21. Experiment 2 produced greater overall frontal activation (Table 2) and greater relative left-frontal asymmetry (Table 1). The only difference between studies 1 and 2 was that the EEG epochs analyzed in the latter were those during which the infant was fixating on the video monitor. The lesser overall activity in study 2 is likely to be a function of the infant's visual attention, which is associated with generalized alpha blocking [for example, O. Creutzfeldt, G. Grunewald, W. Siminova, H. Schmitz, in *Attention in Neurophysiology*, C. R. Evans and T. B. Mulholland, Eds. (Butterworth, London, 1969)]. The greater relative left-frontal asymmetry (across condition) in study 2 may be a function of greater interest displayed during periods of fixation to the video stimulus. The association of interest with approach behavior [C. E. Izard, *Human Emotions* (Plenum, New York, 1977)] and of approach behavior with left-frontal activation have also been proposed (*8, 17*). Differences in the predicted direction in relative frontal asymmetry were obtained irrespective of the differences in overall amplitude between the two studies.

22. The duration of visual fixation to the happy epoch was 48.15 ± 19.61 seconds and to the sad, 62.36 ± 11.46 seconds [$t(13) = 2.34$, $P = .04$]. The longer fixation to the sad stimulus, possibly reflecting greater interest, may have accentuated left-frontal activation during this segment. Despite this difference in visual fixation, asymmetries in frontal activation in the predicted direction were still obtained.
23. M. Kinsbourne, in *Asymmetrical Function of the Brain*, M. Kinsbourne, Ed. (Cambridge Univ. Press, New York, 1978).
24. This research was supported in part by a grant from the Foundation for Child Development. These data were collected while N.A.F. was in the pediatric service, St. Lukes Roosevelt Hospital, New York. We would like to thank Clifford Saron for his technical expertise and many methodological contributions, Annie Hernandez for assistance in running the subjects, Mara Kalnins for assistance in data reduction, and Diana Angelini for help in manuscript preparation.

30 December 1981; revised 8 June 1982

Substantia Nigra: Site of Anticonvulsant Activity Mediated by γ-Aminobutyric Acid

Abstract. *Localization of the anatomic substrate for anticonvulsant activity mediated by γ-aminobutyric acid (GABA) was examined using intracerebral injections of GABA agonists. Blockade of tonic hindlimb extension in the maximal electroshock test and blockade of tonic and clonic seizures produced by pentylenetetrazole and bicuculline were obtained by elevating GABA in the ventral midbrain tegmentum. Elevation of GABA in forebrain and hindbrain areas had no effect on convulsant activity. Blockade of tonic and clonic seizures was also obtained after microinjections of the direct GABA receptor agonist, muscimol, into the midbrain. The substantia nigra was identified as the critical midbrain site for GABA-mediated anticonvulsant activity. Local injection of GABA agonists into the midbrain provided seizure protection without a widespread augmentation of GABA-mediated activity throughout the brain and without impairing either alertness or motor function. Synapses in the substantia nigra appear to represent an important control mechanism for inhibiting the propagation of generalized convulsions.*

The inhibitory neurotransmitter γ-aminobutyric acid (GABA) has been implicated in both the generation (*1*) and blockade (*2, 3*) of seizure processes. Little is known, however, about anatomic sites at which GABA-dependent transmission might influence seizure propagation (*4*).

We undertook a series of studies (i) to establish whether drug-induced elevation of GABA in a selected region of the brain confers protection from generalized motor seizures, (ii) to evaluate the anticonvulsant activity of a direct-acting GABA receptor agonist applied locally into selected brain regions, and (iii) to identify a specific nucleus in which GABA-mediated synapses may control seizure activity. We found that protection from seizures induced by maximal electroshock or by convulsant drugs was obtained as a result of GABA elevation or direct stimulation of GABA receptors within a restricted region of the ventral midbrain tegmentum, the substantia nigra.

We first microinjected γ-vinyl-GABA (GVG) into several brain regions; GVG is an irreversible catalytic inhibitor of GABA transaminase, previously shown to have anticonvulsant effects (*3, 5*). The drug was applied intracerebrally through a 26-gauge cannula positioned stereotaxically into ether-anesthetized male Sprague-Dawley rats.

The injection sites are illustrated schematically on a parasagittal section of rat brain (Fig. 1B). Anticonvulsant activity was assessed with the maximal electroshock seizure test. The seizures consist of a sequential tonic flexion and extension of the fore- and hindlimbs; blockade of the tonic hindlimb extension is the customary index of anticonvulsant activity (*6*). The animals were tested at 6 hours and at 24 hours after GVG microinjection. At 6 hours, significant anticonvulsant activity was obtained only from injections placed in the midbrain tegmentum; this effect was still present at 24 hours (Fig. 1C).

By measuring the increase in GABA content of a number of different brain areas, we assessed the effective diffusion of GVG for each of the groups receiving microinjections (Fig. 1A). All injections produced marked increases in GABA in the immediate vicinity of the injection site. At 6 hours after GVG injection, areas sampled within a 2- to 3-mm radius of the injection site exhibited the greatest increases in GABA content (*7*). The re-

Table 1. Seizure protection after bilateral microinjection of GVG and muscimol into ventral midbrain tegmentum. The values for maximum electroshock seizure (MES) represent the duration of tonic hindlimb extension in seconds. The values for PTZ and bicuculline are derived from a scale that we use to rate the severity of behavioral seizures (*23*). The doses of chemoconvulsants used (PTZ, 40 mg/kg, intravenously; bicuculline, 0.3 mg/kg, intravenously) produced severe, explosive clonic seizures in all controls; tonic forelimb extension was observed in at least 80 percent of these animals. Column headings indicate time between microinjection and seizure test. Rats weighing 300 to 350 g were used in the chemoconvulsant tests. PTZ (Knoll) was diluted in saline and injected intravenously in a volume of 0.1 to 0.15 ml/100 g. Bicuculline was dissolved in a small volume of concentrated HCl and diluted with saline; the *p*H was adjusted to 5.8 with NaOH, and the solution was kept on ice to minimize loss of activity (*24*). The values are means ± standard errors for four to eight rats per group.

Microinjection	Seizure severity score						
	MES			PTZ			Bicuculline, 6 hours
	2.5 hours	5 hours	8 hours	2.5 hours	5 hours	8 hours	
Saline	4.8 ± 0.2	6.5 ± 0.7	6.1 ± 0.5	2.3 ± 0.2	2.6 ± 0.2	2.8 ± 0.3	2.1 ± 0.3
GVG, 5 μg		0.6 ± 0.6*†			1.2 ± 0.4*†		0.5 ± 0.2
Muscimol							
25 ng	1.8 ± 0.6*	4.8 ± 2.1		1.0 ± 0.2*	1.3 ± 0.9		
50 ng	0.0 ± 0.0*	3.8 ± 1.5*	6.0 ± 0.7			2.6 ± 0.4	
75 ng		0.7 ± 0.7*					

*Significantly different from saline-injected controls ($P < .05$; Student's *t*-test). †Measured at 6 hours after injection.

0036-8075/82/1217-1237$01.00/0

gional analysis of GABA elevation allowed us to define the extent of brain tissue required for the anticonvulsant effect of midbrain GVG injections. Anticonvulsant actions were associated with GABA elevation within a circumscribed portion of the midbrain, extending from the midcollicular level to the rostral border of the substantia nigra. A severalfold elevation of GABA in frontal cortex, striatum, hippocampus, thalamus, and hypothalamus (after caudate and thalamic injections of GVG) or in pons and medulla (after pontine injection of GVG) was not sufficient to confer protection against maximal electroshock (Fig. 1). Thus, the ability of GABA-elevating drugs to afford protection against tonic-clonic seizures results not from inhibitory actions throughout the central nervous system, but rather is confined to a site within the midbrain (*8*). Furthermore, the absence of anticonvulsant activity 6 hours after injection of GVG bilaterally into the superior colliculus eliminates the tectum and the dorsal aspects of the tegmentum as candidate sites for the anticonvulsant effects of midbrain GVG injections (Fig. 1C).

The onset and offset of anticonvulsant activity coincided with the increase and decline in GABA content in the vicinity of the injection site. Complete blockade of tonic hindlimb extension was observed at 6 hours, lasted for 72 hours, and was no longer evident by 96 hours. The net increase in GABA in the midbrain tegmentum paralleled the time course of anticonvulsant activity; the maximum effect (160 nmole per milligram of protein) was achieved by 6 hours and was maintained through 72 hours; the effect then decreased to less than 25 percent of maximum by 96 hours.

The injections of GVG into the ventral midbrain were placed 1 mm to the left of the midline. When the injection was more than 1.5 mm lateral to the midline, the animal was not protected at 6 hours, but was protected at 24 hours. This indicated that the anticonvulsant action required spread of drug across the midline. Subsequent injections were therefore made bilaterally into the ventral midbrain in the vicinity of the substantia nigra. The 10-μg dose used previously for the single midbrain injection was divided so that 5 μg of GVG was placed at each site. This method of application was at least as effective as the single injection of 10 μg in protecting against seizures induced by maximal electroshock (Table 1).

For further evaluation of the anticonvulsant activity of GVG administered intracerebrally, two convulsant agents, pentylenetetrazole (PTZ) and bicuculline, were used to challenge animals 6 hours after GVG (5 μg) was injected bilaterally into the ventral midbrain. Control rats received injections of equal volumes of saline into the same sites. The microinjection of GVG into the ventral tegmentum completely blocked the tonic and major clonic components of seizures induced by intravenously administered bicuculline and PTZ (Table 1). The tonic component of seizures produced by subcutaneously administered PTZ was also blocked, and all animals were protected from the normally lethal effects of this treatment (not shown). Thus, the irreversible inhibition of GABA degradation and the concomitant elevation of GABA in ventral midbrain can suppress or eliminate the manifestations of generalized convulsions induced by pharmacological as well as electrical treatments.

Table 2. Seizure protection after bilateral microinjection of muscimol into substantia nigra. Bicuculline (0.45 mg/kg) was given intravenously; this dose produced tonic forelimb extension in 100 percent of the control rats tested. Muscimol (5 ng in 0.5 μl of saline) was administered to awake, freely moving animals through indwelling intracerebral cannulas, 20 minutes before the seizure test. The bilateral guide cannulas were implanted stereotaxically in ether-anesthetized rats 8 hours before the experiment. Scoring of seizure severity was done according to the rating scale used in previous experiments (*23*). The values are means ± standard errors for five or six rats per group.

Microinjection	Seizure score
Saline	3.0 ± 0.0
Muscimol (intranigral)	0.6 ± 0.1*
Muscimol (2 mm dorsal to substantia nigra)	2.8 ± 0.1

*Significantly different from saline-injected controls ($P < .01$).

To test the hypothesis that direct activation of GABA receptors in this region might also confer seizure protection, we injected a potent GABA receptor agonist, muscimol, into the ventral midbrain (Table 1). Bilateral injection of muscimol (25 to 75 ng) reduced the duration of tonic hindlimb extension in the maximal electroshock seizure test in a dose-dependent fashion. Midbrain injections of muscimol also attenuated seizures induced by intravenously administered PTZ. Eight hours after muscimol injection, the seizure responses to maximal electroshock and to PTZ had returned to control values (*9*). Injection of muscimol in the rostral pontine tegmentum, in doses as high as 500 ng, had no effect on seizure activity, although these injections produced marked sedation of the animals.

To locate more precisely the GABA synapses within the ventral midbrain tegmentum that are responsible for seizure control, we used a low dose of muscimol (5 ng) and tested for anticonvulsant effects within 20 minutes after microinjection in unanesthetized animals previously implanted with intracerebral guide cannulas. Injections were placed 1.5 to 2.0 mm dorsal to the substantia nigra or directly into the substantia nigra. We chose the substantia nigra as our initial target because of its exceptionally high GABA content and high density of GABA synapses and because pathways involving this nucleus have been implicated in seizure propagation (*10*).

Microinjection of a 5-ng dose of muscimol bilaterally into the substantia nigra suppressed both clonic and tonic components of seizures produced by intravenously administered bicuculline (Table 2). Injections of muscimol dorsal to the substantia nigra did not attenuate seizure activity. In two animals in which only one substantia nigra was injected (the contralateral injections were too dorsal) no protection was observed. Seizure protection appeared to be obtained only when muscimol application was placed bilaterally into the substantia nigra.

After midbrain application of GVG or muscimol, no sedation or deficits in motor function were observed in any of the animals; neurological function (reflexes, gait, and responsiveness) was normal. Animals treated with GVG were slightly more active than controls, and those receiving muscimol intranigrally exhibited stereotyped sniffing and gnawing (*11*). Thus, the anatomic substrate mediating the anticonvulsant action of these drugs is clearly distinguishable from those mediating other characteristic GABA agonist effects such as sedation and ataxia. Taken together, the results obtained with GVG and muscimol demonstrate that activation of GABA synapses associated with the substantia nigra is sufficient for preventing the propagation of generalized seizures.

These results are consistent with our proposal (*3, 4*) that a select group of GABA-containing synapses is responsible for exerting anticonvulsant effects in response to drug-induced augmentation of GABA transmission. The apparently integral involvement of the substantia nigra in seizure processes may underlie the high correlation we obtained between increases in nerve terminal GABA in this tissue and anticonvulsant effects of various GABA-elevating drugs (*3, 12*).

Our findings also indicate that measurements of GABA in whole brain, or even in major subdivisions, are unlikely to be sensitive to changes specifically related to the propagation or control of generalized seizures. A relatively selective change in GABA content or utilization in nigral nerve terminals could be sufficient to afford protection against tonic-clonic convulsions, and yet go undetected in an analysis of large divisions of brain tissue (*13*).

Electrophysiological studies have implicated the substantia nigra and associated basal ganglia structures in the propagation of seizures elicited from the motor cortex and the limbic system (*14, 15*). These findings and results from ablation studies (*10*) have prompted a view of the substantia nigra as the last relay station "from whence the attack is propagated to the final common pathway" (*14*).

The basal ganglia thus appear to constitute a critical portion of a preferred path for seizure propagation. The seizure process may be initiated and sustained at more rostral levels, subsequently funneling through a circuit in which the substantia nigra is an essential link. Enhancing inhibition on nigral efferent neurons in pars reticulata (*16*) could then act as a barrier to the further progress of seizure activity to more caudal reticular and spinal levels. Alternatively, convulsive activity may propagate through other structures that receive projections from the substantia nigra. In this case, inhibition of nigral efferent output—most of which is also inhibitory (*17*)—to thalamus, tectum, and reticular formation could modulate the progression of seizure discharge through these systems. An augmentation of GABA transmission in substantia nigra might result in a net disinhibition of these efferent target areas, causing a desynchronization of convulsive activity that impedes further propagation (*18*).

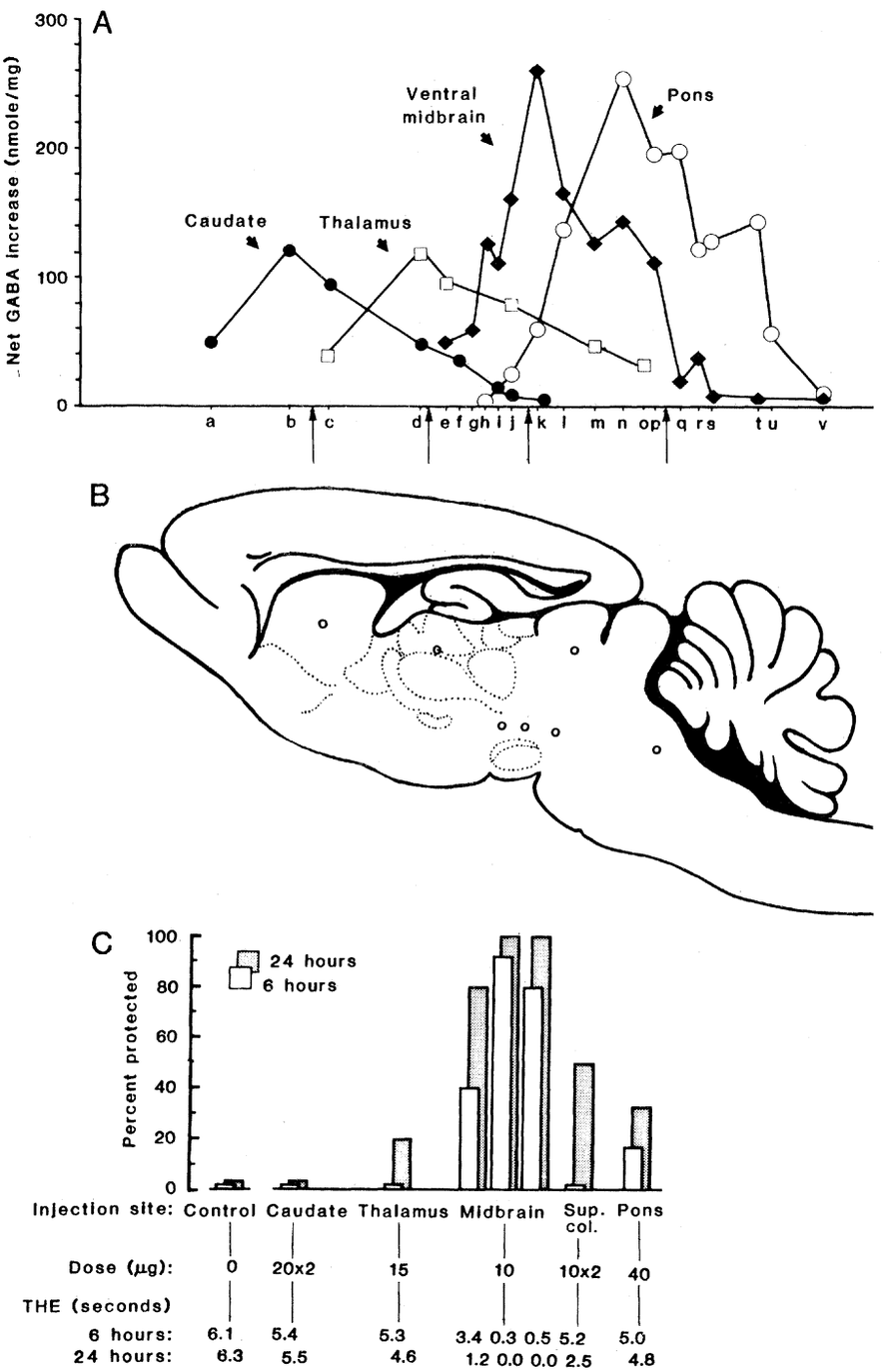

Fig. 1. (A) The net increase in GABA (over the respective control value for each region) is shown for several brain regions 6 hours after GVG microinjection (*3*). Vertical arrows along the abscissa indicate the position of the microinjection sites relative to the brain areas sampled for GABA measurement [assayed as previously described in (*3, 4*)]. The brain areas are placed in proportion to their relative distance from the injection sites. Brain areas sampled followed by the control baseline values for GABA in nanomoles per milligram of protein are: *a*, frontal cortex, 22; *b*, motor cortex, 21; *c*, caudate, 24; *d*, thalamus, 21; *e*, hypothalamus, 74; *f*, hippocampus, 32; *g*, right substantia nigra, 100; *h*, right superior colliculus, 54; *i*, left substantia nigra, 96; *j*, midbrain tegmentum, 26; *k*, left superior colliculus, 56; *l*, pontomesencephalic tegmentum, 23; *m*, left inferior colliculus, 35; *n*, dorsal tegmental nucleus, 60; *o*, right inferior colliculus, 36; *p*, left locus coeruleus, 30; *q*, left pons, 21; *r*, right locus coeruleus, 28; *s*, right pons, 22; *t*, left, and *u*, right medulla, 20; and *v*, cerebellum, 12. GABA levels in cervical cord (10.0) were not elevated in any of the groups receiving microinjections. Standard errors were less than 10 percent of the means for all measurements. (B) Microinjection sites shown on a parasagittal section of the brain. The sites are indicated by a circle, and each circle represents a separate group of rats: from left to right, caudate nucleus (bilaterally), thalamus, three sites in ventral midbrain (unilaterally, 1 mm left of midline), superior colliculus (bilaterally), and pontine reticular formation. GVG was dissolved in 1.0 μl of saline; the infusion rate was 0.2 μl/min at each site. All microinjections were made stereotaxically in rats weighing 125 to 175 g. Doses of GVG are shown below graph in (C). (C) Effect of intracerebral injection of GVG on maximal electroshock seizures. Bar graph shows percentage of animals protected from tonic hindlimb extension (*THE*) at 6 and 24 hours after microinjection of GVG into the brain sites identified in (B). The dose of GVG and the mean duration of the tonic hindlimb extension for each test session are shown below the graph. Each group was composed of five to eight rats. At 24 hours after injection into the superior colliculi (*Sup. col.*), significant protection was obtained; at this time there was marked elevation of GABA in the ventral midbrain (*7*).

Whatever the precise relationship of the substantia nigra to seizure-propagating circuits, inhibition of nigral outflow, as accomplished by GABA agonist drugs (*17, 19*), appears to deter seizure generalization. This proposal is supported by preliminary evidence from our laboratory that electrolytic or kainic acid lesions of the substantia nigra can attenuate bicuculline-induced convulsions (*20*). In addition, intranigral injections of GVG or muscimol do not preclude the animal's ability to exhibit the motor components of a seizure. A dose of convulsant, two to three times that normally required for inducing tonic seizures, elicits a full tonic seizure in an animal that had been given bilateral injections of GVG or muscimol (*21*). A similar shift in the dose-response for the convulsants is observed with nigral lesions.

Although we do not believe that a decrease in GABA-mediated transmission in substantia nigra is likely to generate seizures (*22*), such a process could facilitate the generalization of seizure activity emanating from more rostral loci. In this case, a loss of inhibitory tone in substantia nigra (or augmentation of excitatory transmission at this site) might enhance the probability of obtaining generalized seizures. Thus, the substantia nigra must be considered as a site at which pathology could alter the susceptibility to generalized convulsions. The appearance of overt clinical seizures may thus depend on both an epileptogenic focus (for example, in the forebrain) and a compromised inhibitory control mechanism at critical synapses in the substantia nigra.

MICHAEL J. IADAROLA*
KAREN GALE†

Department of Pharmacology, Georgetown University Schools of Medicine and Dentistry, Washington, D.C. 20007

References and Notes

1. D. B. Tower, in *GABA in Nervous System Function*, E. Roberts, T. N. Chase, D. B. Tower, Eds. (Raven, New York, 1976), p. 461; B. S. Meldrum, *Int. Rev. Neurobiol.* **17**, 1 (1975).
2. B. S. Meldrum, *Clin. Neuropharmacol.* **6**, 293 (1982).
3. K. Gale and M. J. Iadarola, *Science* **208**, 288 (1980). In contrast to systemic administration, direct intracerebral injection of GVG rapidly increases GABA in nerve terminals, reaching a maximum by 6 hours [M. Casu and K. Gale, *Life Sci.* **29**, 681 (1981)]. We therefore tested for anticonvulsant activity starting at 6 hours after microinjection of GVG.
4. M. J. Iadarola, A. Raines, K. Gale, *J. Neurochem.* **33**, 1119 (1979); K. Gale and M. J. Iadarola, *Eur. J. Pharmacol.* **68**, 233 (1980).
5. P. J. Schechter, Y. Tranier, M. J. Jung, A. Sjoerdsma, *J. Pharmacol. Exp. Ther.* **201**, 606 (1977); W. Loscher, *Naunyn Schmiedebergs Arch. Pharmakol.* **315**, 119 (1980).
6. Stimulus parameters were 200 mA, 0.2 second, 60 Hz; corneal electrodes were used. Electroshock apparatus was described by L. A. Woodbury and V. D. Davenport [*Arch. Int. Pharmacodyn. Ther.* **92**, 97 (1952)]. A preliminary electroshock was administered to all rats at least 24 hours before microinjection; rats with durations of tonic hindlimb extension of 4 seconds or less were eliminated (this represented less than 15 percent of rats tested).
7. At 6 hours, GABA elevation was less than maximum at distances beyond 3 mm and was not significant beyond 6 mm from the injection site. In all groups, the volume of tissue in which GABA elevation was observed at 24 hours was three to four times greater than that affected at 6 hours; this may account for partial anticonvulsant effects seen 24 hours after thalamic and pontine injections of GVG.
8. The anticonvulsant effect of intracerebral injections of GVG is associated with increases in GABA in the midbrain comparable to those observed when GVG is administered systemically in anticonvulsant doses (*3*).
9. The injections of muscimol produced a characteristic behavioral stereotypy consisting of repetitive, compulsive sniffing and gnawing. The time course of seizure protection and stereotypy closely coincided.
10. D. Jinnai, T. Yoshida, T. Souji, F. Kosaka, *Acta Med. Okayama* **8**, 26 (1954); T. Hayashi, *Jpn. J. Physiol.* **3**, 46 (1953); *ibid.* p. 306.
11. The presence of stereotypy itself does not, however, influence the seizure response; we have found that the dopamine agonist apomorphine (1 to 5 mg/kg subcutaneously), which induces strong sniffing and gnawing stereotypies, does not attenuate bicuculline-induced convulsions (unpublished observations).
12. M. J. Iadarola and K. Gale, *Brain Res. Bull.* **5** (Suppl. 2), 13 (1980); ——, in *Advances in Epileptology: XIth Epilepsy International Symposium*, R. Conger, F. Angeleri, K. J. Penry, Eds. (Raven, New York, 1980), p. 449.
13. See for example, discussion by W. Loscher [*J. Neurochem.* **36**, 1521 (1981)].
14. W. H. Faeth, A. E. Walker, O. J. Andy, *Epilepsia* **3**, 37 (1954).
15. R. G. Heath, *J. Neurol. Neurosurg. Psychiatry* **39**, 1037 (1976).
16. It is unlikely that the anticonvulsant effects are mediated by the dopamine neurons in pars compacta since neither dopamine agonists nor antagonists produce significant anticonvulsant activity in the tests employed (K. Gale and M. Iadarola, unpublished observations; H. Kupferberg, personal communication).
17. A large proportion of zona reticulata efferents are inhibitory GABA neurons, which are themselves GABA-receptive [I. C. Kilpatrick, M. S. Starr, A. Fletcher, T. A. James, N. K. MacLeod, *Exp. Brain Res.* **40**, 55 (1980); G. Di Chiara, M. L. Porceddu, M. Morelli, M. L. Mulas, G. L. Gessa, *Brain Res.* **176**, 273 (1979); M. Anderson and M. Yoshida, *ibid.* **137**, 361 (1977); J. A. Childs and K. Gale, *Soc. Neurosci. Abstr.* **7**, 196 (1981)].
18. A disinhibitory effect upon the reticular formation may act, by ascending reticular connections with the cortex, to suppress focal or diffuse cortical seizure activity. Such an effect has been demonstrated in primates receiving intravertebral injections of Metrazol [P. Gloor, *Epilepsia* **9**, 249 (1968)].
19. A. A. Grace and B. S. Bunney, *Eur. J. Pharmacol.* **59**, 211 (1979); B. Waszczak, N. Eng, J. R. Walters, *Brain Res.* **188**, 185 (1980).
20. D. Garant, M. J. Iadarola, K. Gale, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **41**, 1064 (1982).
21. This may be because structures other than those in the preferred circuit are recruited by the higher doses of convulsant drug.
22. Neither intranigral injections of bicuculline (up to 0.5 μg) nor isoniazid (up to 70 μg) elicited seizure activity in rats (unpublished data). Bilateral intranigral application of picrotoxin did not provoke seizures, but elicited a cataleptic state in rats [M. C. Olianas, G. M. DeMontis, G. Mulas, A. Tagliamonte, *Eur. J. Pharmacol.* **49**, 233 (1978)]. Electrical stimulation of nigra does not produce seizures, although stimulation of the adjacent reticular formation may do so [F. A. Gibbs and E. L. Gibbs, *Arch. Neurol. Psychiat.* **35**, 109 (1936); A. Kreindler *et al.*, *J. Neurophysiol.* **21**, 430 (1958); F. Bergmann, K. A. Costin, J. Gutman, *Electroenceph. Clin. Neurophysiol.* **15**, 683 (1963)]. Cobalt injections confined to the substantia nigra do not provoke overt convulsions [R. G. Fariello and O. Hornykiewicz, *Exp. Neurol.* **65**, 202 (1979)].
23. PTZ or bicuculline produced a tonic seizure in 1 to 3 seconds; the maximum response observed was tonic extension of forelimbs. Seizure intensity was rated as follows: 0, no seizure; 0.5, mild clonic with forepaw clonus; 1.0, moderate clonic with twisting of body; 2.0, severe clonic with explosive motor activity; 3.0, tonic forelimb extension. With few exceptions, PTZ was fatal to controls; bicuculline seizures rarely caused death.
24. R. W. Olsen, M. Ban, T. Miller, *Brain Res.* **102**, 283 (1976).
25. Supported by HHS grants DA 02206 and MH32359. We thank Centre de Recherche, Merrell International, for their gift of GVG. These results were presented in preliminary form at the Society for Neuroscience meeting, November 1981.
* Present address: Laboratory of Preclinical Pharmacology, St. Elizabeths Hospital, Washington, D.C. 20032.
† Send requests for reprints to Department of Pharmacology, Georgetown University School of Medicine, Washington, D.C. 20007.

13 September 1982

Fish Vision and the Detection of Planktonic Prey

Abstract. *Planktivorous sunfish of various sizes were studied to ascertain whether growth-related changes in the retina are related to the ability to capture small planktonic crustaceans. Behaviorally, the larger fish detected and captured crustaceans that subtended smaller visual angles. Histological examination of the retinas revealed that the distance between cones, measured in minutes of visual angle, decreased as the animals grew, suggesting that the larger retinas could resolve smaller objects. These correlated behavioral and anatomical results suggest that improved visual resolution contributes to improved predation. This finding provides a selective advantage for the continuous retinal growth noted in many fish.*

Predation by fish is an important factor in the structure of freshwater zooplankton communities, because the fish feed selectively on certain sizes and species of the zooplankters (*1*). The capture of the prey often depends on visual detection; therefore, efforts have been directed toward discovering what makes some prey more visible than others (*2*). In these studies it was assumed that the predator's visual system did not vary. This assumption warrants examination in that the retinas of some fish acquire a higher acuity as the fish grow (*3*). Such a change might affect visual detection and recognition of prey (*4*) and therefore make the zooplankton community's structure dependent on the size distribution of the predators.

In our behavioral and anatomical

 0036-8075/82/1217-1240$01.00/0