Experimental epilepsy: developmental aspects

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EPIDEMIOLOGIC studies indicate that in humans, seizures occur more frequently early in life.[1,2] During the first few years some of the seizure types are age-specific[3,4] and difficult to control with conventional therapies.[5] The high incidence of seizures cannot be attributed only to the greater number of insults that may occur during the newborn period and early infancy. Experimental evidence suggests that the immature central nervous system (CNS) is more susceptible to seizures than its mature counterpart,[6–14] at least during a specific stage of development. Ontogenetic seizure studies have demonstrated that 15-to-18-day-old rat pups are more prone to the development of bilateral, asynchronous convulsions and status epilepticus than adult rats regardless of the seizure model used to induce the seizures.[6–10] These behavioral observations parallel the human epidemiologic and behavioral data concerning the expression of seizures as a function of age.[3,4] Ongoing studies suggest that some of the age-related differences in seizure susceptibility may be due to a functional immaturity of the substantia nigra (SN).[15–19]

ROLE OF THE SN IN SEIZURES OF ADULT ANIMALS

The SN is considered to be a critical site involved in the expression of generalized seizures in adult animals.[15,20,21] It has been repeatedly demonstrated that electrographic seizure activity propagates in the SN.[22,23] Autoradiographic studies of 2-deoxyglucose (DG) indicate that during a seizure there is an increase in DG uptake in the SN.[15,24–27] Furthermore, information has accumulated suggesting that in adult rats, the gamma-aminobutyric-acid (GABA)-sensitive substantia nigra pars reticulata (SNR) neurons may be responsible, in part, for the termination of seizures. Infusions of GABA agonists (such as muscimol) into the SNR can suppress seizures.[20,21,28–30] SN lesions[20,31] or electrical stimulation[32,33] can also suppress seizures; the effect of electrical stimulation can be reversed by picrotoxin, a GABA antagonist.[32]

These observations suggest that treatments which decrease the GABAergic output of the SNR can attenuate or terminate seizures, probably by disinhibiting postsynaptic neurons in nigral projection sites, which include the thalamus, neostriatum, superior colliculus and pontine reticular formation.[34] There is evidence that seizures can deplete nigral levels of the GABA-synthesizing enzyme, glutamic acid decarboxylase.[35,36] This may indicate that during a seizure there is an accelerated production of GABA in the SNR which represents an endogenous compensatory mechanism of the brain to stop a seizure. Bonhaus et al[22] have shown that during an electrographic afterdischarge (AD) the firing pattern of the SNR cells changes drastically. The cells fire in bursts of action potentials often time-locked with the AD. As their data show, however, the overall firing rate diminishes during the electrographic seizure, suggestive of increased GABA release.[37] The end result is a decrease of the GABA-sensitive nigral output similar to that observed with local microinfusions of the GABA agonists, muscimol or gamma-vinyl GABA. After study of these data, we have proposed that in adult animals the SNR is able to control the propaga-

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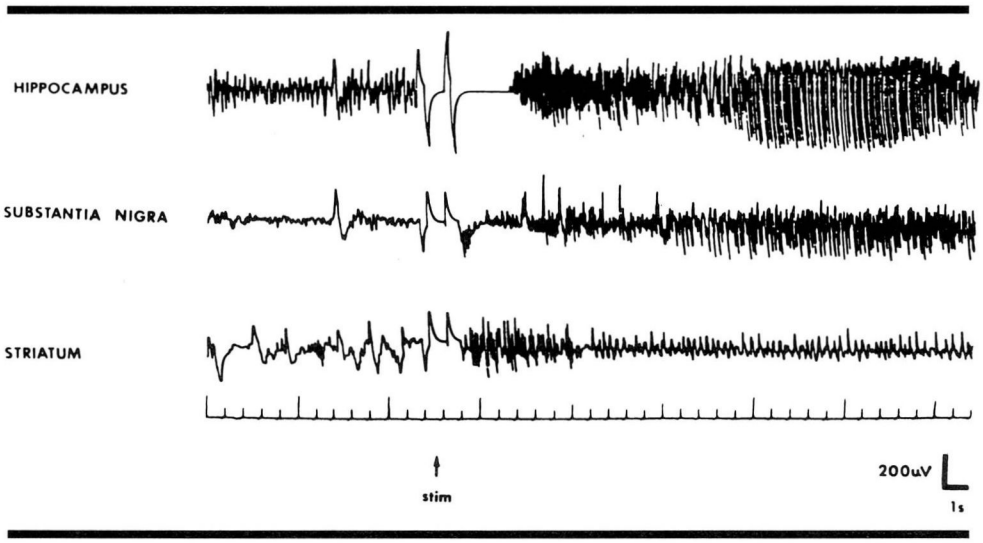

FIGURE 1. Propagation of electrographic seizure activity in substantia nigra and striatum during hippocampal kindling in 16-day-old rats.

tion of seizures. This hypothesis is now accepted by others.[38]

ROLE OF THE SN IN SEIZURES OF DEVELOPING ANIMALS

The protective role of the SNR is not present in developing animals. Rat pups are more prone to develop seizures and status epilepticus than adults,[7,8,10] and DG autoradiographic studies show a lack of metabolic activation of the SN during seizures.[10,15,39] Prepubescent (30-to-35-day-old) rats are more resistant to the development of generalized seizures than pups or adults, and their autoradiographs reveal an age-specific pattern of metabolic activation of the SNR.[10] We therefore suggest that functional immaturity of the SN may be responsible, in part, for the increased seizure susceptibility of the immature brain.

Does the SNR have a role in seizures of developing animals? Electrographic recordings obtained from the hippocampus, striatum and SN of 16-day-old pups during kindling or kainic acid seizures indicate that the epileptic discharges propagate in the SN (*Figure 1*).

These results suggest that the SN-based circuit is involved in seizures of rat pups, since the SN afferents appear to be functioning. To evaluate the functional integrity of the SNR proper and its output pathways, the GABA agonist muscimol (25 to 200 ng/0.25 L) was infused in the SNR bilaterally in 16-day-old pups.[17,18] Muscimol in the SNR produced stereotypies similar to those observed in adults. Stereotypies first appeared immediately after completion of the infusions and persisted for at least 60 minutes. Since stereotypic movements can easily be confused with seizures in this age group, rat pups implanted with amygdala or cortical electrodes were monitored electrographically for 40 minutes after completion of the muscimol infusions. The rat pups were loosely restrained to decrease movement artifacts. Neither electrographic nor behavioral seizures were observed.[18] These results indicate that muscimol infusions are not convulsants per se.

Bilateral nigra muscimol infusions in rat pups facilitated the development of flurothyl seizures in a dose-response and time-dependent manner (*Figure 2*).

Low doses (100 ng/0.25 L) of muscimol did not affect the thresholds while higher doses (100 and 200 ng/0.25 L per site) significantly decreased the latency of onset of seizures.[18] With the dose of 100 ng/0.25 L, this proconvulsant effect was apparent within 15 minutes, became maximal at 30 minutes, and decreased somewhat at 60 minutes after infusions.[17] This effect is the opposite of that observed in adult rats in which bilateral infusions of muscimol suppress seizures.[16,17,20,21,28,30]

It is conceivable that the increases in stereotypies produced by muscimol might be associated with an increase in respiration and greater inhalation of the flurothyl vapors which may in turn account for the earlier seizure onset. This does not appear to be the case since it has been reported that nigral muscimol decreases respiration in rodents.[40,41] Furthermore, whereas both adult rats and rat pups exhibited stereotypies, muscimol acted as an anticonvulsant in adults and as a proconvulsant in rat pups. Moreover, in rat pups all doses of muscimol were generally associated with mild or severe stereotypies whereas only the higher doses produced a significant degree of seizure facilitation.

The age-related effects cannot be attributed to a differential spread of the drug in the SN and surrounding areas following the intracranial infusions. By con-

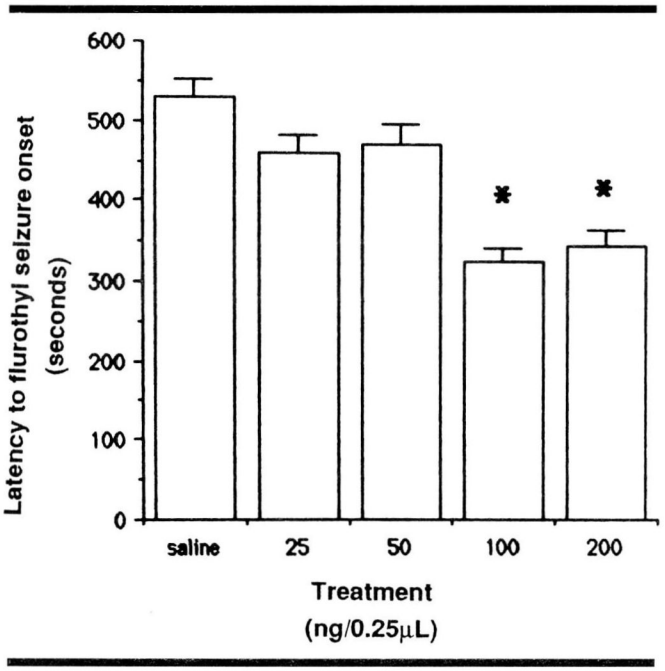

FIGURE 2. The effect of intranigral muscimol infusions on the latency of flurothyl seizure onset as a function of dose in rat pups. *Significantly different from other doses or controls, $P < 0.03$ ($n = 5$ to 13 per group). High doses of muscimol facilitate the development of seizures.

trolling for size of cannula and injection volume, we have determined that the spread of radioactive muscimol is similar in both age groups with 80% of the radioisotope present within a radius of less than 1 mm at 30 minutes after injection (*Figure 3*).

Time-response curves in rat pups[17] and other evidence from the literature[28] indicate that a maximal effect of muscimol can be observed at this time point. The amount of muscimol present within the SN region represents 1% of the original infused volume; this final concentration approaches the physiologic concentrations that activate receptors.[42] Additional studies indicate that the age-dependent effect of muscimol on seizures is site-specific. Infusions of muscimol above the SNR region do not produce any changes in seizure susceptibility in either age group.[17,18,20,28]

The data then suggest that the GABA nigral system is involved in the seizure circuitry of rat pups, but this GABA nigral system differentially mediates seizures as a function of age. *Table 1* depicts the effects of nigral infusions of two GABAergic drugs on seizures as a function of age.

MATURATIONAL CHANGES OF NIGRAL GABA RECEPTORS

In the CNS there are at least two types of GABA receptors: GABAA which are bicuculline-sensitive, and GABAB which are bicuculline-insensitive but sensitive to baclofen. A third type of GABA receptor has been proposed which is insensitive to both bicuculline and baclofen.[43,44] Muscimol has a high affinity for the GABAA subtype although it also binds weakly to the GABAB receptor.[44] Bicuculline is a classic GABAA receptor antagonist and exerts its effects by blocking the receptor to endogenous GABA.[45,46] Bicuculline can also produce neuronal excitation by nonspecifically altering the neuronal membrane conductance.[47] If the effects of nigral muscimol on seizures were produced by activation of the GABAA receptors, then blocking of these receptors by bicuculline infusions should produce an opposite effect on seizures since, according to our hypothesis, endogenous GABA is already involved in the suppression of seizures in adult animals. Infusions of bicuculline methobromide (25 to 200 ng/0.25 μL) in the SNR produced intense stereotypies with all dosages tested, but no spontaneous seizures.[48] These infusions of bicuculline significantly facilitated the onset of flurothyl seizures in a dose-dependent manner.[48] The results are the opposite from those observed with muscimol infusions and suggest that in adult rats the effects of muscimol on seizures may be mediated by the GABAA receptor subtype.

As previously stated, nigral muscimol infusions produce a proconvulsant effect in pups. To better understand the mechanism by which this effect is induced, we investigated the effects of various doses of bilateral nigral bicuculline infusions on the development of seizures in rat pups.[18] All doses of bicuculline (12.5 to 100 ng/0.25 μL) produced various degrees of stereotypies which were not dose-related. Rats implanted with cortical and amygdala electrodes and monitored electrographically did not exhibit any spontaneous behavioral or electrical seizures. The effects of bicuculline methobromide on the flurothyl thresholds were determined five minutes after completion of the bilateral infusions, as in the adults.

Bilateral nigral infusions of bicuculline facilitate the development of flurothyl seizures in a dose-response manner. The higher doses of bicuculline, 25, 50, 100 ng/0.25 μL per site, significantly decreased the latency of seizure onset while the lowest dose, 12.5 ng/0.25 μL, did not differ in effect from the saline controls (*Figure 4*).

These results indicate that both bicuculline and

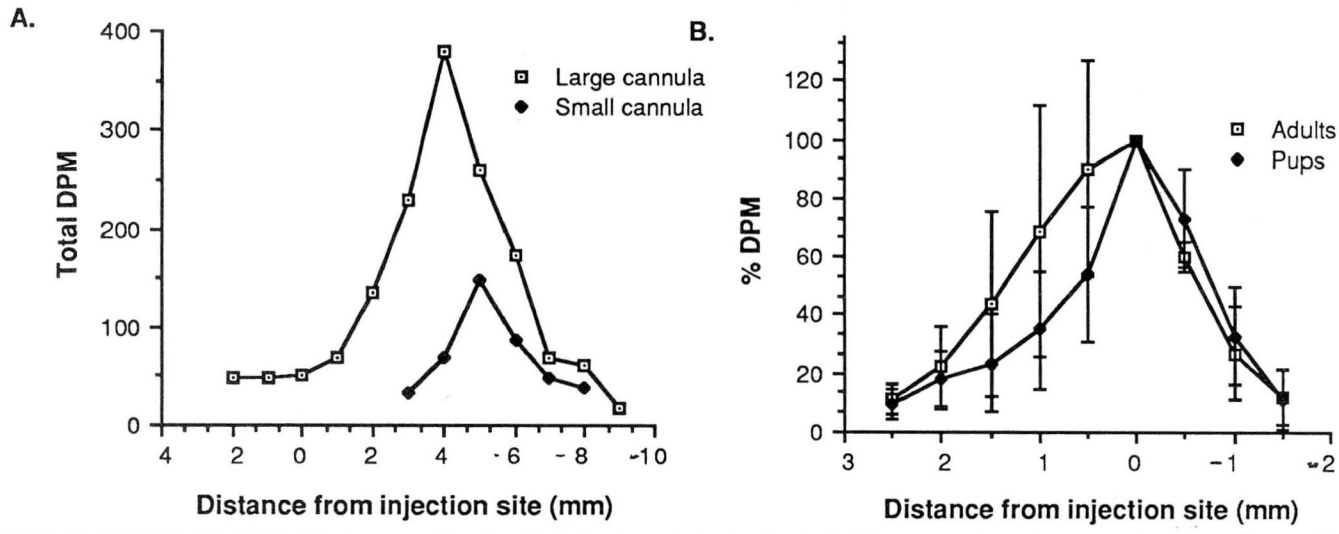

FIGURE 3A. Spread of 3H-muscimol from the SN injection site as a function of infusion volume and cannula size (n = 1 per group). Bregma is 0 point on the horizontal axis. The rat with the large cannula (23 gauge) received 0.5 μL volume, while the rat with the small cannula (28 gauge) received 0.25 μL; both increased volume and increased cannula size result in greatly increased spread of 3H-muscimol away from the site of infusion. FIGURE 3B. Spread of 3H-muscimol from the SN injection site in four adults and four pups, at 30 min post-infusion. Values are means ± SE, and represent the percent of DPM from the amount present at the injection site (0 point on horizontal axis). The degree of spread is similar in the two age groups. (*DPM* = deteriorations per minute)

TABLE 1
EFFECTS OF NIGRAL INFUSIONS OF TWO GABAergic DRUGS ON SEIZURES AS A FUNCTION OF AGE

Drug	Adult seizures	Pup seizures
Muscimol ($GABA_A$ receptor agonist)	Suppression	Facilitation
Bicuculline ($GABA_A$ receptor antagonist)	Facilitation	Facilitation

muscimol facilitate the development of seizures in rat pups, while in adult rats the two agents produce opposite effects. Data from adults suggest that the GABAergic effect on seizures may be mediated by the GABAA receptor, since both drugs have a high affinity for this receptor.[43,45,46] In contrast, pup data suggest that the nigral muscimol effects on seizures may not be mediated by the GABAA receptor, for if the receptors in the SN were developed and functioning properly, both muscimol and bicuculline would act on this site and produce opposite effects, as in the adult.

To determine the status of GABAA (muscimol) receptors, we performed receptor-binding studies of the SN and the cerebellum. The purpose was to evaluate whether the age-specific pharmacologic actions of muscimol in the SN of adults and rat pups are due to differences in the type, affinity or number of local receptors.[19] Computer-assisted Scatchard analysis revealed two affinity sites for muscimol binding in the SN and cerebellum in the two age groups. The binding affinity (Kd) of muscimol receptors did not differ between the two age groups in either SN or cerebellum. In contrast, significant site-specific age-related differences were found in the receptor density of the high affinity site. In the SN of 16-day-old pups, this density was 13% of adult levels (32.5 fmol/mg protein in pups and 253 fmol/mg in adults, *Figure* 5). There were no differences in the receptor density of low-affinity receptors in either site.

The results suggest that lack of anticonvulsant action of muscimol in the SN of rat pups may be due to a relative paucity of high-affinity muscimol receptors as compared to adults. Interestingly, adult rats genetically predisposed to audiogenic seizures also show decreases in the nigral high-affinity muscimol receptors compared to controls.[49] The proconvulsant effect in pups may be due to an unmasking of the effect produced by activation of the low-affinity sites. Other factors such as differences in receptor-ionophore complexes, anatomi-

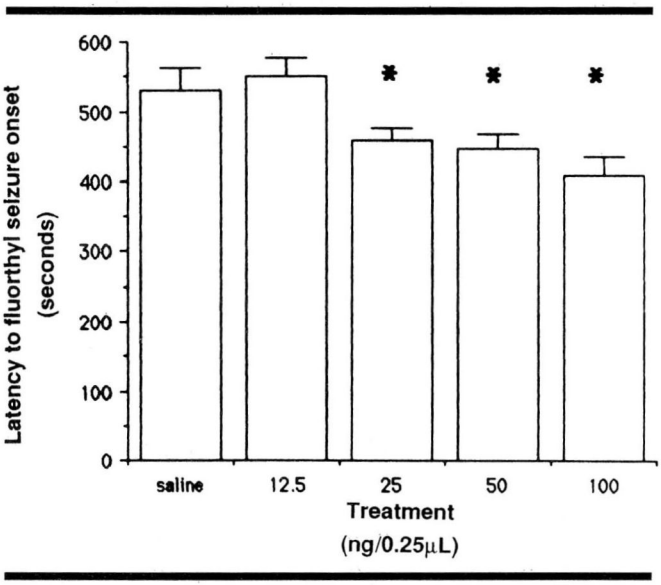

FIGURE 4. The effect of intranigral bicuculline methobromide infusions on the latency of flurothyl seizure onset as a function of dose in rat pups. Bilateral nigral infusions of bicuculline facilitate development of FE seizures in a dose-responsive manner. The higher doses of bicuculline, 25, 50, 100 ng/0.25 μL per site, significantly (*$P < 0.04$) decreased latency of seizure onset, while the lowest dose, 12.5 ng/0.25 μL, did not differ from saline controls ($n = 10$ to 14 per group).

cal localization of the existing receptors on dendrites or soma, differential activation of GABAA or GABAB receptors, changes in the number of effective synaptic sites or intrinsic connectivity of SNR neurons may have an important role.[50–53] Another possibility is that the lack of anticonvulsant action may really be a proconvulsant effect by failing to inhibit a nigral projection site responsible for the early appearance of seizures, since the net effect of any local cellular changes is a difference in functional activity of the nigral efferents which ultimately mediate the modulatory effects on seizures.

CHARACTERIZATION OF THE NIGRAL EFFERENTS INVOLVED IN SEIZURES AS A FUNCTION OF AGE

Adults

The GABA-sensitive cells of the SNR project to the ventromedial nucleus of the thalamus, deep layers of superior colliculus, tegmental pontine reticular formation, and via the pars compacta to the neostriatum.[34] To determine which of the nigral efferent systems participates in the seizure circuitry in adult rats, we performed bilateral lesions of the ventromedial thalamic nuclei and exposed the rats to flurothyl. The lesions failed to alter flurothyl seizure thresholds.[54] These data argue against a role of the ventromedial thalamus in seizures of adult rats.[55] Garant and Gale[55] have presented evidence that the nigrotegmental pathway also may not participate. We have found that a pure dopaminergic lesion of the nigrostriatal pathway does not alter the rate of development of kindled seizures.[56] To date, the most likely pathway appears to be the nigrocollicular. Thus, Garant and Gale[55] reported that lesions of the superior colliculus block the anticonvulsant effect of nigral muscimol infusions.

We have used DG autoradiography to map the structures that show changes in glucose utilization after unilateral muscimol infusions in the SNR. Rats which had previously responded with contralateral turning to a test dose of nigral muscimol had catheters inserted in the femoral vessels. Two hours later, muscimol (100 ng/0.25 μL) or saline was infused into the SNR. After 25 minutes, DG was injected and the rats were observed for 45 minutes, then killed, and the brains prepared for quantitative DG autoradiography. The data (rates of local glucose utilization) were analyzed by first determining side-to-side differences within a treatment group and then by comparing ipsilateral or contralateral rates across the two groups. Muscimol-infused rats exhibited stereotypies and contralateral turning (at least six to eight turns per minute). Analysis of the autoradiographs revealed significant ($P < 0.05$) changes in glucose utilization of several structures ipsilaterally to the infusion site including the superior colliculus (*Table 2*).

The superior colliculus has already been implicated as a potentially crucial site capable of modifying the effect of nigral muscimol on seizures.[55] Our data support the nigrocollicular hypothesis since we found ipsilateral increases in glucose utilization in the deep layer of the superior colliculus following the unilateral nigral infusion of muscimol.

Developing rats

In rat pups, the nigral pathways involved in the muscimol-induced facilitation of seizures may be different from the pathways which mediate suppression in adults. We have shown that in rat pups, nigral muscimol infusions increase dopamine concentrations in the striatum without altering concentrations of dopamine metabolites (3,4-dihydroxyphenylacetic acid and homovanillic acid). This effect of muscimol is an

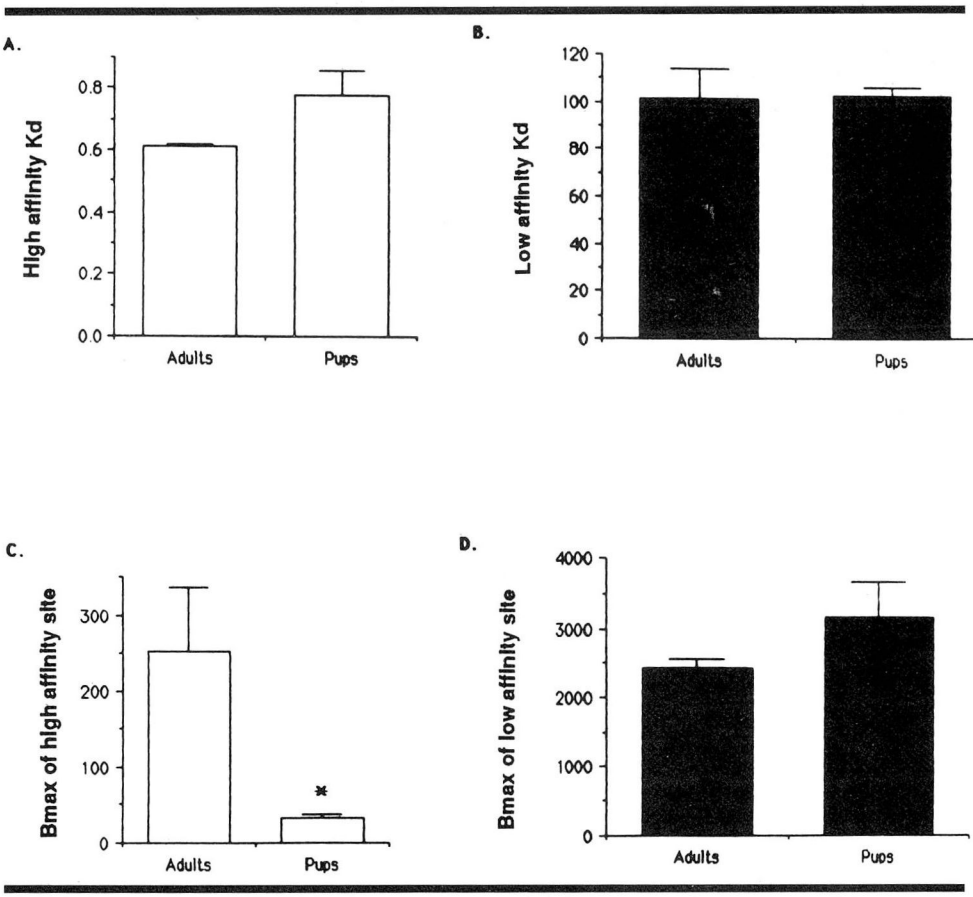

FIGURE 5. Binding of muscimol in the substantia nigra in 16-day-old pups and adult rats. FIGURE 5A and B. Changes in Kd in nM as a function of age. There are no differences in binding affinity of either high (A) or low (B) affinity site. FIGURE 5C and D show changes in Bmax in fmoles/mg protein as a function of age. Early in life there is a marked paucity of high affinity sites (*$P < 0.05$, in C), while there are no statistical differences in the number of low sites (D).

TABLE 2
EFFECTS OF UNILATERAL NIGRAL MUSCIMOL INFUSION ON BRAIN METABOLISM IN ADULT RATS

Ipsilateral* decrease	Ipsilateral increase
Globus pallidus	Lateral habenula
	Deep layer of superior colliculus

* Ipsilateral refers to the infusion site.

age-specific phenomenon.[57] With maturation, as its effect on seizures switches from proconvulsant to anticonvulsant, nigral muscimol infusions do not produce any increase in striatal dopamine concentrations but increase the concentrations of dopamine metabolites.[57–59] The results imply that nigral muscimol not only produces differential age-related effects on seizures but also produces developmental changes in striatal dopamine activity which may be important in mediating the proconvulsant effects of muscimol early in life.

To further delineate nigral efferents that mediate the effects of localized muscimol infusions, we utilized the DG technique. Rat pups that had previously responded with contralateral turning to a test dose of nigral muscimol were infused with muscimol (100 ng/0.25 μL) or saline (0.25 μL) in the SNR and injected with 10 μCi (37×10^4 Bq) of DG intraperitoneally, 25 minutes after the completion of the intracranial infusions. Muscimol-infused rat pups exhibited stereotypies and contralateral turning (at least six to eight turns per minute), similar to the patterns in adults. Analysis of the saline groups did not reveal any side-to-side differences, while in the muscimol group significant differences were observed for several structures examined. *Table 3* illustrates the significant differences across sites and groups.

Both age groups showed ipsilateral increases in glucose utilization of the deep layer of superior colliculus. This may be related to the stereotypies present in both age groups.[60] On the other hand, Garant and Gale[55] have shown that in adult rats, lesions of the superior colliculus can abolish the anticonvulsant effect of nigral muscimol. The observation that changes in the deep layer of the superior colliculus are similar in the two age groups suggests that age-related differences in seizure susceptibility may be due to alterations of activity of superior colliculus efferents. Our DG data

TABLE 3
EFFECTS OF UNILATERAL NIGRAL MUSCIMOL INFUSION ON BRAIN METABOLISM IN RAT PUPS

Ipsilateral decrease	Ipsilateral increase	Contralateral increase	Bilateral increase
Parietal cortex	Dorsal Striatum Globus pallidus DSC	PO thalamus	Forelimb sensory cortex Pontine reticular formation

* Ipsilateral refers to infusion site; DSC = deep layer of superior colliculus; PO = posterior thalamic nucleus.

may support this hypothesis. For example, the posterior thalamic nucleus receives collicular efferents,[61] yet only in pups did we identify changes in glucose utilization in the posterior nucleus. Muscimol-infused adult rats did not differ from those infused with saline. The posterior thalamic nucleus in turn projects to both sensory-parietal cortex[62] and striatum,[62,63] structures that also show changes in glucose utilization in pups but not in adults. While it is still unclear which of the above changes are due to stereotypies, it is tempting to speculate that the differences in the thalamic-cortico-striatal circuit may be responsible in part for the age-related changes that originate in the SNR. It is still possible, however, that in pups the differences in the striatal glucose utilization may be due to the changes in activity of the nigrostriatal pathway described earlier. These data imply that the activity of the striatum may change with age, and in pups this pathway may participate in the facilitation of seizures. Finally, the role of the pontine reticular formation needs to be explored, since the nucleus that shows increases in glucose utilization only in pups receives a direct GABA-sensitive input.

The long-term goal is to develop a better understanding of the processes that are involved in the suppression of seizures with maturation. Eventually these studies may lead to the development of new antiepileptic drugs that take into account the maturational stage of the CNS and thereby achieve better control of age-specific seizure disorders.

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