Epilepsia, 35(Suppl. 5):S77–S80, 1994
Raven Press, Ltd., New York

Gabapentin: Discussion

Gerhard H. Fromm*

Department of Neurology, University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania, U.S.A.

Summary: Gabapentin (GBP, Neurontin) is a novel antiepileptic drug (AED) that was shown to be effective against refractory partial seizures in five placebo-controlled trials. However, a number of patients with complex partial seizures experienced an increase in seizure frequency, suggesting that patients suffering from complex partial seizures are not a homogeneous group. In fact, we found that currently available AEDs are likely to be ineffective when staring is a prominent component of complex partial seizures. The poor response of this group of patients may reflect the fact that staring spells are inhibitory seizures and that the AEDs prescribed for partial seizures appear to facilitate inhibitory mechanisms. GBP resembles phenytoin (PHT) and carbamazepine (CBZ) in depressing segmental and reticular excitatory mechanisms and facilitating segmental inhibitory mechanisms, just as it resembles PHT and CBZ in efficacy against some partial seizures and against secondarily generalized seizures. Perhaps the patients in whom GBP increased seizure frequency had complex partial seizures with staring and were therefore unlikely to benefit from drugs such as GBP, CBZ, and PHT, which enhance inhibitory mechanisms in the brain. These findings suggest that future AED trials would greatly benefit from a categorization of complex partial seizures into nosologically distinct groups. **Key Words:** Anticonvulsants—Gabapentin—Partial complex seizures—Absence seizures—Trigeminal nucleus—Drug toxicity.

As described in the preceding report (Leiderman, 1994), gabapentin (GBP, Neurontin) is a novel antiepileptic drug (AED) with a molecular structure that resembles γ-aminobutyric acid (GABA) but with a unique mechanism of action that does not appear to involve GABA receptors. GBP appears to be a very safe AED, having demonstrated no organ toxicity or teratogenicity. In addition, GBP is easy to administer, as it is not protein-bound and does not induce hepatic enzymes or interact with other AEDs. Like all the experimental AEDs tested in the last decade, the efficacy of GBP has been investigated in the treatment of refractory partial seizures. In each of five placebo-controlled trials, the patients receiving GBP had fewer seizures than those who received placebo (Leiderman, 1994). However, it was also found that seizure frequency increased in some patients when GBP was added to their medication regimen (McLean et al., 1994). This phenomenon was particularly evident in the group with complex partial seizures (Ojemann et al., 1992). Such a discrepancy in the response suggests that patients suffering from complex partial seizures do not constitute a homogeneous group.

A number of clinical, physiologic, and pharmacologic observations suggest that absence seizures are caused by paroxysmal activity in inhibitory pathways (Fromm, 1986). That GABA agonists exacerbate and $GABA_B$ antagonists suppress the ictal activity in experimental models of absence seizures (Liu et al., 1992; Marescaux et al., 1992; Snead, 1992*a,b*) provides further evidence in support of this hypothesis. It appears that the staring spells associated with some complex partial seizures may also be caused by paroxysmal discharges in inhibitory pathways in the brain (Fromm, 1986). One would therefore expect such seizures to be refractory to the AEDs generally used in the treatment of partial seizures, as these drugs usually facilitate inhibitory mechanisms (Fromm et al., 1981, 1982).

A review of 58 patients attending the University of Pittsburgh Epilepsy Center who have complex partial seizures with a well-documented history of presence or absence of staring spells did, in fact, show a significant difference in degree of seizure control (Lassiter et al., 1992). The average longest seizure-free interval was only 4.3 weeks for the patients with staring spells (Fig. 1), whereas it was 32.9 weeks for the patients without staring spells (Fig. 2). These observations in-

Address correspondence and reprint requests to Dr. B. H. Eidelman at Department of Neurology, University of Pittsburgh, School of Medicine, 325 Scaife Hall, Pittsburgh, PA 15261, U.S.A.
* Deceased, January 1994.

FIG. 1. Longest seizure-free interval, rounded to the nearest month, in 35 patients suffering from complex partial seizures with staring spells.

dicate that complex partial seizures associated with staring are different in their response to AEDs from complex partial seizures without staring. The poor response of the staring type of complex partial seizure may reflect the fact that staring spells represent paroxysmal activity in inhibitory CNS pathways, and the medications used in the treatment of partial seizures facilitate such inhibitory mechanisms. The bimodal distribution of the longest seizure-free interval in the patients without staring (Fig. 2) suggests a further heterogeneity regarding pharmacologic response in this group of complex partial seizures. The heterogeneous nature of complex partial seizures is therefore one potential reason for the discrepancy in response to GBP noted by Ojemann et al. (1992) and by McLean et al. (1994).

A further source of difficulty in the development of new AEDs is the lack of a completely satisfactory experimental model of epilepsy in the sense of long-term, spontaneously recurring seizures. Alternatively, there has been an increasingly molecular approach to the experimental study of epilepsy. These techniques have produced major advances in our understanding of the normal and abnormal functioning of the nervous system. However, molecules and receptor complexes cannot have epileptic seizures. Driven to its ultimate conclusion, a purely molecular approach would be akin to an attempt to elucidate the greatness of "Hamlet" by analyzing the content of the ink and paper used by Shakespeare. As we proceed from behavioral observations in awake animals to recording in vivo to recording from tissue slices and cultured neurons, and eventually to patch clamping of single channels and investigations of receptor structure, we progressively increase the precision of the measurements and control over the neurons' environment. However, we simultaneously lose the connectivity of these neurons to the rest of the nervous system, which normally plays a large role in determining its behavior. We are thus confronted with a Biological Uncertainty Principle (Fig. 3) akin to Heisenberg's Uncertainty Principle (Fromm, 1992*a,b*). Heisenberg's Principle states that in theory it is impossible to measure both the position and the velocity of an electron simultaneously, as measuring either one disturbs the other. In studying the nervous system, increasing the precision of the measurement decreases the connectivity of the neurons under observation and vice versa.

We have found the trigeminal system to be a useful intermediate step between behavioral observations on intact animals and studies on isolated neurons and receptor complexes (Fromm and Terrence, 1985, 1987). The jaw and face muscles are prominently involved in the motor manifestations of nonconvulsive as well as convulsive seizures, and interneurons in the trigeminal complex play a major role in the organization and coordination of such movements. Moreover, the trigeminal nucleus provides a variety of segmental and suprasegmental, excitatory and inhibitory pathways on which drug effects can be tested. In keeping with these premises, our model has demonstrated characteristic profiles for the various classes of AEDs that reliably correlate with their clinical spectrum of activity.

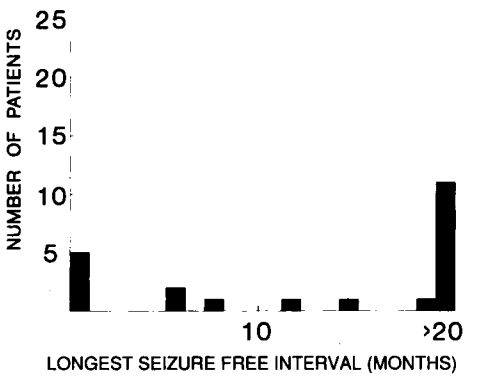

FIG. 2. Longest seizure-free interval, rounded to the nearest month, in 23 patients suffering from complex partial seizures without staring spells.

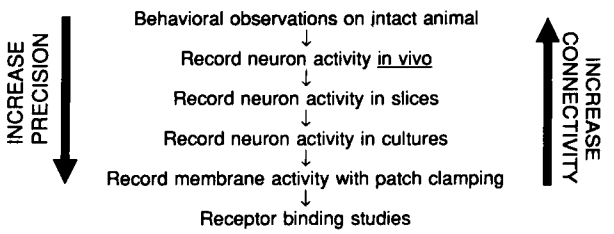

FIG. 3. Ongoing from behavioral observations in awake animals to recording single neuron activity in vivo and on to recording from more and more isolated neurons in vitro and eventually studying subcellular fragments, there is a progressive increase in the precision of the measurements but at the same time a progressive decrease in the neuron's connections to the rest of the nervous system.

As shown in Table 1, drugs effective against absence seizures [ethosuximide (ESM), trimethadione (TMO)] selectively depress inhibitory pathways, especially inhibitory pathways in the reticular formation (Fromm and Kohli, 1972; Fromm et al., 1980, 1981; Shibuya et al., 1987), in agreement with the substantial clinical and experimental evidence that absence seizures are due to paroxysmal activity in cerebral inhibitory pathways (Fromm, 1986, 1988, 1992*c*; Liu et al., 1992; Marescaux et al., 1992; Snead, 1992*a,b*). Drugs effective against tonic–clonic and partial seizures (CBZ, PHT) facilitate segmental inhibitory mechanisms while depressing segmental excitatory mechanisms and reticular pathways (Fromm and Killian, 1967; Fromm et al., 1981, 1982, 1984; Fromm, 1985) accounting for their ability to prevent the spread and generalization of paroxysmal activity from the epileptogenic focus (Fromm, 1992*a*). Valproate (VPA) is effective against tonic–clonic and partial as well as absence seizures, and it depresses excitatory pathways in the reticular formation in addition to segmental and reticular inhibitory mechanisms (Fromm et al., 1980, 1981), thus partly resembling CBZ and PHT and partly ESM and TMO in our experimental model (Fromm, 1992*b*). Baclofen is an antineuralgic but not an AED (Terrence et al., 1983). It resembles CBZ and PHT in depressing segmental excitatory and facilitating segmental inhibitory mechanisms, but facilitates rather than depresses reticular inhibitory pathways and has little effect on reticular excitatory pathways (Fromm et al., 1984; Fromm, 1985; Fromm and Terrence, 1987).

These observations indicate that the ability to depress the reticular formation in the brainstem is an important characteristic of AEDs (Fromm, 1985; Fromm and Terrence, 1985, 1987) and that the ability to depress inhibitory pathways in the CNS is a prominent feature of antiabsence drugs (Fromm, 1986). GBP resembles CBZ and PHT in depressing segmental and reticular excitatory mechanisms and facilitating segmental inhibitory mechanisms (Table 1). However, GBP differed from CBZ and PHT in enhanced inhibitory mechanisms descending from the reticular formation, and its effect on segmental and descending inhibitory mechanisms was somewhat erratic (Kondo, et al., 1991). In agreement with other reports that GBP is not a $GABA_A$ agonist (Leiderman, 1994), our experiments also showed no similarity between the spectrum of activity of GBP and that of the $GABA_A$ agonists muscimol and 4,5,6,7-tetrahydroisoxazolo-5,4-C-pyridine-3-ol (THIP) (Table 2). At high doses, GBP resembles the $GABA_B$ agonist baclofen in depressing segmental excitatory mechanisms and facilitating segmental inhibitory mechanisms, but differs in that it depresses descending excitatory mechanisms. Similarly, GBP has been found to mimic $GABA_B$-receptor activation, but to do so by a GABA-receptor–independent mechanism (Reimann, 1983; Schlicker et al., 1985).

It appears, therefore, that the efficacy of GBP against some complex partial seizures and against secondarily generalized seizures (McLean et al., 1994) is related to its ability to depress segmental and reticular excitatory mechanisms and to facilitate segmental inhibitory mechanisms. Perhaps the patients who experienced an increased seizure frequency (Ojemann et al., 1992; McLean et al., 1994) had complex partial seizures with staring and were therefore unlikely to benefit from AEDs such as GBP, CBZ, and PHT, which enhance inhibitory mechanisms in the brain. The precision of future AED trials could be considerably enhanced by categorizing patients suffering from complex partial seizures into nosologically distinct groups.

TABLE 1. *Drug action on excitatory and inhibitory mechanisms in the spinal trigeminal nucleus*

Drug	Segmental excitation	Segmental inhibition	Descending inhibition	Descending excitation
ESM	0	−	−	0
VPA	0	−	−	−
PHT	−	+	−	−
CBZ	−	+	−	−
GBP	−	+	+	−
BCF	−	+	+	0

0, no effect; −, depression; +, facilitation.
ESM, ethosuximide; VPA, valproate; PHT, phenytoin; CBZ, carbamazepine; GBP, gabapentin; BCF, baclofen.

TABLE 2. *Drug action on excitatory and inhibitory mechanisms in the spinal trigeminal nucleus*[a]

Drug	Segmental excitation	Segmental inhibition	Descending inhibition	Descending excitation
MUSC	0	±	±	
THIP	0	0	0	
GBP	−	+	+	−
BCF	−	+	+	0

0, no effect; −, depression; +, facilitation.
MUSC, muscimol; THIP, 4,5,6,7-tetrahydroisoxazolo-5,4-C-pyridine-3-ol; GBP, gabapentin; BCF, baclofen.

Acknowledgment: I thank Dr. Henry B. Higman for critical review of the manuscript. This work was supported in part by a grant (NS 19889) from the National Institutes of Health.

Obituary: On January 6, 1994, while this article was in press, Dr. Gerhard Fromm unexpectedly died of cancer at Montefiore University Hospital. He was 62 years of age. Dr. Fromm was Professor of Neurology at the University of Pittsburgh and an international authority on pain and epilepsy research. He is survived by his wife, Ann, and their children Allison and Devin.

Born in Germany in 1931, Dr. Fromm moved to Puerto Rico in 1939 and became an American citizen at the age of 14. He was graduated from Jefferson Medical School at the age of 21 years, which, at the time, made him the youngest American to be graduated from a U.S. medical school. He founded Pitt's Department of Neurology in 1968 with Dr. Henry Higman, who later served as the department's chairman.

Dr. Fromm was instrumental in developing medical treatments for epilepsy and trigeminal neuralgia. His work was and is respected worldwide, and researchers from many countries studied with Dr. Fromm in his laboratories.

The editors of this supplement have lost not only an important contributor, but also a great personality, an outstanding contemporary researcher, and, for many of us, one of our best friends.

Heinz-Gregor Wieser

REFERENCES

Fromm GH. Effects of different classes of antiepileptic drugs on brainstem pathways. *Fed Proc* 1985;44:2432–5.

Fromm GH. Role of inhibitory mechanisms in staring spells. *J Clin Neurophysiol* 1986;3:297–311.

Fromm GH. Concepts of the neurophysiological action of antiepileptic drugs. *Am J EEG Technol* 1988;28:185–95.

Fromm GH. Antiepileptic actions of carbamazepine. In: Faingold CL, Fromm GH, eds. *Drugs for control of epilepsy: action on neuronal networks involved in seizure disorders.* Boca Raton, FL: CRC Press, 1992*a*:425–35.

Fromm GH. Antiepileptic actions of valproate. In: Faingold CL, Fromm GH, eds. *Drugs for the control of epilepsy: actions on neuronal networks involved in seizure disorders.* Boca Raton, FL: CRC Press, 1992*b*:453–61.

Fromm GH. Antiepileptic actions of ethosuximide. In: Faingold CL, Fromm GH, eds. *Drugs for the control of epilepsy: actions on neuronal networks involved in seizure disorders.* Boca Raton, FL: CRC Press, 1992*c*:477–84.

Fromm GH, Chattha AS, Terrence CF, Glass JD. Do phenytoin and carbamazepine depress excitation and/or facilitate inhibition? *Eur J Pharmacol* 1982;78:403–9.

Fromm GH, Glass JD, Chattha AS, Martinez AJ. Effect of anticonvulsant drugs on inhibitory and excitatory pathways. *Epilepsia* 1981;22:65–73.

Fromm GH, Glass JD, Chattha AS, Martinez AJ, Silverman M. Antiabsence drugs and inhibitory pathways. *Neurology* 1980;30:126–31.

Fromm GH, Killian JM. Effect of some anticonvulsant drugs on the spinal trigeminal nucleus. *Neurology* 1967;17:275–80.

Fromm GH, Kohli CM. The role of inhibitory pathways in petit mal epilepsy. *Neurology* 1972;22:1012–20.

Fromm GH, Terrence CF. Trigeminal nucleus as a model for testing antiepileptic drugs. In: Bartholini G, Bossi L, Lloyd KG, Morselli PL, eds. *Epilepsy and GABA receptor agonists: basic and therapeutic research.* New York: Raven Press, 1985:149–57 (L.E.R.S., vol 3).

Fromm GH, Terrence CF. Effect of antiepileptic drugs on the brainstem. In: Fromm GH, Faingold CL, Browning RA, Burnham WM, eds. *Epilepsy and the reticular formation: the role of the reticular core in convulsive seizures.* New York: Alan R. Liss, 1987:119–36.

Fromm GH, Terrence CF, Chattha AS. Differential effect of antiepileptic and non-antiepileptic drugs on the reticular formation. *Life Sci* 1984;35:2665–73.

Kondo T, Fromm GH, Schmidt B. Comparison of gabapentin with other antiepileptic and GABAergic drugs. *Epilepsy Res* 1991;8:226–31.

Lassiter A, Fromm G, Becker J. Heterogeneity of complex partial seizures: possible pathophysiologic and therapeutic implications. *Epilepsia* 1992;33(suppl 3):68.

Leiderman DB. Gabapentin as add-on therapy for refractory partial epilepsy: results of five placebo-controlled trials. *Epilepsia* 1994;35(suppl 5):S74–6 (this issue).

Liu Z, Vergnes M, Depaulis A, Marescaux C. Involvement of intrathalamic $GABA_B$ neurotransmission in the control of absence seizures in the rat. *Neuroscience* 1992;48:87–93.

Marescaux C, Liu Z, Bernasconi R, Vergnes M. $GABA_B$ receptors are involved in the occurrence of absence seizures in rats. *Pharmacol Commun* 1992;2:57–62.

McLean MJ, Ramsay RE, Leppik IE, Rowan AJ, Shellenberger MK, Wallace J. Gabapentin as add-on therapy in refractory partial epilepsy: a double-blind, placebo-controlled, parallel-group study. *Neurology* 1994 (in press).

Ojemann LM, Wilensky AJ, Temkin NR, Chmelir T, Ricker BA, Walace J. Long-term treatment with gabapentin for partial epilepsy. *Epilepsy Res* 1992;13:159–65.

Reimann W. Inhibition by GABA, baclofen and gabapentin of dopamine release from rabbit caudate nucleus: are there common or different sites of action? *Eur J Pharmacol* 1983;94:341–4.

Schlicker E, Reimann W, Göthert M. Gabapentin decreases monoamine release without affecting acetylcholine release in the brain. *Arzneimmittelforschung* 1985;35:1347–9.

Shibuya T, Fromm GH, Terrence CF. Differential effect of ethosuximide and of electrical stimulation on inhibitory and excitatory mechanisms. *Epilepsy Res* 1987;1:35–9.

Snead OC III. Evidence for $GABA_B$-mediated mechanisms in experimental generalized absence seizures. *Eur J Pharmacol* 1992*a*;213:343–9.

Snead OC III. $GABA_B$ receptor mediated mechanisms in experimental absence seizures in rat. *Pharmacol Commun* 1992*b*;2:63–9.

Terrence CF, Fromm GH, Roussan MS. Baclofen: its effect on seizure frequency. *Arch Neurol* 1983;40:28–9.