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Age-Dependent Vulnerability to Seizures

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Seizure disorders frequently occur early in life. Seizures are classified as reactive, symptomatic, or idiopathic depending on whether their cause can be identified. Reactive seizures are the result of acute environmental perturbations. Early in life, many stressors can produce seizures and the ultimate outcome may depend on the particular precipitating factor and its intensity. Febrile convulsions are the most common reactive seizures, although they must be differentiated from symptomatic seizures precipitated by fever. Symptomatic seizures are often associated with varying degrees of central nervous system (CNS) insults, including congenital malformations and metabolic storage diseases of the gray matter. These seizures may have age-specific characteristics and may at times be difficult to treat with conventional antiepileptic treatments.

To develop a better understanding of the pathophysiology of seizures early in life, we have extensively used animal models of epilepsy. In this chapter, we report our findings with a rat model of developmental cortical dysplasias produced by intrauterine injections of methylazoxymethanol acetate. These rats are more susceptible to kainic acid, flurothyl, and hyperthermic seizures than normal rats. Rats with severe cortical dysplasia are most susceptible to seizures. We have also studied the mechanisms involved in the control of seizures during development because status epilepticus is more prevalent in infants than in adults. Our data suggest that the substantia nigra may play a crucial role in status epilepticus as a function of age. In the adult substantia nigra two regions mediate opposing effects on seizures following infusions of γ-aminobutyric acid type A ($GABA_A$) agents. One region is located in the anterior substantia nigra, and muscimol infusions in this region mediate anticonvulsant effects. The second region is in the posterior substantia nigra, and here muscimol infusions produce proconvulsant effects. *In situ* hybridization data demonstrate that, at the cellular level, neurons in the two substantia nigra regions differ in the amount of hybridization grains for $GABA_A$ receptor α1 and γ2L subunit mRNAs. In developing male rats, only the "proconvulsant" region is present up to the age of 21 days. The transition from the immature to mature substantia nigra mediated seizure control occurs between age 25 and 30 days. The identification of age-dependent functional networks involved in the containment of seizures may lead to possible new pharmacologic strategies to control seizures, thus aiding the development of age-appropriate treatments of seizure disorders.

INTRODUCTION

Epidemiologic studies indicate that a greater propensity is found in young children to develop seizures and epilepsy in comparison with adults. This increase in seizure susceptibility is most prominent during the first few months of life, substantially declines after age 5 years, and reaches adult levels of vulnerability after adolescence (1). This general trend holds across a variety of seizure disorders; however, specific types of seizures occur exclusively in infancy or childhood. Therefore, it appears that the

age of onset of seizures is developmentally determined. Furthermore, evidence indicates that electrographic characteristics, behavioral manifestations, response to treatment, and long-term outcome of seizures are also age-dependent (2).

During development, classification of seizures may be difficult because seizure components are not always apparent or uniform. For example, in young children, the early clinical manifestations of partial seizures can be subtle. The early indicators of a focus may not be apparent and as a result these seizures are often classified as generalized tonic-clonic. Also characteristic of partial seizures in young children is the variability in clinical manifestations between bouts: the patterns of spread are not well established and the seizures do not appear to be stereotypic. In addition, during specific developmental periods, focal dysfunction can produce multifocal seizures that can result in bilateral manifestations. These can be loosely described as "generalized" seizures (e.g., infantile spasms), whereas typical generalized seizures (e.g., absence seizures) emerge after the fourth year of life (3).

The increased seizure susceptibility of human infants has been replicated in animal models of epilepsy using both *in vitro* and *in vivo* paradigms, especially during the second and third postnatal week in the rat (4–6). Some of the reasons underlying the heightened seizure susceptibility of the rat brain may include precocious development of excitatory synapses, delayed development of inhibition, GABA-mediated excitatory responses, heterogeneity of receptor subunits, differences in ionic microenvironment, or maturation of circuits that can modify the expression of seizures. Several of these factors, which have been studied using *in vitro* models, are discussed in other chapters in this volume (see Chapters 9, 10, and 11). *In vivo* experiments including neocortical focal epileptogenesis, amygdala and hippocampal kindling, and systemic administration of a variety of chemoconvulsants (2) have shown that increased susceptibility to seizures during the second and third postnatal week is not restricted to a single structure or a specific seizure model and probably represents a widespread phenomenon. The predominant characteristics of enhanced epileptogenicity at this age are rapid secondary generalization of seizures, emergence of multifocal seizures, decreased refractory periods, and a propensity to develop status epilepticus.

Both human and animal studies are in agreement that the normal immature brain is more vulnerable to seizures. Clinical research suggests that children with brain damage have a greater propensity for seizures and seizure recurrence than children without brain damage (7,8). Brain damage is the result of many different insults no studies currently link specific patterns of damage to changes in seizure susceptibility. Similarly, preliminary studies in developing rats also suggest an increased likelihood of seizures following lesion-induced brain damage (9). However, more research is needed to determine the relationship between brain damage and seizure susceptibility in the young brain. In this chapter, we address this issue in studies of seizure susceptibility in rat pups following *in utero* brain damage. In addition, we report our data involving the mechanisms participating in the control of seizures during development, because infants are more susceptible to express generalized seizures and status epilepticus than are adults.

CORTICAL DYSPLASIAS AND SEIZURE SUSCEPTIBILITY

Cortical dysplasia is a pathologic condition resulting from malformation of the cortex *in utero*. It is characterized by laminar or columnar disorganization, abnormal appearing cells, alterations in cortical thickness, and increased number of cells in the molecular layer and subcortical white matter (10). Several types of cortical dysplasia exist, depending on the location (unilateral or bilateral) and extent (focal or diffuse) of the histologic abnormalities. These include agyria, macrogyria (pachygyria), polymicrogyria, schizencephaly, hemimegalencephaly, and more subtle forms as heterotopias and microdysgenesis.

The most common clinical characteristics of cortical dysplasia include neurologic deficits (e.g., cerebral palsy, developmental delays, and learning disabilities), mental retardation, and seizures. Such clinical features vary along a wide spectrum, presumably depending on the degree of brain damage. However, the relationship between damage and clinical manifestations is not an obvious one because similar lesions have been associated with varying degrees of clinical symptoms (10).

A link between epilepsy and cortical dysplasia was suggested based on tissue specimens of epileptic patients who had undergone surgical resections (11, 12). More recently, through the use of magnetic resonance imaging, an increasing number of patients with epilepsy have been reported to have cortical dysplasia (13, 14). In fact, studies have indicated that seizures associated with cortical dysplasia are more common in children, more likely to be intractable, and have a

poorer prognosis (15–18). One of the factors limiting our understanding of cortical dysplasia and seizure susceptibility is the lack of an experimental model that closely mimics the clinical histopathology.

The underlying mechanism of cortical dysplasia is unknown at present. However, several clinical similarities are seen between cortical dysplasia and neuronal migrational disorders (NMD). Both are associated with cognitive impairment and seizures. Cortical dysplasia and NMD are characterized by a broad range of cytoarchitectural anomalies including small discrete heterotopias to gross cortical laminar disorganization. As a result of the many parallels between the two disorders, cortical dysplasias are typically categorized as NMD.

Experimentally methylazoxymethanol acetate (MAM) can be used to produce NMD. MAM is a synthetic ester of a natural occurring compound in the leaves and nuts of tropical cyad plants. It is a neurotoxic teratogen and potent alkylating agent that produces methylation of nucleic acid during neuroblast division (19,20). MAM disrupts DNA synthesis, resulting in cell demise 2 to 24 hours after the pregnant female is injected. Maximal drug effects occur 12 to 13 hours posttreatment (19). MAM treatment of pregnant rats on embryonic day 15 (E15) results in a reduction in cortical, striatal, and hippocampal mass (21–23), apparently because these areas of the brain are undergoing mitosis at this time.

In a series of experiments, we studied pathologic changes, particularly in the cortex and hippocampus, that result from MAM exposure *in utero* (24,25). Pregnant rats were injected with MAM on E13, E14, E15, or E16. Results demonstrated that both the incidence and the severity of NMD were significantly greater when MAM was injected on E15. All E15 MAM-treated rats had NMD ranging from moderate to severe. The abnormalities observed in rats treated on E13, E14, and E16 rats were categorized as mild and were not present in all the rats. In contrast, abnormalities characteristic of rats injected on E15 were more severe. These rats had decreases in cortical thickness, total brain, and body weight and were from significantly smaller litters. These findings confirmed the specificity of the MAM effects during gestation.

Histologic characterization of the cortex and hippocampus was performed (24). Several of the features that we observed are present in humans with NMD and with cortical dysplasia. For example, clusters of cells found in cortical layers II–V were often large, irregular in shape, and abnormally oriented (Fig. 1). Marginal neuronal heterotopias in the subarachnoid space were also observed. In addition, ectopic neurons in cortical layer I and heterotopic neurons in the subcortical white matter were present. In the hippocampus, histopathologic alterations following MAM treatment included areas of neuronal ectopia within and adjacent to the CA1 pyramidal cell layer. In rats with mild characteristics, ectopic areas were not present; however, the CA1 cell layer had a "wavy" appearance that was associated with discrete areas of cell loss.

The hippocampal ectopic areas were studied to determine whether the receptors on these cells were aberrant. Initial studies (24,25) using *in situ* hy-

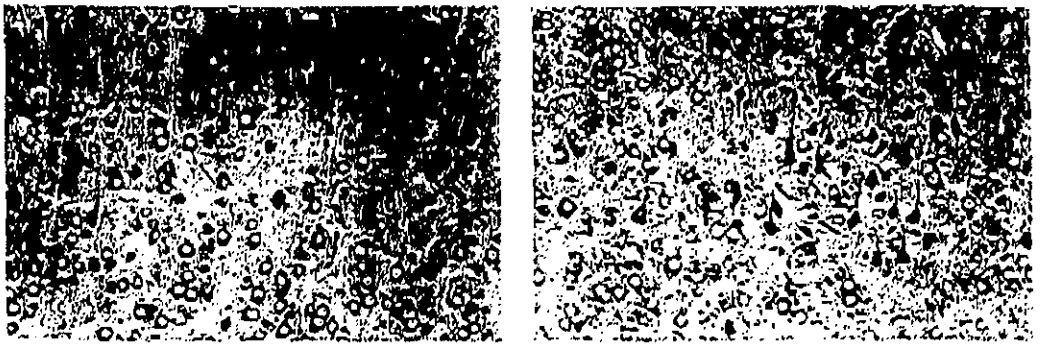

FIG. 1. Photomicroraph of coronal section of a 14-day-old control and methylazoxymethanol acetate (MAM)-treated rat. In the control section (**A**), both the morphology of the somata and the orientation of the cells are uniform within cortical lamina III and IV. In contrast (**B**), tissue from an MAM-treated rat show the presence of a cluster of abnormally migrated cells (*arrows*) with irregular somata, abnormal orientation, and a loss of cortical lamination.

bridization examined changes in the distribution of the $GABA_A$ ($\alpha 1$) and glutamate (GluR2) receptor subunits in ectopic neurons of the CA1 hippocampal subfield. Quantitation of autoradiographs by densitometric analysis indicated significant differences in the distribution of both receptor subunit mRNAs in the MAM-treated rats. $GABA_A$ $\alpha 1$ and GluR2 mRNA expression were lower in the ectopic area compared with the expression in adjacent areas in the same rat or with the expression in analogous areas in untreated age-matched control animals. Further, emulsion-dipped sections showed the reduction was in mRNA content per neuron within the ectopic areas.

To determine whether seizure vulnerability is altered in immature rats that have brain damage induced *in utero*, several litters of rats were exposed to MAM. Seizure susceptibility was determined in 2-week-old MAM-treated rats following systemic administration of kainic acid (26). Several parameters were monitored to assess seizure threshold, including latency to seizure onset, behavioral seizure severity, seizure duration, and mortality rate. The increased seizure susceptibility positively correlated with NMD. Immature rats with severe NMD had a significantly shorter onset to kainic acid-seizure compared with age-matched control rats (Fig. 2A). We observed a similar increase in seizure vulnerability in 2-week-old MAM-treated rats following hyperthermia-induced seizures (28). The incidence of seizures and mortality was greater in rats with NMD compared with normal control rats (Fig. 2B). Both seizure and mortality rates were positively correlated with the duration of hyperthermia (120 or 150 seconds). Others have also reported an increase in susceptibility to kainic acid and bicuculline seizures in MAM-treated immature rats (27) or flurothyl seizures in MAM-treated adult rats (29). Along these lines, *in vitro* studies have demonstrated that hippocampal tissue slices containing the ectopic area were more epileptogenic than slices from normal adult rat brains (30). These findings suggest that brain damage induced by MAM increases the likelihood of seizures in both developing (2-week-old) and adult rats.

Together, the results of these studies indicate that an increase in vulnerability to seizures occurs in the developing brain and, furthermore, an even greater propensity exists toward seizures if brain damage was present early in life. Such findings are important in terms of treatment of children with seizure disorders. It appears that more aggressive treatment of seizures in brain-damaged children may be necessary than in children with seizures and otherwise normal-appearing brains.

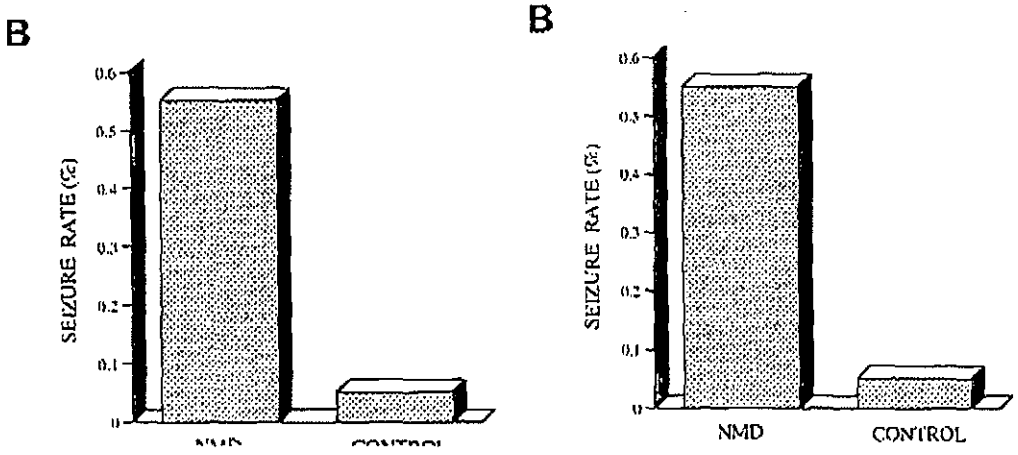

FIG. 2. Two-week-old rats with neuronal migrational disorders had an increased susceptibility to seizures. A: Normal control rats and rats with severe neuronal migrational disorders (NMD) were injected with kainic acid (5 mg/kg, intraperitoneally) to induce status epilepticus. Latency to the onset of status epilepticus was significantly shorter in rats with NMD ($p < .001$, N = 10 rats per group). B: Normal control and rats with NMD were exposed to hyperthermia (core body temperature > 42°C for 150 seconds). The incidence of behavioral seizure was greater in rats with NMD. Data are expressed as percentages of total number of animals in each group (N = 10 rats per group).

AGE-DEPENDENT MECHANISMS OF SEIZURE CONTROL BY THE SUBSTANTIA NIGRA

The increased vulnerability of the immature brain to seizures may be a result of developmental differences in the maturation of neuronal networks in the brain that participate in the control of seizures. The substantia nigra has been implicated in the control of seizures (31–33). Initial pharmacologic studies from our laboratory demonstrated that the regulation of seizures by the GABA-sensitive substantia nigra pars reticulata (SNR) is age-dependent. Nigral infusions of the $GABA_A$ agonist muscimol had the opposite results in mature and 2-week-old rats: anticonvulsant effects in adults and proconvulsant effects in 2-week-old rats (34,35). These findings were supported by our receptor binding studies, which demonstrated a developmental lag of $GABA_A$ high-affinity receptors in 2-week-old rats (36).

It is possible that the developmental changes in the role of the SNR on seizures may be the result of either an alteration in the composition of the GABA receptor in the SNR or changes in the SNR output systems (37). In the present studies, we utilized pharmacologic manipulations of the SNR and *in situ* hybridization histochemistry to study the role of the SNR in the regulation of seizures during development.

In the adult SNR, two topographically discrete $GABA_A$-sensitive regions are located in the anterior and posterior SNR (Fig. 3). These regions differ in the expression of the $GABA_A$ receptor $\alpha 1$ and $\gamma 2L$ subunit mRNAs, mediate opposing effects on seizures, and alter metabolism in divergent nigral projections. The differences indicate the existence of separate anticonvulsant and proconvulsant SNR networks. Infusions of muscimol in the anterior SNR have anticonvulsant effects, whereas infusions of muscimol in the posterior SNR have proconvulsant effects. The anticonvulsant anterior network appears to involve the

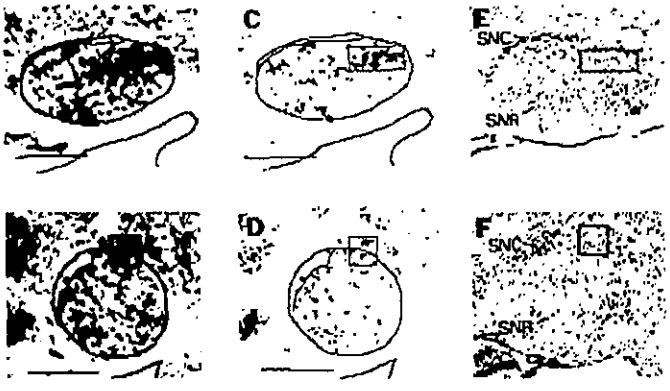

FIG. 3. Age-related differences in the patterns of mRNA expression of the γ-aminobutyric acid type A $GABA_A$ α1 subunit in the rat substantia nigra. Marker bars = 1 mm. The images are sagittal brain sections 2.4 to 2.6 mm lateral to the midline. **A:** In the adult rat, digitized autoradiogram shows overall high mRNA expression throughout the substantia nigra pars reticulata (SNR) with minimal expression in the substantia nigra compacta (SNC). A large region of highest mRNA expression of the $GABA_A$ α1 subunit is seen in the posterior-dorsal SNR (*boxed area*). **B:** In the 2-week-old rat, digitized autoradiogram shows an uneven distribution of small clusters of the $GABA_A$ α1 mRNA throughout the SNR. The *boxed area* shows a small region with the highest density of mRNA expression. **C:** Image analysis using a thresholding (isodensity map) procedure localizes the regions of highest density of mRNA expression of the $GABA_A$ α1 subunit for the adult shown in **(A)**. The largest region of high density is in the dorsal posterior area of the SNR (*boxed area*). **D:** Image analysis localizes the regions of highest density of mRNA expression of the $GABA_A$ α1 subunit of the 2-week-old rat shown in **(B)**. The largest region of high density (*boxed area*) is on the border of the SNR and the adjacent region. **E, F:** The thionin stained section within 100 μm of the autoradiograms in **(A)** and **(B)**. The *boxed area* indicates the region of highest density of mRNA expression. Note that the increased expression of α1 mRNA in the posterior SNR of the adult rat is caused by the increased cellular density in that region (47). Vellskova et al. (46) have recently demonstrated that the neurons in the posterior SNR are actually expressing lower amounts of α1 mRNA than neurons located in the anterior SNR. (From ref. 37, with permission.)

ventromedial thalamus, whereas the proconvulsant posterior network may involve the striatum and globus pallidus. In contrast, in 2-week-old rats, infusions of muscimol produce only proconvulsant effects and appear to use the same pathway as the adult proconvulsant (posterior) network. These results suggest that the segregation of these seizure-controlling networks occurs with maturation. This segregation is not present in 2-week-old rats in which only the proconvulsant muscimol-sensitive nigral system is functional (37).

The initial observations were extended by infusing 2-week-old and adult rats with several GABAergic agents into the SNR prior to flurothyl seizures. These included THIP ($GABA_A$ high-affinity receptor agonist) (38), bicuculline ($GABA_A$ low-affinity receptor agonist) (35,39), ZAPA (predominantly a $GABA_A$ low-affinity agonist) (40), and GVG (GABA transaminase inhibitor) (41,42) (Table 1).

In the adult anterior SNR, infusions of ZAPA and bicuculline produced opposite results: ZAPA had anticonvulsant effects, whereas bicuculline had proconvulsant effects. Because ZAPA is a $GABA_A$ low-affinity receptor agonist and bicuculline a $GABA_A$ low-affinity receptor antagonist, the data suggest that the opposing effects of ZAPA and bicuculline are mediated by the $GABA_A$ low-affinity receptors. The proposed role of anterior nigral low-affinity $GABA_A$ receptors on seizures is further supported by data demonstrating that the anticonvulsant effect of GVG infusions in the anterior SNR can be blocked with bicuculline.

It is conceivable that the anticonvulsant effects of ZAPA in the anterior SNR may be caused, in part, to its action on high-affinity $GABA_A$ receptors that mediate the anticonvulsant effects of the mixed agonist effects of drugs such as muscimol, THIP, and GVG. The effect of ZAPA may be direct via its albeit weak action on high-affinity $GABA_A$ receptors or by competing with endogenous GABA for uptake transport and thereby enhancing GABA concentrations (43). GABA could then be acting on both receptor populations. We therefore propose, in adult rats, GABAmimetic stimulation of the anterior SNR induces anticonvulsant effects in the flurothyl seizure model by activating both high- and low-affinity receptor sites (40).

In contrast to the anterior SNR, in the adult posterior SNR, the effects of ZAPA and bicuculline on seizures are not in the opposite direction. Bicuculline

TABLE 1. *Effects of intranigrally microinfused GABA agents on clonic fluorothyl-induced seizure threshold. The results indicate that the GABAergic effects are sit specific for the adult SNR and that some features of the 2-week-old SNR persist in the adult posterior SNR. See text for details.*

TREATMENT	Adult anterior SNR	Adult posterior SNR	Two-week-old SNR
Muscimol			
–25 ng	Anticonvulsant	Not tested	0
–50 ng	Anticonvulsant	Not tested	0
–100 ng	Anticonvulsant	Proconsulvant	Proconvulsant
THIP			
–250 ng	Anticonvulsant	Not tested	0
–500 ng	Anticonvulsant	Not tested	Proconvulsant
Bicuculline			
–12 ng	0	Not tested	0
–25 ng	0	Not tested	Proconsulvant
–50 ng	0	Not tested	Proconsulvant
–100 ng	Proconsulvant	0	Proconvulsant
ZAPA			
–1 µg	Not tested	Not tested	0
–2 µg	0	0	Anticonvulsant
–4 µg	0	0	Not tested
–8 µg	Anticonvulsant	Proconvulsant	Proconsulvant
GVG			
–1 µg	0	Not tested	0
–5 µg	0	Not tested	Anticonvulsant
–10 µg	0	Not tested	Anticonvulsant
–20 µg	Anticonvulsant	Proconvulsant	Anticonvulsant
GVG/muscimol	±Anticonvulsant	Not tested	0
GVG/bicuculline	0	Not tested	0

SNR, substantia nigra pars reticulata; THIP, 4,5,6,7-tetrahydrolisoxazolo[5,4-C]pyridin-3-ol; ZAPA, (2)-3-[(aminoiminomethyl)thio]prop-2-enoic acid; GVG, gamma-vinyl-GABA; 0, no effect.

has no effect on flurothyl seizure thresholds, whereas ZAPA has a proconvulsant effect. The incongruent effects of ZAPA and bicuculline may suggest a differential distribution of $GABA_A$ low-affinity receptor sites in the anterior and posterior SNR. Low-affinity $GABA_A$ receptors may be absent in the posterior SNR. If this is the case, the proconvulsant effects of ZAPA may be caused by its other GABAergic actions, and its effects on flurothyl seizures may be mediated by different receptors than that mediating the ZAPA effects in the anterior SNR (40).

In the posterior SNR, muscimol, GVG, and high doses of ZAPA have proconvulsant effects. At these doses, ZAPA may act as a high-affinity $GABA_A$ agonist, mimicking the muscimol effect, or as a GABA uptake substrate, increasing endogenous GABA levels in the synaptic cleft and, thereby, simulating the GVG effects. We propose that the $GABA_A$ receptors located in the posterior SNR have a distinct molecular subunit composition and binding characteristics (a high-affinity proconvulsant receptor subtype). Photographic emulsion studies of *in situ* hybridization using $\alpha 1$ and $\gamma 2L$ probes revealed that the neurons in the posterior SNR have a lower density of silver grains than neurons in the anterior SNR. Thus, the proconvulsant effects are associated with a nigral region consisting of neurons with low expression of $GABA_A$ $\alpha 1$ and $\gamma 2L$ mRNA subunits, suggesting that this population of receptors is composed of different $GABA_A$ receptor subunits than in the anterior SNR. The inability of bicuculline to alter seizure threshold suggests that the low concentration of the $\alpha 1$ and $\gamma 2L$ subunits may denote a high-affinity $GABA_A$ receptor subtype that mediates proconvulsant effects. However, the exact receptor subunit composition remains to be elucidated.

The effects of the SNR on seizures are age-specific. Accordingly, in the 2-week-old rat, we were not able to demonstrate a topographic organization for the effects of any GABAergic agent we tested including ZAPA. We found that, in 2-week-old rats, a low dose of ZAPA (2 μg per site) had anticonvulsant effects, whereas a larger dose (8 μg per site) was proconvulsant (40). The anticonvulsant action of ZAPA may be mediated by low-affinity $GABA_A$ receptors, either because of its direct action or indirectly by blockade of GABA uptake. The latter may result in a GVG-like effect and an increased amount of endogenous GABA in the synaptic cleft, which enhances GABA action at the abundant low-affinity $GABA_A$ receptors. Indeed, GVG infusions have anticonvulsant effects. Previous studies indicated that low-affinity $GABA_A$ receptors are present in the 15-day-old SNR at slightly higher densities (130%) than in the adult SNR (36). Furthermore, infusions of bicuculline are proconvulsant or block the anticonvulsant action of GVG in this age group (42). The effect of the higher ZAPA dose may be caused by its action on high-affinity $GABA_A$ receptors as suggested by the proconvulsant effects of muscimol (both a high- and low-affinity $GABA_A$ receptor agonist) and THIP (a high-affinity $GABA_A$ receptor agonist) (44,45). Furthermore, nigral muscimol treatment can also block the anticonvulsant action of GVG (42).

These results suggest that the 2-week-old, undifferentiated SNR has the features of the posterior SNR in terms of the presence of the proconvulsant high-affinity $GABA_A$ receptor site. Indeed, in 2-week-old rats, the amount of $\alpha 1$ and $\gamma 2L$ mRNA per neuron throughout the SNR was similar to the amount of mRNA in the posterior SNR of adult rats. However, in the young SNR, the low-affinity sites were also present. Binding studies of low- and high-affinity $GABA_A$ receptors in the SNR of rat pups support this conclusion. A greater number of low affinity sites were found in rat pups (30% more than adults); however, fewer high-affinity $GABA_A$ receptors were found (13% of adult levels) (36).

We hypothesize that, in 2-week-old rats, both low- and high-affinity $GABA_A$ receptors are present and functional. The low-affinity $GABA_A$ receptors mediate anticonvulsant activity. The high-affinity receptors mediate proconvulsant effects and are similar to the proconvulsant $GABA_A$ high-affinity receptors that exist in posterior SNR of adult rats. The full anticonvulsant properties of the anterior SNR emerge with development as the density of high-affinity receptors of different subunit composition increases to mature levels. Yet, in the posterior SNR a small proportion of the existing high-affinity $GABA_A$ receptors retain their immature features, leading to their proconvulsant effects. Additional studies using recombinant GABA receptors are needed to prove the hypothesis that specific combinations of $GABA_A$ subunits change the binding affinity and the pharmacologic effect of GABAmimetic stimulation.

To determine the age at which the segregation of the two nigral systems occurs, we studied the effects of specific nigral muscimol infusions in rats of various ages (15, 21, 25, 30, and 35 days) on flurothyl seizure thresholds. Results indicate that adult topographic organization becomes apparent at 25 days and is fully functional at 30 days. Interestingly, *in situ* hybridization studies suggest that the segregation of the $GABA_A$ $\alpha 1$ and $\gamma 2L$ subunits in the posterior SNR is already apparent at age 21 days (46).

These pharmacologic and molecular studies may provide mechanistic explanations for the age-specific effects of antiepileptic drugs. In addition, maturational changes in the local circuitry and efferent connections (37) may play a role. The identification of functional networks may lead to possible new pharmacologic strategies to control seizures, thus aiding the development of age-appropriate treatments of seizure disorders.

CONCLUSION

Epidemiologic studies indicate that infants and young children have a higher propensity to develop seizures and epilepsy than do adults. The increase in epileptic potential varies with specific seizure types and syndromes; nevertheless, reactive seizures in response to intense environmental stimuli occur more frequently in infancy and early childhood. Experimental studies in animal models of epilepsy in normal and morphologically abnormal animals are useful because they allow for the investigation of the substrates underlying the critical periods of enhanced epileptogenesis and control of seizures. These models can be used to determine the development of age-specific antiepileptic treatments. The nigral system may be a target for the development of such therapies.

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