5,7-DHT as adults (group 5,7-DHT/D180) were there significant changes in the onset and duration of hindlimb extension. Compared to controls, the onset of extension was prolonged by 49% to 12.4 sec. Some of these rats were retested when they were 270-days-old (data not included) and the changes in latency to onset and duration of extension were approximately 50% less in magnitude. Moreover, when 330-days-old, there was no longer a significant difference between control and treated animals in onset and duration of extension in spite of a persistent 43% reduction in serotonin levels. We also repeated the 5,7-DHT/D3 and 5,7-DHT/D16 treatment regimens and

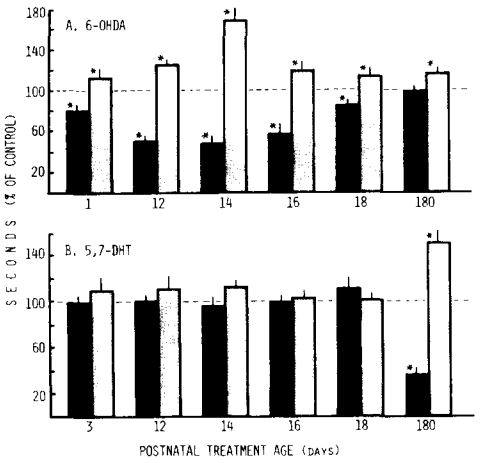

FIG. 1. The latency to onset and the duration of tonic hindlimb extension in adult rats treated with 6-OHDA or 5,7-DHT at different ages during postnatal development. The neurotoxins or vehicle were administered intracisternally as described in the Method section. The rats were tested when 210-days-old and the results are expressed as % of vehicle-injected controls. Solid bars are latency to onset of extension and hatched bars are duration of extension. The control latency to onset of extension=2.5 sec and the duration=13.8 sec. Vertical bars represent the S.E.M. for 20–25 rats per treatment. *Indicates significant from control, $p<0.05$.

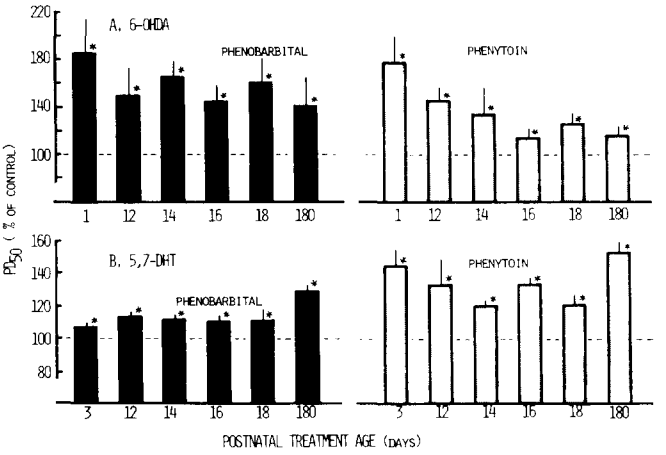

FIG. 2. Effect of postnatal 6-OHDA or 5,7-DHT treatment on the effectiveness of phenobarbital or phenytoin prevent tonic hindlimb extension. The neurotoxins or vehicle were administered intracisternally as described in Method section. Rats were tested when 210-days-old and the results are expressed as % of vehicle-injected controls. Control PD50's (95% confidence interval) for phenobarbital and phenytoin were 5.60 (5.5–5.7) and 9.25 (9.1–9.4) mg/kg, respectively. Vertical bars represent 95% confidence intervals. *Indicates significant from control, $p<0.05$.

found that two weeks later there was a significant decrease in the onset of extension which was also significantly prolonged in duration (data not included).

Anticonvulsant Drug Effects

The protective dose 50 (PD50) of phenobarbital and phenytoin in adult control rats was 5.60 mg/kg and 9.25 mg/kg, respectively. In all 6-OHDA treated animals, the PD50 for phenobarbital or phenytoin to prevent hindlimb extension was increased (Fig. 2). The greatest difference between control and treated animals was found in the 6-OHDA/D1 group in which the PD50's for phenobarbital and phenytoin were 10.3 mg/kg and 16.3 mg/kg, respectively, representing almost two-fold increases above the control PD50 values. At these doses, all control rats were protected from tonic extension. The PD50 for phenobarbital in the remaining treatment groups was significantly elevated by comparable amounts (42–65%). However, the association of elevated phenytoin PD50's with catecholamine reduction decreased with the age of 6-OHDA treatment; in rats first treated when 16-, 18- and 180-days-old, there was a small but significant 15–30% elevation in the PD50.

The several treatments with 5,7-DHT to reduce serotonin levels were also associated with significant increases in the dose of phenobarbital and phenytoin required to prevent hindlimb extension (Fig. 2). The greatest elevation of the PD50 for phenobarbital was found in rats treated with 5,7-DHT as adults (7.2 mg/kg; 130% of control). In all five groups treated when neonates, the phenobarbital PD50 was comparatively elevated by 8–15%. In contrast, the PD50 for phenytoin was increased by approximately 50% in rats treated on postnatal three or as adults to 13.2 mg/kg and 14.0 mg/kg, respectively. In the remaining four 5,7-DHT treatment groups, the PD50 for phenytoin was elevated by a lesser amount to between 120–130% of control.

DISCUSSION

We have previously reported that treatment of one and two day-old rats with 6-OHDA decreases the tonic threshold as early as postnatal day four [40]. However, the threshold returns to control levels by postnatal day 16 in spite of persisting catecholamine reduction. In adult rats, serotonin depletion, but not catecholamine depletion, is associated with a decreased tonic convulsive threshold [5, 6, 9, 12, 18]. Therefore, it was not unexpected that only adult rats treated with 5,7-DHT either postnatally, or as adults, showed a significant reduction in the tonic convulsive threshold. The age of the pups when treated with 5,7-DHT was not a factor. All six 5,7-DHT treatment regimens, differing only in the age of the rats when treated and not the magnitude of serotonin reduction, were associated with comparable decreases in the tonic threshold. Reduction of the threshold for tonic convulsions has been attributed to enhanced spread of seizure discharge in the brain [34]. Therefore, these results suggest that damage to central serotonergic neurons during postnatal development results in long-lasting interference with the ability of the brain to limit the spread of seizure activity.

The pattern (i.e., type of convulsion) and the severity (latency to onset and the duration) of the convulsion produced by maximal electroshock are also considered experimental measures of the spread of seizure discharge [36, 37, 41]. We have previously reported that treatment of three day-old rats with 5,7-DHT results in a greater incidence of hindlimb extension by postnatal day 12 [40]. This neonatal effect is persistant into adulthood since the present results indicate that all neonatal 5,7-DHT treatments were associated with a greater incidence of hindlimb extension when the rats reached an adult age. The effect also had no relationship to the age of the rats when treated. In contrast to the threshold and pattern results, a more severe hindlimb extension response was found only in the rats treated with 5,7-

DHT when 180-days-old. However, we did observe a more severe hindlimb extension response two weeks following the neonatal 5,7-DHT treatments and found the more severe response in rats treated as adults subsided with time following the 5,7-DHT treatment. Apparently, regardless of the age of the rat when damage to central serotonin neurons is caused, the brain is capable of adapting to, or compensating for, the serotonin reduction and counteracting the increased severity of the convulsive response to maximal electroshock. This apparent adaptation was not related to a recovery of serotonin levels during maturation based on both whole brain and regional analyses. The persistent effects of the neonatal 5,7-DHT treatments on the tonic threshold and pattern, but not on the severity of the tonic convulsion, illustrate the complexity of the regulatory role of serotonergic neurons in seizure discharge. This complexity may relate to the threshold, pattern and severity of the tonic convulsion reflecting different processes or mechanisms during the spread of seizure activity [34].

All six 6-OHDA treatments were associated with a greater incidence of hindlimb extension in adult rats. Like the results of the 5,7-DHT treatments, this effect was not related to the age of the rats when treated with neurotoxin. However, unlike the 5,7-DHT treatments, catecholamine reduction initiated in neonates was also associated with an increase in the severity of hindlimb extension responses in the rats when an adult age, reflected by shorter onsets and prolonged durations of extension. This persistent effect on convulsive severity suggests that the brain does not compensate to the continued catecholamine depletion as it apparently can to serotonin depletion. In this regard, monoamine analysis revealed a small recovery of norepinephrine and dopamine levels in brain stem-midbrain regions. This is consistent with the reported persistent depletion of monoamines following neonatal, intracisternal injection of 6-OHDA [31], as we used, in contrast to the hyperinervation of brainstem regions following the neonatal, systemic injection of 6-OHDA [15,19]. In spite of the small recovery of monoamine levels, the increased severity of the convulsive response to electroshock persisted, discounting the influence of the recovery of catecholamine neurons on the severity of the convulsive response.

Moreover, treatment of adult rats with 6-OHDA only prolonged the duration of extension and had no effect on the onset of extension. Browning and Maynert [2] found a similar effect of 6-OHDA on hindlimb extension in adult rats. These results suggest that injury to central catecholamine systems during postnatal maturation results in a greater interference with their role in the control of seizure spread than does injury when the systems are mature. This conclusion is supported by the finding that the magnitude of the 6-OHDA mediated effect on the latency to onset, and especially the duration, of extension was the greatest in adult rats treated with 6-OHDA on postnatal days 14 and 15. This difference was apparent in spite of similar magnitudes of catecholamine depletion resulting from all of the 6-OHDA treatments. Days 14 and 15 are at the beginning of the third postnatal week when rapid maturation of convulsive phenomena and neurotransmitter systems is taking place. It is also the age when the influence of early postnatal 6-OHDA on the tonic threshold is diminishing [40]. Therefore, postnatal days 14 and 15 may be a critical period in the maturation of catecholaminergic involvement in convulsive responses. Injury to catecholamine neurons at this time may have the greatest impact on the balance and the interaction among catecholaminergic and other neurotransmitter systems involved in the control of seizure spread in the adult rat.

The effectiveness of phenobarbital and phenytoin to prevent hindlimb extension was decreased in adult rats following all (neonatal and adult) neurotoxin treatments. Compared to control animals, higher doses of each drug were required for comparable protection. The requirement for higher doses to protect treated rats may be due to altered distribution of the drugs in the brain of treated rats. This is unlikely since the effects were observed with two chemically different anticonvulsant compounds and with neurotoxins specific to catecholaminergic or serotonergic neurons.

Gray and Rauh [10] reported that reserpine-induced brain monoamine depletion decreases the anticonvulsant effectiveness of phenytoin in mice but that this effect is similar in magnitude to the increased CNS excitability produced by reserpine. However, the present results indicate changes in excitability that do not correlate well with the persistent changes in the anticonvulsant effect of phenytoin or of phenobarbital as well. For example, all neurotoxin treatments resulted in comparable increases in the incidence of hindlimb extension but had differing magnitudes of effect on the two anticonvulsant drugs depending on the age of treatment. Although treatment of one and two day-old rats with 6-OHDA resulted in the greatest elevation of the adult PD50 for phenobarbital and phenytoin, it was the treatment at 14 and 15 days that caused the greatest increase in convulsive severity. Also, the neonatal 5,7-DHT treatments had a greater effect on phenytoin than on phenobarbital, yet resulted in no change in convulsive severity. Therefore, our results are consistent with the suggestion by others [3, 4, 25, 29, 30] that brain monoamines may in some way be directly involved in the anticonvulsant effects of phenobarbital and phenytoin. The decreased effectiveness of these two drugs in adult rats which received neonatal neurotoxin treatment supports our conclusion that neonatal injury to monoaminergic neurons results in a persistent alteration of the ability of the brain to control seizure discharge.

In summary, selective injury to monoaminergic systems during postnatal development resulted in altered maximal electroshock thresholds and responses and anticonvulsant drug effects in the same rats six months later when adults. The changes were found to be variable depending on the neurotoxin used, the age of the treatment with the neurotoxin and on the testing procedure indicating that the postnatal maturation of monoaminergic influences on seizure processes is complex. The results also suggest that interference with the normal maturation of these monoaminergic influences can have a long-lasting impact on the ability of the brain to limit seizure generation and spread and on the effectiveness of anticonvulsant drugs.

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