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# Age-Dependent Reduction in Maximum Electroshock Convulsive Threshold Associated with Decreased Concentrations of Brain Monoamines[1]

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LONDON, E D, S B WALLER, F J VOCCI AND G G BUTERBAUGH *Age-dependent reduction in maximum electroshock convulsive threshold associated with decreased concentrations of brain monoamines* PHARMAC BIOCHEM BEHAV **16**(3) 441–447, 1982.—This study investigated modification of the tonic convulsive threshold to maximum electroshock in 15- and 30 day old rats treated with drugs which reduce steady-state concentrations of monoamines. On postnatal day 15, reduction of central catecholamine concentrations by 6-hydroxydopamine or of central serotonin concentrations by 5,7-dihydroxytryptamine or p-chloroamphetamine did not alter the tonic convulsive threshold. However simultaneous depletion of catecholamines and serotonin by tetrabenazine was associated with a significant decrease in the tonic threshold. This effect could be reversed partially by simultaneous administration of the catecholamine and serotonin precursors, L-dihydroxyphenylalanine and 5-hydroxytryptophan, respectively. On postnatal day 30, reduction of brain serotonin concentration but not catecholamine concentrations, was associated with a significant decrease of the tonic convulsive threshold. In a previous study, in which 7–8 day old rats were used, a tetrabenazine-induced decrease in the tonic convulsive threshold was prevented by L-dihydroxyphenylalanine but not 5-hydroxytryptophan. Furthermore, intracisternal 6-hydroxydopamine, but not 5,7-dihydroxyhyptamine, decreased the threshold on postnatal day 8. Therefore, the results of the present study involving 15- and 30 day old rats, together with the earlier findings in 7–8 day old rats, [28] suggest an apparent developmental transition from catecholaminergic to serotonergic dominance in regulation of the tonic convulsive threshold during the first postnatal month.

Monoamines Electroshock Convulsions Development Catecholamines Serotonin

SINCE 1954, when Chen *et al* [7] reported that reserpine decreased the thresholds for electroshock- and pentylenetetrazol-induced convulsions in mice, numerous investigations have addressed the question of monoaminergic involvement in convulsive phenomena [1, 4, 11, 12, 19, 22, 23, 24, 34, 42]. The results of these studies indicate that pharmacologic reduction of brain monoamine concentrations in general, or specific depletion of catecholamines or serotonin, decreases convulsive thresholds and/or intensifies convulsive patterns in adult rodents.

Similarly, reduction of brain catecholamine and serotonin concentrations by reserpine or tetrabenazine (TBZ) decreases maximal electroshock convulsive thresholds in neonatal (7–8 day old) rats [28]. The TBZ-induced decrease in the threshold is prevented by the catecholamine precursor, L-dihydroxyphenylalanine (L-dopa), but not the serotonin precursor, 5-hydroxytryptophan (5-HTP). Furthermore, intracisternal 6-hydroxydopamine (6-OHDA), which selectively reduces brain catecholamine concentrations [2], decreases the tonic threshold on postnatal day 8, 5,7-dihydroxytryptamine (5,7-DHT), which selectively reduces brain serotonin concentrations [9], does not decrease the threshold [28]. These results suggest that in early postnatal development catecholaminergic systems are more

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TABLE 1

EFFECTS OF p-CHLOROAMPHETAMINE, 6-HYDROXYDOPAMINE (6-OHDA) AND 5,7-DIHYDROXYTRYPTAMINE (5,7-DHT) ON WHOLE BRAIN MONOAMINE CONCENTRATIONS IN 15 DAY OLD RATS*

| | Monoamine Concentrations (ng/mg tissue)† | | |
|---|---|---|---|
| Treatments | Norepinephrine | Dopamine | Serotonin |
| Intraperitoneal | | | |
| Control‡ | 0 16 ± 0 02 (6) | 0 37 ± 0 01 (5) | 0 40 ± 0 03 (a) |
| PCA | 0 15 ± 0 01 (3) | 0 37 ± 0 04 (4) | 0 29 ± 0 04 (7)¶ |
| Intracisternal | | | |
| Control§ | 0 24 ± 0 01 (8) | 0 38 ± 0 02 (8) | 0 32 ± 0 01 (8) |
| 6-OHDA | 0 13 ± 0 01 (5)# | 0 26 ± 0 01 (5)# | 0 33 ± 0 01 (5) |
| 5,7-DHT | 0 25 ± 0 01 (4) | 0 36 ± 0 01 (14) | 0 16 ± 0 01 (4)# |

*PCA was administered intraperitoneally (7 5 mg/kg) on days 13 and 14 6-OHDA was administered intracisternally on days 12 (100 μg) and 13 (50 μg), 5,7-DHT was administered intracisternally on day 12 (50 μg) one hour after desipramine (25 mg/kg, IP)

†Each value is reported as the mean ± S E M for the number of rats indicated in parentheses

‡Two separate groups of rats served as controls for the PCA treatment (1 ml/kg body weight of saline 24 and 48 hours before sacrifice) and the tetrabenazine treatment (Table 2) (1 mg/kg body weight of distilled water at 4 hours and at 45 min before sacrifice) Because monoamine values for these groups were not different they were combined

§Two separate groups of rats served as controls for the 6-OHDA and 5,7-DHT treatments Because brain monoamine values in these two groups were almost identical, data from the two groups were combined

¶Significantly different from intraperitoneal control, $p<0$ 05

#Significantly different from intracisternal control, $p<0$ 05

important than serotonergic systems in attenuating electroshock responses

The present study was designed to obtain information about the relative importance of catecholaminergic and serotonergic systems to seizure susceptibility during later postnatal development The effects of the 6-OHDA, 5,7-DHT and p-chloroamphetamine (PCA) on tonic convulsive thresholds in 15- and 30 day old rats were determined PCA acts to selectively reduce brain serotonin levels [25,35] L-dopa or 5-HTP were administered to TBZ-treated rats to evaluate the effects of catecholamine or serotonin repletion, respectively, on tonic convulsive thresholds

## METHOD

### *Animals and Animal Care*

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

### *Electroshock Procedures*

Animals were tested between 0800 and 1500 hr Electroshock was not administered to one treatment group at a time Instead, individual rats were tested, in turn, from each treatment group under investigation with an animal from an appropriate control group This was done to reduce the possible effects of diurnal variation in seizure threshold Single shocks of 60 Hz alternating current, 200 msec duration, were delivered through an electroshock apparatus (Wahlquist Instruments) using corneal electrodes Isotonic saline was applied to the eyes of each rat before electrode placement to insure good contact Rats were restrained by gloved hand and released immediately after stimulation to permit observation of the convulsion throughout its entire course

To determine tonic convulsive thresholds, four to seven current intensities of electroshock were administered, with 6 to 14 animals per current intensity For each intensity, approximately equal numbers of male and female rats were taken from at least three similarly treated litters The tonic convulsive threshold (median convulsive current, $CC_{50}$), was defined as the current intensity required to produce a tonic forelimb extension in 50 percent of the animals tested

### *Drug Treatments*

Tetrabenazine methanesulfonate (TBZ, Hoffman-LaRoche, Inc ), L-dopa and 5-HTP (Sigma Chemical Co ) were dissolved in distilled water p-Chloroamphetamine-HCl (PCA, Sigma Chemical Co ) and desipramine-HCl (Merrell National Laboratories) were dissolved in 0 9% NaCl TBZ (25 mg/kg), L-dopa (150 mg/kg), 5-HTP (150 mg/kg), desipramine (25 mg/kg) and PCA (7 5 mg/kg) were administered by intraperitoneal injection, each in a volume of 1 ml per kg body weight Corresponding control animals were injected

with equal volumes of the respective carrier at the same times that drugs were administered

PCA was administered on two successive days of age (13 and 14 or 28 and 29) TBZ was injected on postnatal day 15, 4 hr prior to electroshock testing Effects of L-dopa and 5-HTP on monoamine levels and the tonic convulsive threshold in TBZ-treated rats were assessed by injecting L-dopa, 5-HTP, or the combination of L-dopa and 5-HTP 45 min before electroshock testing

6-hydroxydopamine-HBr (6-OHDA) and 5,7-dihydroxytryptamine-creatinine sulfate (5,7-DHT, Sigma Chemical Co ) were dissolved in 0 9% NaCl containing 0 4 mg/ml ascorbic acid as an antioxidant The drugs were administered intracisternally under light ether anesthesia Animals receiving 6-OHDA were treated on two successive days of age (either postnatal days 12 and 13 or 27 and 28) On the first day, they received 100 $\mu$g of 6-OHDA (free base) followed 24 hr later by another 50 $\mu$g 5,7-DHT (50 $\mu$g, free base) was given as a single injection on postnatal day 12 or 27, one hour after desipramine (25 mg/kg, IP), which was administered to protect catecholaminergic terminals from the neurotoxin [9] In all cases, control animals received equal volume (10 $\mu$l) intracisternal injections of vehicle using similar schedules These 6-OHDA and 5,7-DHT treatment regimens did not significantly alter brain weights or body weights on days 15 or 30

*Monoamine Analysis*

Unshocked animals were decapitated between 0800 and 1300 hr, their brains were rapidly removed, frozen in liquid nitrogen and stored in liquid nitrogen for a maximum of 10 days before determination of norepinephrine, dopamine and serotonin concentrations In experiments which utilized PCA or TBZ as a monoamine reducing agent, norepinephrine and dopamine in brain homogenates were assayed radioenzymatically, according to the method of Coyle and Henry [8], and serotonin content was estimated fluorimetrically after solvent extraction by the method of Snyder *et al* [36] In later experiments using 6-OHDA or 5,7-DHT as the monoamine reducing agents, monoamines were analyzed fluorometrically by the method of Jacobowitz and Richardson [16] Whole brain control monoamine concentrations obtained using these different methods did not differ significantly

*Statistical Analyses*

$CC_{50}$ values with 95% confidence intervals were calculated by probit analysis including tests for parallelism and heterogeneity [27] A difference between $CC_{50}$ values in drug-treated and control groups was considered significant if the potency ratios with 95% confidence limits did not include unity Statistical significance ($p<0$ 05) of differences between monoamine concentrations among drug-treated and control groups was assessed by one-way analysis of variance [37] and Duncan's new multiple range test [14]

## RESULTS

*Postnatal Day 15*

6-OHDA significantly reduced the whole brain concentrations of norepinephrine and dopamine to 54% and 68% of control, respectively, with no significant effect on serotonin levels (Table 1) or the tonic convulsive threshold (Fig 1) In

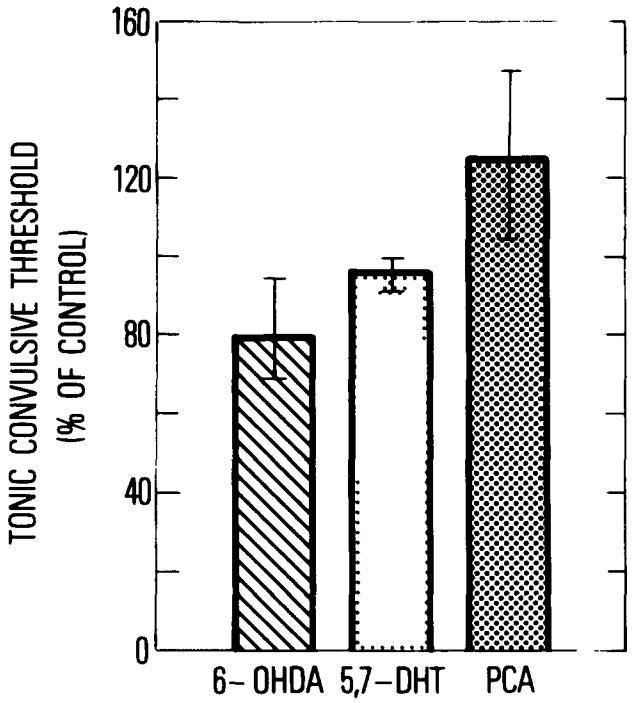


FIG 1 Effects of 6-hydroxydopamine (6-OHDA), 5,7-dihydroxytryptamine (5,7-DHT), and p-chloroamphetamine (PCA) on the tonic convulsive threshold in 15 day old rats 6-OHDA was administered intracisternally on days 12 (100 $\mu$) and 13 (50 $\mu$g), 5,7-DHT was administered intracisternally on day 12 (50 $\mu$g) one hr after desipramine (25 mg/kg, IP), PCA was administered intraperitoneally (7 5 mg/kg) on days 13 and 14 Tonic convulsive thresholds obtained on day 15 are expressed as percentages of the control thresholds with 95% confidence intervals (vertical brackets) On day 15, the threshold was 113 (96–130) mA in controls for the PCA treatment The threshold was 115 (102–119) mA in controls for the 6-OHDA and 5,7-DHT treatments

5,7-DHT-treated rats, norepinephrine and dopamine levels were not significantly affected, but the serotonin concentration was reduced to 50% of control (Table 1) Similarly, PCA did not alter norepinephrine or dopamine levels but significantly reduced serotonin levels to 72% of control (Table 1) Neither 5,7-DHT nor PCA significantly altered the tonic threshold (Fig 1) Thus, reductions of up to about 50% in concentrations of brain catecholamines or serotonin alone were not associated with significant decreases in the tonic convulsive threshold on postnatal day 15

Effects of TBZ (25 mg/kg, 4 hr prior to tonic convulsive threshold determination) are shown in Fig 2 TBZ significantly reduced brain concentrations of norepinephrine and dopamine and serotonin to 25%, 14% and 80% of control, respectively (Table 2) The tonic convulsive threshold was decreased to 22% of control Administration of L-dopa (150 mg/kg) to TBZ-treated rats 45 minutes prior to electroshock did not affect norepinephrine or serotonin, but increased concentrations of dopamine to 86% of control 5-HTP (150 mg/kg) in TBZ-treated rats did not significantly affect norepinephrine or dopamine, but increased the concentration of serotonin to 202% of control Neither treatment alone affected the TBZ-induced decrease in the convulsive threshold However, combined administration of L-dopa and 5-HTP to TBZ-treated rats elevated levels of norepinephrine

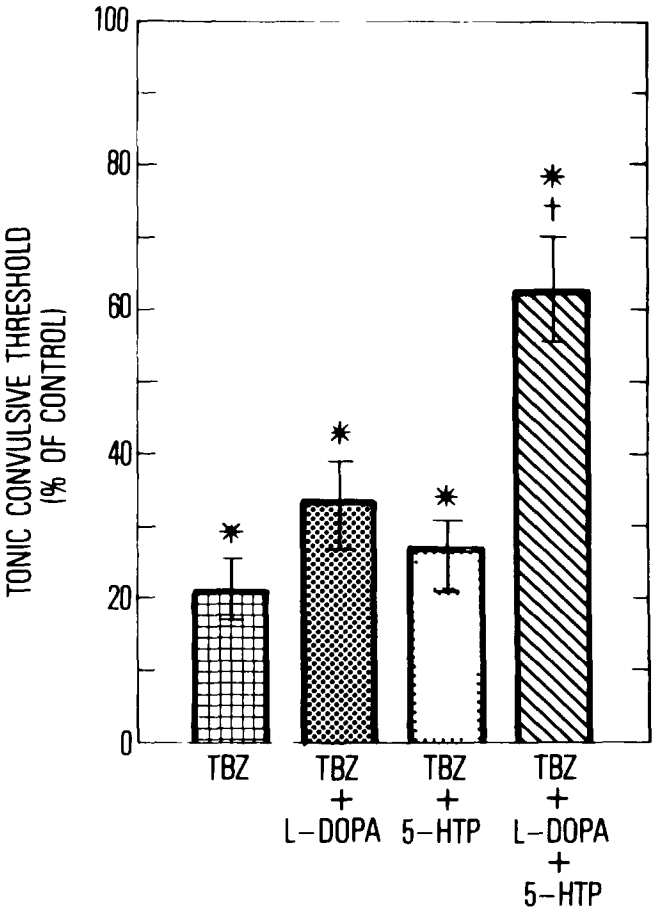


FIG 2 Effects of L-dopa and 5-hydroxytryptophan (5-HTP) on tetrabenazine (TBZ)-induced reduction in the tonic convulsive threshold TBZ (25 mg/kg, IP) was administered to 15 day old rats Tonic convulsive thresholds were obtained 4 hours later 45 minutes after IP administration of 150 mg/kg L-dopa or 5-HTP or 150 mg/kg L-dopa plus 150 mg/kg 5-HTP Tonic convulsive thresholds obtained on day 15 are expressed as percentages of the control threshold with 95% confidence intervals (vertical brackets) On day 15, the control threshold was 113 (96–130) mA *indicates significant difference from control ($p<0.05$), †indicates significant difference from threshold in TBZ-treated rats ($p<0.05$)

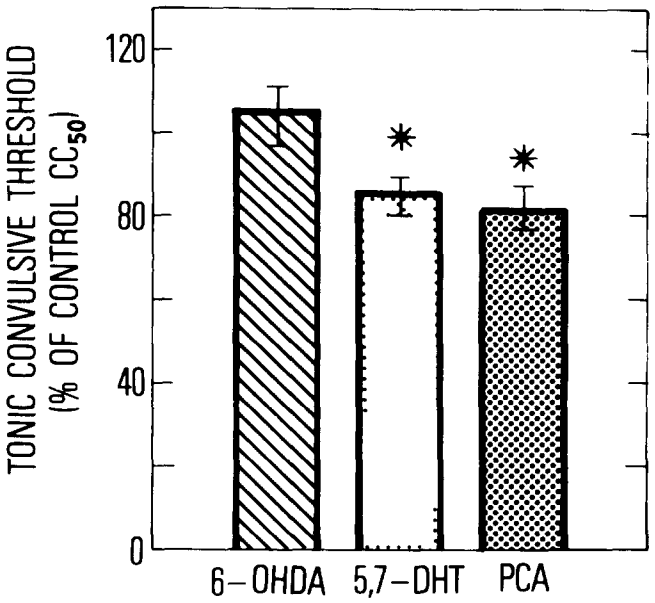


FIG 3 Effect of 6-hydroxydopamine (6-OHDA) 5 7-dihydroxytryptamine (5,7-DHT) and p-chloroamphetamine (PCA) on the tonic convulsive threshold in 30 day old rats 6-OHDA was administered intracisternally on days 27 (100 μg) and 28 (50 μ) 5,7-DHT was administered intracisternally on day 27 (50 μg) one hour after desipramine (25 mg/kg IP) PCA (7 5 mg/kg, IP) was administered on days 28 and 29 Tonic convulsive thresholds were obtained on day 30, and are expressed as percentages of the control threshold with 95% confidence intervals (vertical brackets) On day 30 the threshold in controls for the PCA treatment was 37 6 (36 5–39) mA The threshold was 35 2 (33–38) mA in controls for the 6-OHDA and 5 7-DHT treatments

to 44%, dopamine to 362% and serotonin to 277% of control, and significantly reversed the TBZ decrease in the tonic convulsive threshold from 20% to 60% of control The serotonin concentration in rats treated with TBZ and L-DOPA + 5-HTP did not differ significantly from the concentration in rats treated with TBZ + 5-HTP

*Postnatal Day 30*

In control rats, whole brain concentrations of norepinephrine, dopamine and serotonin were higher on day 30 than on day 15 in controls for the PCA and intracisternal treatments (Table 3) Tonic convulsive thresholds on postnatal day 30 are presented in Fig 3 as percentages of the control threshold The tonic threshold in rats which served at controls for the PCA treatment was 37 (36 5–39) mA, and was decreased by 67% from the control threshold on day 15 Similarly, the tonic threshold in rats which served as controls for the 6-OHDA and 5,7-DHT treatments was 35 (33–38) mA, and was decreased by 70% from day 15 6-OHDA did not significantly decrease the tonic convulsive threshold or central serotonin levels, but significantly reduced norepinephrine and dopamine levels to 53% and 68% of control, respectively In 5,7-DHT-treated rats, catecholamine levels were not significantly affected, but the serotonin concentration was significantly reduced to 60% of control Similarly, PCA did not significantly affect norepinephrine and dopamine, but significantly reduced the concentration of serotonin to 43% of control Both 5,7-DHT and PCA significantly decreased tonic convulsive thresholds (83% and 81% of control, respectively)

## DISCUSSION

The present results demonstrate a developmental decline in the maximum electroshock convulsive threshold, which is consistent with previous observations [28,40] Concomitantly, there are increases in whole brain concentrations of norepinephrine, dopamine and serotonin reflecting maturation of monaminergic systems

Previous findings indicate that catecholamines have greater functional importance than serotonin in seizure processes during early postnatal development (days 7–8) [28] However, whereas some studies in adult rodents present evidence for greater importance of catecholamines in attenuating electroshock intensity [3, 18, 19, 38] others

TABLE 2

EFFECTS OF L-DIHYDROXYPHENYLALANINE (L-DOPA), 5-HYDROXYTRYPTOPHAN (5-HTP) AND TETRABENAZINE (TBZ) ON WHOLE BRAIN MONOAMINE CONCENTRATIONS IN 15 DAY OLD RATS*

| Treatments | Monoamine Concentrations (ng/mg tissue)† | | |
|---|---|---|---|
| | Norepinephrine | Dopamine | Serotonin |
| Control‡ | 0 16 ± 0 02 (6) | 0 37 ± 0 01 (5) | 0 40 ± 0 03 (9) |
| TBZ + vehicle | 0 04 ± 0 02 (4)§ | 0 05 ± 0 01 (4)§ | 0 32 ± 0 03 (5)§ |
| TBZ + L-dopa | 0 04 ± 0 01 (4)§ | 0 32 ± 0 06 (5)¶ | 0 31 ± 0 02 (3) |
| TBZ + 5-HTP | 0 02 ± 0 02 (3)§ | 0 09 ± 0 02 (5)§ | 0 81 ± 0 25 (3)¶ |
| TBZ + L-dopa + 5-HTP | 0 07 ± 0 02 (6)§ | 1 34 ± 0 17 (4)¶ | 1 11 ± 0 64 (3)¶ |

*Vehicle (distilled water), L-dopa (150 mg/kg), 5-HTP (150 mg/kg) or L-dopa (150 mg/kg) plus 5-HTP (150 mg/kg) was administered intraperitoneally 45 minutes before TBZ (25 mg/kg, IP), which was administered 4 hours before sacrifice

†Each value is reported as the mean ± S E M for the number of rats indicated in parentheses

‡See Legend, Table 1

§Significantly different from control, $p<0\ 05$

¶Significantly higher than TBZ, $p<0\ 05$

TABLE 3

EFFECTS OF p-CHLOROAMPHETAMINE (PCA), 6-HYDROXYDOPAMINE (6-OHDA) AND 5 7-DIHYDROXYTRYPTAMINE (5,7-DHT) ON WHOLE BRAIN MONOAMINE CONCENTRATIONS IN 30 DAY OLD RATS*

| Treatments | Monoamine Concentrations (ng/mg tissue)† | | |
|---|---|---|---|
| | Norepinephrine | Dopamine | Serotonin |
| Intraperitoneal | | | |
| Control | 0 23 ± 0 03 (4) | 0 67 ± 0 04 (3) | 0 61 ± 0 05 (6) |
| PCA | 0 21 ± 0 03 (3) | 0 59 ± 0 09 (3) | 0 26 ± 0 06 (6)‡ |
| Intracisternal | | | |
| Control | 0 30 ± 0 11 (8) | 0 68 ± 0 01 (8) | 0 52 ± 0 01 (8) |
| 6-OHDA | 0 16 ± 0 01 (4)§ | 0 46 ± 0 01 (4)§ | 0 54 ± 0 01 (4) |
| 5 7-DHT | 0 31 ± 0 01 (4) | 0 66 ± 0 004 (4) | 0 31 ± 0 004 (4)§ |

*PCA (7 5 mg/kg) was administered intraperitoneally on days 28 and 29 6-OHDA was administered intracisternally on days 27 (100 μg) and 28 (50 μg) 5 7-DHT was administered intracisternally on day 27 (50 μg) one hour after desipramine (25 mg/kg, IP)

‡Each value is reported as the mean ± S E M for the number of rats indicated in parentheses

‡Significantly different from intraperitoneal control, $p<0\ 05$

§Significantly different from intracisternal control, $p<0\ 05$

suggest a more significant serotonergic involvement [5, 6, 22, 23]

In the present study, reductions of up to 50% in whole brain concentrations of either catecholamines or serotonin, by 6-OHDA or 5,7-DHT, respectively, did not alter the tonic convulsive threshold on postnatal day 15 In addition, preliminary studies using higher doses of 6-OHDA or 5,7-DHT to produce drastic (up to 90%) depletions of either catecholamines or serotonin did not alter the tonic threshold These larger neurotoxin dosages significantly reduced brain weight and body weight on postnatal day 15 (Waller and Buterbaugh, unpublished) While 6-OHDA-induced reductions in catecholamine concentrations of up to 50% were not associated with threshold decreases on day 15, greater reductions in catecholamine concentrations along with a 20% reduction in the concentration of serotonin by TBZ accompanied significant threshold decreases Repletion of either dopamine or serotonin to control levels by L-dopa or 5-HTP, respectively, did not significantly elevate the tonic threshold above than in rats treated with TBZ alone These results suggest that on day 15, neither catecholamines nor serotonin alone regulate seizure susceptibility, but that catecholamines in combination with serotonin may have functional relevance in this regard

Administration of L-dopa with 5-HTP to TBZ-treated rats on day 15 partially repleted norepinephrine to 44% of control

and elevated dopamine and serotonin to extremely high levels (362% and 277% of control, respectively) This combined precursor treatment partially reversed the TBZ-induced reduction in the tonic convulsive threshold It seems that the reversal of the threshold could have resulted from the high, non-physiological concentrations of dopamine and serotonin, possibly having no relationship to the normal, physiological function of the amines Alternatively the return of the convulsive threshold toward the control level may reflect elevation of catecholamines and serotonin toward or above levels which allow their normal participation in regulating the convulsive threshold The incomplete recovery of the tonic convulsive threshold by precursor treatment may have resulted from the fact that norepinephrine (44% of control) was still not repleted to a physiological level Alternatively, this may reflect the participation of non-catecholaminergic, nonserotonergic neurotransmitter systems other than catecholaminergic and serotonergic may be important in regulating the tonic threshold at that time TBZ reduces brain levels of γ-aminobutyric acid (GABA) as well as catecholamines and serotonin [25, 26, 28, 32, 33] Furthermore, an influence of developing GABAergic systems in convulsive phenomena is suggested by the linear increase in the $CD_{50}$ for the GABA antagonist picrotoxin during the first postnatal month in rats [41] Therefore, the importance of GABAergic transmission to the tonic electroshock convulsive threshold in 15 day old rats may warrant further study

In 30-day old rats, 40–57% reductions in serotonin concentration were associated with decreased thresholds, whereas decreases in catecholamine concentrations (45% decrease in NE, 17% decrease in dopamine) were not accompanied by threshold decreases Therefore, it seems that serotonergic involvement in regulating the tonic convulsive threshold at 30 days is more important than catecholaminergic involvement Thus, the results of the present study involving 15- and 30 day old rats, together with the earlier findings in 7–8 day old rats [28], suggest a transition from early catecholaminergic to later serotonergic dominance in regulation of the tonic convulsive threshold It appears that the transition is complete by day 30

Our findings regarding the functional participation of catecholaminergic and serotonergic systems in the maximum electroshock convulsive threshold are in agreement with information on maturation of these neurotransmitter systems in the rat brain In this regard, Kellogg and Lundborg [20,21] demonstrated functional catecholaminergic synapses and receptors in the newborn rat Additionally, catecholamine agonists such as L-dopa and amphetamine, which depend on functional presynaptic catecholaminergic neurons for their pharmacological effects, produce characteristic behavioral responses in the newborn rat [13, 15, 30] In contrast, central serotonergic systems apparently do not become functional until the third postnatal week [29,39] Although most of the serotonergic cell bodies are present at birth, [10, 31, 39] several parameters of serotonergic neuronal function such as serotonin content, high-affinity synaptosomal uptake and enzyme inactivation mechanisms are at less than one-third of their respective adult values but reach approximately three-fourths of their adult values by the third postnatal week [31,39] More importantly, it is after postnatal day 14 that the characteristic serotonin-mediated behavioral responses of an adult rat can be first produced by drug treatments [17] Further study of the apparent developmental transition described here may provide information concerning the development of neurotransmitter interactions or balances important for seizure control

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