Pharmacology Biochemistry & Behavior, Vol. 11, pp. 265–271. Printed in the U.S.A.

Effects of γ-Acetylenic GABA and γ-Vinyl GABA on Metrazol-Activated, and Kindled Seizures

M. S. MYSLOBODSKY,[1] R. F. ACKERMANN AND J. ENGEL, JR.

Department of Neurology, Reed Neurological Research Center, UCLA School of Medicine Los Angeles, CA 90024

Received 19 March 1979

MYSLOBODSKY, M. S., R. F. ACKERMANN AND J. ENGEL, JR. *Effects of γ-acetylenic GABA and γ-vinyl GABA on metrazol-activated, and kindled seizures.* PHARMAC. BIOCHEM. BEHAV. 11(3) 265–271, 1979.—Pretreatment of adult male Sprague-Dawley rats with a single dose of γ-vinyl GABA (GVG) (1200 mg/kg, IP) or γ-acetylenic GABA (GAG) (100 mg/kg, IP) did not affect the threshold of metrazol-activated generalized seizures, but increased their duration to the point of status epilepticus. In rats with epilepsy kindled by amygdaloid stimulation, a single dose of GVG (800 mg/kg, IP) and five subsequent daily administrations of GAG (80 mg/kg, IP) tended to reduce the motor manifestations of seizures leaving unaffected their electrographic pattern. The effects of GVG and GAG are attributed in part to decreased arousal. Practical implications of these findings are discussed.

GABA-T inhibitors Metrazol Kindled epilepsy Wave-spike discharges

THE GABA system is commonly regarded as a major apparatus directly or indirectly involved in control of epileptiform activity [20,35]. Evidence for this view has derived largely from the fact that GABA is a major brain inhibitory transmitter [17] and that a variety of GABA-mimetics have proved to be effective anticonvulsants (see [35] for review), while GABA antagonists are known to increase brain excitability [17]. Correspondingly, an increase in brain GABA concentration has been found to protect against seizures while its depletion is accompanied by an increase in seizure susceptibility [21]. Potentiation of GABA's effects can be achieved via inhibition of its degrading enzyme, GABA-transaminase (GABA-T). In agreement with the above observations, GABA-T inhibitors have been shown to have antiepileptic properties both in animals [31,32] and in humans [6]. However, at least one GABA-T inhibitor, amino-oxyacetic acid has reportedly induced convulsions in animals [18], and in an experiment recently conducted in our laboratory (in preparation) we found that GABA-T inhibitors can greatly increase the duration of anesthesia induced by ketamine, which some writers believe is a mild convulsant [38]. Ketamine anesthesia is accompanied by electrographic patterns resembling 'slow wave—sharp wave' complexes [26,38]. GABA-T inhibitors may potentiate ketamine anesthesia indirectly by reducing arousal; if this assumption is correct, it could be expected that certain arousal-sensitive epileptic fits [25] would be facilitated rather than alleviated by compounds inhibiting GABA-T.

The present study was designed to test this implication with two GABA-T inhibitors γ-vinyl GABA (GVG) and γ-acetylenic GABA (GAG) which have previously been shown to possess anticonvulsive properties in the audiogenic [31,32] and photosensitive epilepsy [24] models. In the present study, two models of epilepsy were employed: acute petit mal and grand mal seizures were produced by metrazol administration (metrazol is believed [12] not to act via the GABA system in the cerebral cortex), and chronic brain epileptisation was modelled by kindling epilepsy. 'Kindling' is a term describing the progressive development of generalized behavioral seizures in response to initially ineffective electrical stimulation applied repetitively to the amygdala or other brain regions [11]

METHOD

Subjects

Naive, male Sprague-Dawley rats (Simonsen) weighing 400–550 g were maintained in a standard laboratory environment with water and food ad lib. Normal day-night cycle (12 hr light/12 hr darkness) was maintained by artificial lighting. Animals were randomly assigned to three groups: (1) control (saline pretreatment); (2) γ-vinyl GABA (GVG) pretreatment; and (3) γ-acetylenic GABA (GAG) pretreatment (both substances were supplied by Merrell). Metrazol effects were assessed in all three groups. In a separate fourth

[1]Correspondence to the first author. Permanent address: Psychobiology Research Unit, Department of Psychology, Tel-Aviv University, Tel-Aviv, Israel.

group, epilepsy was kindled with electrical stimulation of the amygdala.

Surgery

Animals in all three groups were implanted with electrodes 7–8 days prior to experiments.

Rats were anesthetized with ketamine (Ketalar, Parke-Davis) (100 mg/kg, IP) followed by xylazine (Haver-Lockhard) (20 mg/kg, IM) and placed in a Kopf stereotaxic instrument. Four holes for recording electrodes, located over symmetrical points of the visual cortex and sensorimotor cortex, were drilled with precautions taken to avoid dura damage. Two holes for anchoring stainless steel jeweler's screws were drilled on the midline over the frontal cortex and over the cerebellum. An additional hole for an indifferent electrode was drilled over the cerebellum on the midline. The cortical and indifferent electrodes were silver balls presoldered to Amphenol microminiature pins.

In some of the kindled animals cortical electrodes were located over the symmetrical points of only the visual cortex, and in all kindled animals the depth electrode was stereotaxically positioned into either the left or the right amygdala. The coordinates were A - 1.5, L - 3.5, D - 8.9, incisor bar: - 3.5 mm. The subcortical electrode consisted of two 0.25 mm twisted enamel-coated nichrome wires with the tips separated by the thickness of the insulation. The electrodes were attached to a 5-contact Amphenol plug which was fixed to the skull with dental acrylic and two jeweler's screws.

Procedure and Apparatus

1. Metrazol-induced seizures. Metrazol injections began 4 hr after pretreatment of animals with a single dose of either GVG (1200 mg/kg, IP) or GAG (100 mg/kg, IP). The dose and the time between pretreatment and metrazol challenge were chosen on the basis of Schechter *et al.* [31,32] findings. Injections of metrazol (10–12 mg/kg) were repeated every 5 min until the development of generalized convulsions.

The experiment with the GVG group was conducted in a Plexiglas testing chamber. EEG (Grass, Model 8) recordings were obtained both before and after metrazol injections. GAG-pretreated animals were observed in the testing chamber and in rotometer bowls.

The control group was pretreated with saline (0.9%, 1 ml/kg) 4 hr prior to metrazol challenge and also observed in rotometers. The number and duration of seizures were noted.

2. Kindling. Kindling stimulation consisted of 1 sec 60 Hz, 25–200 μA, electrical current given once per day. Current was continuously monitored on an oscilloscope. Current intensity was determined individually beginning from 25 μA until the development of the first self-sustained afterdischarge. Stimulation at the threshold intensity (for the afterdischarge generation) was subsequently repeated each day and the gradual development of motor seizures was rated according to the scale of Racine [29]: (1) facial movements only; (2) facial movements and head nodding; (3) facial movement, head nodding and contralateral forelimb clonus; (4) stage 3 components followed by bilateral forelimb clonus and rearing; (5) stage 4 components and loss of axial postural tonus. Animals were considered fully kindled upon attaining stage 5 seizures on three consecutive days. EEG records were taken several minutes before and after the stimulation.

Eight animals with stage 5 kindled seizures were selected for further study with GABA-T inhibitor pretreatment.

Animals were pretreated with 800 mg/kg of GVG and electrically stimulated in the observation chamber as described above between 4–5 hr after the pretreatment. The animals' EEG and behavioral response to a single dose of GVG, and any changes in seizure threshold were noted. All the animals were then given GAG once a day at a dose 80 mg/kg, IP for 5 successive days. EEG and behavior were compared with that before GVG and GAG administration.

3. Behavioral observations. A series of behavioral tests were administered to rats before and 4–6 hr after GAG and GVG administration. The test included the following: (a) handling; (b) reaction to tail-pinch; (c) walking on the narrow (25 mm) path; (d) movement in the observation cage. The behavior categories noted were walking, rearing with forepaws touching a wall, rearing with forepaws hanging free, grooming, attending to auditory and photic stimuli. (e) postural changes were evaluated by qualitative assessment of postural asymmetry created by the attempt of the rat, lifted for 10–15 sec by its tail, to restore normal head position.

RESULTS

Behavior

Both agents caused similar reduction in exploratory behavior and diminished responsiveness to photic and auditory stimuli. A decreased sensitivity to tail-pinch and passive behavior during handling were also noted. There were periods of muscular relaxation suggested by stretched out forelimbs with the head resting on the floor. That notwithstanding, the ability of the rats to walk on a narrow path was not impaired. In addition all the rats lifted by the tail for 10–15 sec generated a predrug effort in order to restore normal head position.

Twenty-four hours after GVG and GAG administration rats performed normally in the observation cage but seemed to be hyperactive during handling.

EEG Response

In four out of five GVG-pretreated (single dose, 1200 mg/kg) rats, and in four out of five GAG-pretreated (single dose, 100 mg/kg) rats, EEG became hypersynchronized with slow waves and wave-spikes (3–5 Hz) occurring in bursts of 1–3 per min (Fig. 1a). This effect was virtually identical in GVG- and GAG-pretreated animals, and, unlike behavioral changes, lasted over 24 hr in both groups. On no occasion was such a pattern observed in untreated rats or in undrugged kindled rats.

Metrazol Activation

Hypersynchronous activity was potentiated with Metrazol (Fig. 1B–E).

Table 1 summarizes Metrazol effects across the three experimental groups. The most remarkable result was unusually lengthy and violent first convulsions and repetitive (multiple) convulsions which occurred 15–40 min postinjection. Postictal depression was virtually absent. Rather, the animals were motionless for 30–120 min with EEG displaying continuous 1 Hz discharges of the sharp wave–slow wave type in all leads (Fig. 2). These convulsive behavioral phenomena together with continuous EEG discharges resembled status epilepticus which led to death in most GVG-

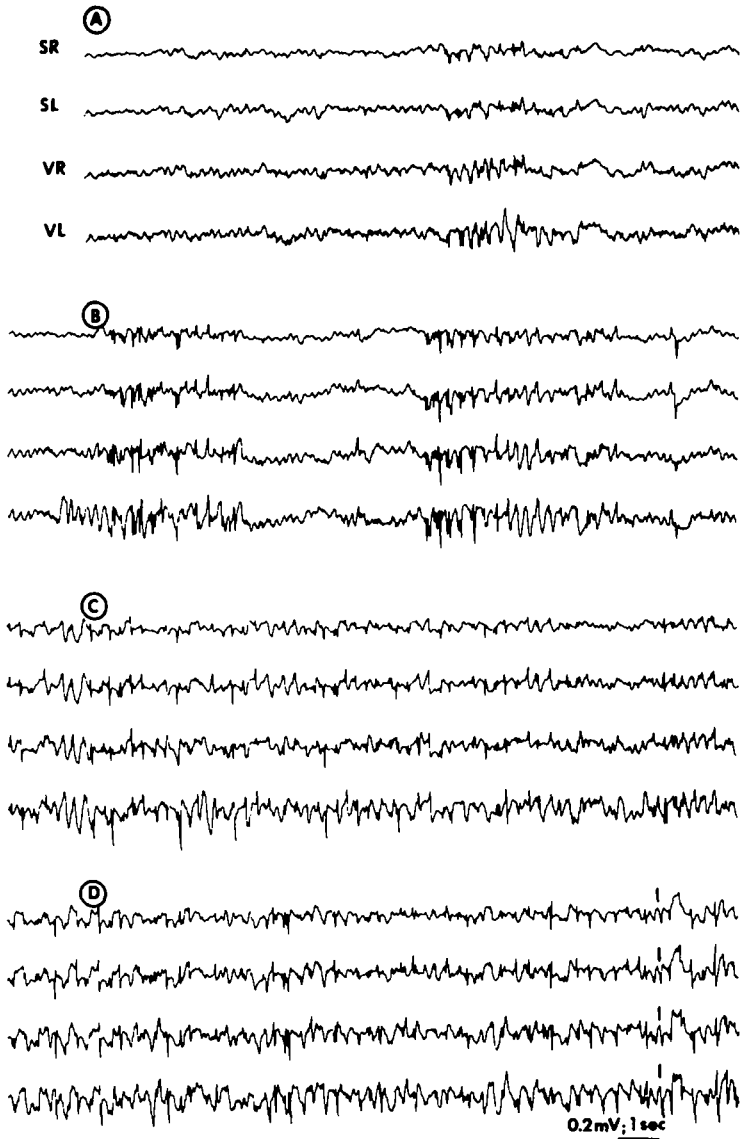

FIG. 1. Effect of metrazol in a GVG-pretreated rat. A: Regular hypersynchronous W-S activity occurring 4 hr after a single dose of GVG (1200 mg/kg, IP). B–D: Buildup of EEG hypersynchrony after repeated metrazol injections. Each EEG fragment (B, C, D) reflects the effect of a successive dose of metrazol (10 mg/kg, IP) administered every 5 min. Abbreviations: SR, SL—Right, and left somatosensory cortex. VR, VL—Right, and left visual cortex.

pretreated animals. The condition of status epilepticus also occurred in GAG-pretreated animals, but 100 mg/kg of GAG was less potent than 1200 mg/kg of GVG and most of the GAG-pretreated animals eventually recovered.

Kindling

An initial dose of GVG (800 mg/kg) resulted in a pronounced decrement in the severity of electrically-induced motor seizures in four of eight kindled rats. Under the influence of GVG, there was a high incidence of 'uncoupled' seizures, i.e., electrographically typical afterdischarges with the usual motor concomitants noticeably diminished or absent altogether. In contrast to unkindled animals, only two of the eight kindled animals displayed spontaneous EEG hypersynchrony following the initial dose of GVG, indicating that GVG-induced hypersynchrony is not a necessary condition for the afterdischarge-behavior uncoupling observed in kindled animals. With repeated daily administration of GAG, seven of the kindled animals subsequently developed hypersynchronous EEG together with a continuation of an unusually high incidence of uncoupled or noticeably diminished motor seizures. Uncoupling was still evident three days after the last drug administration; the seizures had returned to their normal severity in a post-drug retest conducted two weeks after the last drug administration.

TABLE 1

METRAZOL-INDUCED SEIZURES IN CONTROL AND GVG AND GAG PRETREATED RATS (MEANS ± SEM)*

Pretreatment (dose)	N	Metrazol threshold (mg/kg)	Duration of 1st seizure (sec)	No. of multiple seizures	Mortality
Saline	8	56.3 ± 4.5	35.6 ± 9.4†	1.0 ± 0.42	1/8
GVG (1200 mg/kg)	5	70.0 ± 5.6†	76.2 ± 93.7‡	status	4/5
GAG (100 mg/kg)	6	50.0 ± 3.5	283.3 ± 166.7‡	status	2/6

*Note:
†Significantly different from GAG but not from saline at $p<0.05$
‡Significantly different from saline at $p<0.05$

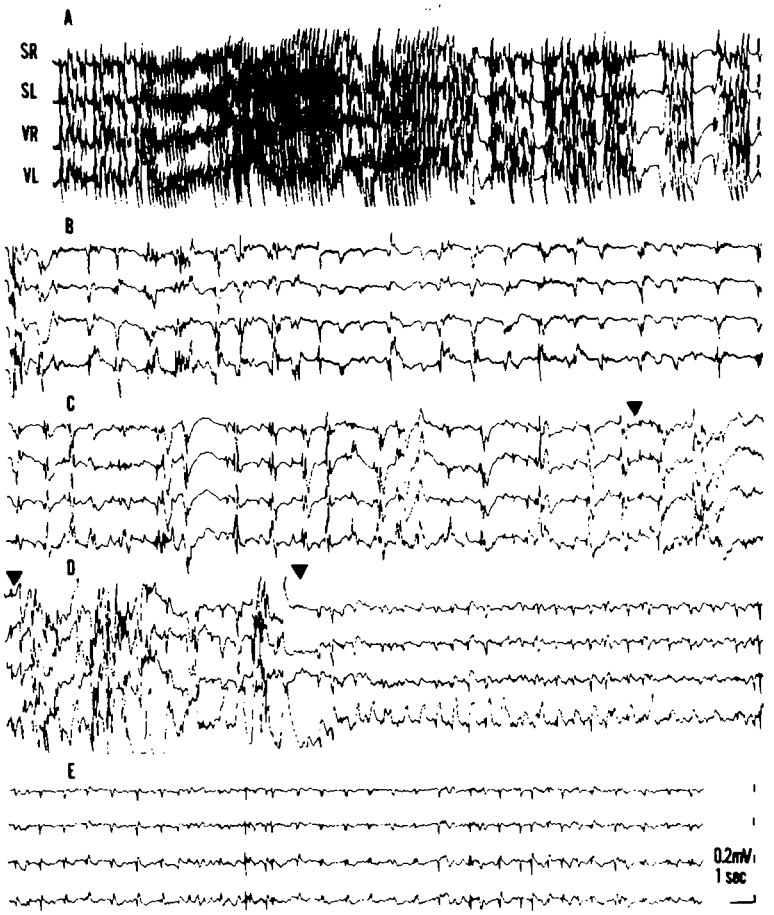

FIG. 2. Samples of EEG tracings obtained during "status" in a GVG-pretreated (1200 mg/kg, IP) rat. A: A sample taken during a generalized seizure. B: Continuation of A. C: A sample taken 3 min later. D: A sample taken 13 min after metrazol injection. E: A sample taken 36 min after metrazol injection, 5 min before death. Throughout B–E, the animal was immobile except for short periods of mild behavioral seizure indicated by arrow heads. Note that in B–E the gain is reduced. Abbreviation as in Fig. 1.

DISCUSSION

In order to consider the possible significance of the observations reported, the following set of axiomatic statements are proposed and discussed:

A. The effect of GAG and GVG could in part be attributed to a decrease in arousal. It has been found that endogenous GABA leakage from the cerebral cortex is greater during sleep than during wakefulness [14], and arousal created by stimulation of the reticular formation is accompanied by reduced GABA output [15]. Therefore, a profound and long-lasting inhibition of GABA-T by GVG and GAG with a corresponding increase of the brain GABA content [27] could mimic a decrease of dopamine-meditated component of arousal produced by other means. In fact, there was a decrease in orienting responses and exploratory behavior at the initial stage of GVG and GAG effects, as well as EEG synchronization and hypersynchronization, which seem to suggest an arousal decrement. Similar behavioral and electrophysiological phenomena have previously been produced with muscimol, baclofen and sodium γ-hydroxybutyrate [33] which have been classified as convulsant anesthetics similar to α-chloralose. Drowsiness was also reported in patients with Huntington's Chorea treated with β-parachlorophenyl GABA, a lipophilic derivative of GABA [1]. Imidazole-4-acetic acid, a GABA agonist, has a pharmacologic profile resembling that of a minor tranquilizer [30].

Although intraperitoneal injection of GVG and GAG could have augmented GABA content throughout the brain thereby facilitating GABA-mediated EEG synchronization, a more localized effect is not excluded. Palfreyman *et al.* [27] have recently reported a decrease in homovanillic acid in the striatum, but not in the nucleus accumbens following administration of 100 mg/kg of GAG, suggesting that GAG decreases striatal dopamine turnover. One could assume that GABA-carrying pallidonigral and striatonigral neuronal pathways [16,22] exert inhibitory control over nigrostriatal and mesolimbic dopamine neurons [5] which are involved in arousal control. The simplicity of this idea makes it attractive but it has one limitation: striatonigral GABA containing fibers may not be involved in the control of dopamine turnover [37].

B. GVG and GAG may aggravate metrazol-induced seizures. The mechanism of aggravation of epileptic seizures and the development of repeated convulsions observed in the present study in supposedly protected animals is not clear. The ability of GABA to cause a suppression of dopamine turnover may be a factor contributing to seizures; dopamine has been implicated in seizure control [8,23]. However, lesions which interrupt the striatonigral GABA-containing pathways in the rat have been shown not to influence normal striatal dopamine turnover or its neuroleptic-induced enhancement [37]. Nevertheless, the ability of increased brain GABA to affect catecholamine levels cannot be ignored. Intraperitoneal and intracarotid injections of GABA results in a significant reduction of brain norepinephrine [40] which many writers report is important in controlling susceptibility to seizures [4,19]. In fact, there is some commonality between 6-OHDA pretreated [19] and GVG and GAG protected animals in the present study: both have multiple seizures. The human analog to these initial multiple seizures seems to be status epilepticus or, considering subsequent prolonged immobility of the rats accompanied by cortical seizure manifestations, electrical status epilepticus [28].

The mechanism of these prolonged seizures remains unclear. There are at least two known mechanisms of seizure cessation. One involves active suppression of epileptic discharges by pre- and postsynaptic influences. The other is created by 'exhaustion' of epileptic neurons which cease to generate discharge when a critical number of elements are inactivated by hyperdepolarization (see [25] for review). It is conceivable that increased potency of synchronization induced by GVG and GAG pretreatment signals the recruitment of additional elements into a seizure which otherwise would have remained uninvolved. The increased potency of hyperpolarization would also facilitate the repolarization of those active cells which otherwise would have ceased to convulse due to Vvedensky inhibition, i.e., the inactivation of the soma impulse-generating mechanism [34]. The disappearance or reduction of postictal depression in GVG and GAG pretreated animals suggests that both mechanisms may contribute to the observed increase in seizure duration. Anecdotal evidence also indicates that increased brain GABA may in fact be associated with seizures which are unresponsive to anticonvulsants [13].

C. In kindled animals GVG and GAG alleviate behavioral seizures without affecting the threshold, duration and complexity of the seizure afterdischarge. At first glance the relative paucity of behavioral events during EEG seizures in GVG and GAG pretreated kindled animals may seem to be related to tranquilizing properties of GABA agonists and their ability to exert myotonolytic effects [3,10]. However, it is recognized that changes of duration and threshold of afterdischarges are poorly related to the development of motor seizures in the process of kindling [29] or to their severity in kindled animals [9]. Therefore, the uncoupling may be a non-specific phenomenon which can be produced in a variety of ways and with a multitude of chemical compounds. Indeed, diazepam, phenobarbital [39] and atropine [2] are known to preferentially block motor ictal manifestation without affecting electrographic seizures in kindled animals.

The mild protective action of GAG and GVG in kindled epilepsy contrasts their potentially harmful effects in metrazol-induced epilepsy. The processes underlying these differences are not clear. They may be associated with differences in the procedure of the treatment (i.e., a single dose vs chronic treatment) or reflect differences between the sensitivity of the two types of epilepsy to GABA-T inhibitors.

D. The practical application of GABA-T inhibitors in epilepsy may depend on the particular form and characteristics of the type of epileptic abnormality. GABA-T inhibitors are considered to be potential anticonvulsant substances. Although GVG and GAG alleviated kindled seizures, they aggravated metrazol-induced epilepsy. The ability of GABA-T inhibitors to decrease alertness and produce synchronization in the EEG thetaband may create favorable conditions for the development of wave-spike discharges [33] and aggravate the state of petit mal patients, as was postulated elsewhere [25]. Therefore, enthusiastic reports of the ability of certain GABA-T inhibitors like di-*n*-propylacetate to prevent petit mal attacks [6] should be taken with caution, especially in view of the observations [7] that β-parachlorophenyl GABA may exacerbate EEG abnormalities.

Theoretically there is always a risk of a prolonged seizure (status) generated by protected neurons in response to an

epileptiform challenge powerful enough to overcome higher thresholds. The other potentially harmful effect of these substances is their ability to reduce arousal (in doses employed) and to synchronize EEG to the extent that the benefit of their antiepileptic action might be infinitesimal compared to the harm caused by their interference with autonomic functions and behavior. Indeed, clinical trials with β-parachlorophenyl GABA [1] and di-*n*-propylacetate [6] have demonstrated somnolence [1,6] and vomiting [6]. On the other hand, the same substances have been demonstrated to alleviate audiogenic epilepsy [31,32] and photosensitive epilepsy [24], and they reduced the behavioral manifestations of the kindled seizures in the present study. A special analysis of the benefit/risk ratio of GABA-T inhibitors is required with different doses and chronic administration in various models of epilepsy.

ACKNOWLEDGEMENTS

Supported in part by funds provided by the Grant of Epilepsy Foundation of USA and the Department of Neurology. The authors wish to thank Dr. M. Weiner (Merrell Research Center) for a gift of GABA-T inhibitors and Mrs. R. Pardee for her generous and skillful secretarial assistance.

REFERENCES

1. Andén, N.-E., P. Dalén and B. Johansson. Baclofen and lithium in Huntington's Chorea. *Lancet* **2:** 93, 1973.
2. Arnold, P. S., R. J. Racine and R. A. Wise. Effect of atropine, reserpine, 6-OHDA and handling on seizure development in the rat. *Expl Neurol.* **40:** 457–470, 1973.
3. Carlidge, N. E., P. Hudgson and D. Weightman. A comparison of baclofen and diazepam in the treatment of spasticity. *J. Neurol. Sci.* **23:** 17–24, 1974.
4. Corcoran, M. E., H. C. Fibiger, J. A. McCaughran and J. A. Wada. Potentiation of amygdaloid kindling and metrazol-induced seizures by 6-hydroxydopamine in rats. *Expl Neurol.* **45:** 118–133, 1974.
5. Corrodi, H., K. Fuxe and P. Lidbrink. Interaction between cholinergic and catecholaminergic neurones in rat brain. *Brain Res.* **43:** 397–416, 1972.
6. de Biolley, D. and L. Sorel. Premiers résultats en clinique d'un nouvel anti-epileptique: Di-n-propyl acetate de sodium (DPA) spécialisé sous la marque Depakine. *Acta neurol. belg.* **69:** 909–913, 1969.
7. de Pinto, O. S., M. Polikar and P. Loustalot. A review of clinical trials with Lioresal. In: *Spasticity: A Topical Survey*, edited by W. Birkmayer. Bern: Hans Huber, 1977, pp. 192–200.
8. Engel, J., Jr. and N. Sharpless. Long-lasting depletion of dopamine in the rat amygdala induced by kindling stimulation. *Brain Res.* **136:** 381–386, 1977.
9. Engel, J., Jr., L. Wolfson and L. Brown. Anatomical correlates of electrical and behavioral events related to amygdaloid kindling. *Ann. Neurol.* **3:** 538–544, 1978.
10. Feldman, R. G., M. Kelly-Hayes, J. P. Conomy and J. M. Foley. Baclofen for spasticity in multiple sclerosis. *Neurology* **28:** 1094–1098, 1978.
11. Goddard, G. V., D. C. McIntyre and C. K. Leach. A permanent change in brain function resulting from daily electrical stimulation. *Expl Neurol.* **25:** 295–330, 1969.
12. Hill, R. G., M. A. Simmonds and D. W. Straughan. A comparative study of some convulsant substances and γ-aminobutyric acid antagonists in the feline cerebral cortex. *Br. J. Pharmac.* **49:** 37–51, 1973.
13. Hsia, Y. E. Disorders of amino acid metabolism. In: *Basic Neurochemistry*, edited by G. J. Siegel *et al.*. Boston: Little, Brown, 1976, pp. 500–541.
14. Jasper, H. H., R. T. Khan and K. A. C. Elliot. Amino acids released from the cerebral cortex in relation to its state of activation. *Science* **147:** 1448–1449, 1965.
15. Jasper, H. H. and I. Koyama. Rate of release of amino acids from the cerebral cortex in the cat as affected by brainstem and thalamic stimulation. *Can. J. Physiol. Pharmac.* **47:** 889–905, 1969.
16. Kim, J. S., I. J. Bak, R. Hassler and Y. Okada. Role of γ-aminobutyric acid (GABA) in the extrapyramidal motor system. 2. Some evidence for the existence of a type of GABA-rich strionigral neurons. *Exp. Brain Res.* **14:** 95–104, 1971.
17. Krnjevic, K. Chemical nature of synaptic transmission in vertebrates. *Physiol. Rev.* **54:** 418–540, 1974.
18. Kuriyama, K., E. Roberts and M. K. Rubenstein. Elevation of γ-aminobutyric acid in brain with amino-oxyacetic acid and susceptibility to convulsive seizures in mice: A quantitative re-evaluation. *Biochem. Pharmac.* **15:** 221–236, 1966.
19. Mason, S. T. and M. E. Corcoran. Forebrain noradrenaline and metrazol-induced seizures. *Life Sci.* **23:** 167–172, 1978.
20. Maynert, E. W., T. J. Marczynski and R. A. Browning. The role of the neurotransmitters in the epilepsies. *Adv. Neurol.* **13:** 79–147, 1975.
21. Maynert, E. W. and H. K. Kaji. On the relationship of brain γ-aminobutyric acid to convulsions. *J. Pharmac. exp. Ther.* **137:** 114–121, 1962.
22. McGeer, P. L. and E. G. McGeer. The GABA system and function of the basal ganglia: Huntington's disease. In: *GABA in Nervous System Function*, edited by E. Roberts, T. N. Chase and D. B. Tower. New York: Raven Press, 1976, pp. 487–495.
23. Meldrum, B., G. Anlezark and M. Trimble. Drugs modifying dopaminergic activity and behaviour, the EEG and epilepsy in *Papio papio*. *Eur. J. Pharmac.* **32:** 203–213, 1975.
24. Meldrum, B. and R. Horton. Blockade of epileptic responses in the photosensitive baboon, *Papio papio*, by two irreversible inhibitors of GABA-transaminase, γ-Acetylenic GABA (4-Amino-hex-5-ynoic Acid) and γ-vinyl GABA (4-Amino-hex-5-enoic Acid). *Psychopharmacologia* **59:** 47–50, 1978.
25. Myslobodsky, M. *Petit Mal Epilepsy: A Search for Precusors of Wave-spike Discharges*. New York: Academic Press, 1976.
26. Myslobodsky, M., R. Ackermann, R. Mansour and V. Golovchinksy. Ketamine-induced rotation and its interaction with naloxone in rats. *Brain Res.*, in press.
27. Palfreyman, M. G., S. Huot, B. Lippert and P. J. Schechter. The effect of γ-acetylenic GABA, an enzyme-activated irreversible inhibitor of GABA-transaminase on dopamine pathways of the extrapyramidal and limbic systems. *Eur. J. Pharmac.* **50:** 325–336, 1978.
28. Patry, G., S. Lyagoubi and A. Tassinari. Subclinical "electrical status epilepticus" induced by sleep in children. *Archs. Neurol.* **24:** 242–252, 1971.
29. Racine, R. J. Modification of seizure activity by electrical stimulation. II. Motor seizure. *Electroenceph. clin. Neurophysiol.* **32:** 281–294, 1972.

30. Roberts, E. and D. G. Simonsen. A hypnotic and possible analgesic effect of imidazoleacetic acid in mice. *Biochem. Pharmac.* **15:** 1875–1877, 1966.
31. Schechter, P. J., Y. Tranier, M. J. Jung and P. Bohlen. Audiogenic seizure protection by elevated brain GABA concentration in mice: effects of γ-acetylenic GABA and γ-vinyl GABA, two irreversible GABA-T inhibitors. *Eur. J. Pharmac.* **45:** 319–338, 1977.
32. Schechter, P. J., Y. Tranier, M. J. Jung and A. Sjoerdsma. Antiseizure activity of γ-acetylenic γ-aminobutyric acid: a catalytic irreversible inhibitor of γ-aminobutyric acid transaminase. *J. Pharmac. exp. Ther.* **201:** 606–612, 1977.
33. Scotti de Carolis, A. and M. Massotti. Electroencephalographic and behavioral investigations on gabaergic drugs: muscimol, baclofen and sodium γ-hydroxybutyrate. *Prog. Neuropsychopharmac.* **2:** 431–442, 1978.
34. Sypert, G. W. and A. F. Reynolds. Single pyramidal-tract fiber analysis of neocortical propagated seizures with reference to inactivation responses. *Expl Neurol.* **45:** 228–240, 1974.
35. Sytinsky, I. A., A. T. Soldatenkov and A. Lajtha. Neurochemical basis of the therapeutic effect of γ-aminobutyric acid and its derivatives. *Prog. Neurobiol.* **10:** 89–133, 1978.
36. Tower, D. B. GABA and seizures: clinical correlates in man. In: *GABA in Nervous System Function*, edited by E. Roberts, T. N. Chase and D. B. Tower. New York: Raven Press, 1976, pp. 461–478.
37. Tulloch, I. F., G. W. Arbuthnott, A. K. Wright, M. G. Garcia-Munoz and N. M. Nicolaou. The striatonigral fibers and the feedback control of dopamine metabolism. *Psychol. Med.* **8:** 471–482, 1978.
38. Winters, W. D. Epilepsy or anesthesia with ketamine. *Anesthesiology* **36:** 309–312, 1972.
39. Wise, R. A. and J. Chinerman. Effects of diazepam and phenobarbital on electrically-induced amygdaloid seizures and seizure development. *Expl Neurol.* **45:** 355–363, 1974.
40. Yessaian, N. H., A. R. Armenian and H. Ch. Buniatian. Effect of γ-aminobutyric acid on brain serotonin and catecholamines. *J. Neurochem.* **16:** 1425–1433, 1969.