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COMMENTARY

NEUROTRANSMITTER ABNORMALITIES AS DETERMINANTS OF SEIZURE SUSCEPTIBILITY AND INTENSITY IN THE GENETIC MODELS OF EPILEPSY

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Introduction

Normal subjects are not considered to be epileptic merely because they exhibit a seizure in response to an appropriate stimulus of sufficient intensity. In epileptics, a relatively weak stimulus will elicit an explosive neuronal response, whereas in a normal individual it will cause only trivial responses. Fortunately, only a few subjects in any given animal or human population are epileptic; however, most if not all epileptics are genetically predisposed to seizures.

The importance of genetic determinants in human epilepsy has become established only recently [1]. Genetic factors probably control seizure susceptibility and, therefore, the likelihood of developing epilepsy [1–8]. The genetic determinant is not solely responsible for the appearance of seizures but is an important contributing component. Seizures probably do not occur in the absence of other factors such as stress, biochemical and hormonal imbalances, or other environmental or physical initiators [1]. Thus, epilepsy is a composite of the individual's genetically controlled seizure propensity plus the presence of one or more seizure triggering factors.

We believe that neurochemical studies in subjects with a genetically determined predisposition to seizures are helping establish the molecular basis of epileptogenicity. However, heretofore most investigations of epilepsy have used animal models with very high degrees of inherited seizure resistance. These are normal animals which are made "epileptic" by the use of various chemical or electrical methods. Except in the kindling model of epilepsy, these normal animals retain their relatively high innate seizure resistance. Although valuable information has been obtained on the initiation of seizures in normal animals, this approach has revealed very little about genetically determined seizure susceptibility.

Genetic models of epilepsy. At least one genetic model of epilepsy is available within each of several animal species, including the rat [9, 10], mouse [11–16], gerbil [17, 18], baboon [19–21], chicken [22–25] and dog [26, 27]. Interestingly, two types of epileptic mice and chickens have been developed: the audiogenic seizure susceptible (audiogenic) mouse [11, 12], the El mouse [13–16], the px chicken [22] and the FD chicken [23]. The specific mode of genetic transmission resonsible for the epileptic traits in the various models has been elucidated only in a few cases [9, 12, 18, 20, 28–31]. Nevertheless, these genetically abnormal animals represent a valuable resource for determining the neurochemical etiology of the seizure-prone state.

All of these models, except the epileptic beagle [27], are susceptible to seizures induced by an environmental stimulus. Sound-induced seizures can be readily elicited in the epileptic rat [10, 32, 33], audiogenic mouse [11, 12], and px [22] and FD [23, 25] chickens. El mice are susceptible to seizures induced by postural stimulation [13], whereas epileptic gerbils exhibit seizures in response to a "novel" environment [17]. Intermittent photic stimuli will cause seizures in the epileptic baboon [19–21]. Some of the genetic models are susceptible to seizures induced by more than one environmental stimulus. For example, FD chickens will exhibit seizures in response to physical exertion, auditory and photic stimuli as well as heat stress [23, 25]. In all models, seizures produced by environmental stimuli are characterized by various behaviors including clonic and tonic convulsions. Although seizures in the epileptic beagle occur spontaneously, they too are characterized by clonic and tonic convulsions [27].

Another apparently common trait of the genetic epilepsy models is that they are abnormally susceptible to chemically- [13, 30, 33, 34–37] and electrically-induced [13, 20, 30, 33, 38–41] seizures. Also, in those models in which comparative experiments have been reported, epileptic animals are abnormally resistant to anticonvulsant drugs [20, 26, 36, 42, 43].

Biological and medical significance of genetically determined seizure proneness in animals. The common traits of the genetic epilepsy models are consonant with the seizure-prone state being under genetic regulation and with greater seizure spread being a concomitant of the epileptic state. In our

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view, resistance to anticonvulsant therapy results from the seizure-prone state of the epileptic animal and from lack of specificity of the antiepileptic agents.

In man there may be a similar genetic control for the seizure-prone state and the seizure spread phenomenon [44]. Whether genetic regulation of the human epilepsy-prone state is monogenic or polygenic remains to be elucidated [1] as does the molecular mode of genetic expression. Many biochemical sites within the CNS are subject to genetic alterations that could lead to abnormal neural function. One of the most obvious is the neurotransmitter systems. Limited reports in man lend credence to this proposition. These studies indicate that neurotransmitter defects in epileptics may be found in the acetylcholinergic [45], serotonergic [46], catecholaminergic [47], and/or GABA-ergic* (or other amino acid containing neurons) systems [48–50].

These human studies indicate that defects within transmitter systems may be etiologically important in epilepsy; however, insufficient data and lack of consistency [51, 52] make interpretation difficult. Nevertheless, support for genetic mechanisms of seizure susceptibility and intensity exists in man and other species. Furthermore, there is a growing awareness that neurotransmitter systems are under genetic control in all species [53–55]. If correct questions are asked of appropriate models, the relationship between central neurotransmitter systems and epilepsy can be clarified.

Neurochemical mechanisms of seizure susceptibility and intensity in genetic models of epilepsy

Norepinephrine. In the epileptic rat, Laird *et al.* [56] and P. C. Jobe and coworkers (unpublished observations) showed that norepinephrine levels are abnormally low in most areas of the brain. Also, both groups of investigators detected decrements in norepinephrine turnover rate in the midbrain, pons-medulla and spinal cord. Whether turnover rate abnormalities exist in other CNS areas is being investigated.

The activity of monoamine oxidase, the enzyme that deaminates norepinephrine, is not abnormal in any brain area of the epileptic rat [57]. On the other hand, the activity of tyrosine hydroxylase, the rate-limiting enzyme in norepinephrine synthesis, is abnormally high in the midbrain [57]. This may represent an incomplete compensatory noradrenergic response to low endogenous norepinephrine content.

Overall, these observations suggest that a defect in noradrenergic transmission exists in the epileptic rat. However, even if present, it may or may not be a cause of seizure susceptibility. One way to test whether deficits in noradrenergic transmission are a cause of seizure proneness would be to produce experimental deficits in non-epilepsy-prone rats and observe the effect on seizure susceptibility. Toward this goal, Jobe *et al.* [58] used Ro 4-1284, a benzoquinolizine which reduces synaptic norepinephrine, dopamine and 5-hydroxytryptamine content by blocking vesicular storage. This drug was tested in two types of subjects: (1) the non-seizure-susceptible progeny of non-epilepsy-prone controls, and (2) the nonsusceptible progeny from epilepsy-prone parents (NSPSP). The capacity of Ro 4-1284 to induce seizure susceptibility was assessed by determining whether it could cause the appearance of susceptibility to sound-induced seizure, one of the distinguishing characteristics of the epileptic rat. Forty-five minutes after Ro 4-1284 administration, a marked depletion of central monoamines occurred in controls and NSPSP concomitant with the appearance of a marked degree of seizure susceptibility in NSPSP. In contrast, only an insignificant fraction of controls exhibited sound-induced seizures following Ro 4-1284.

Thus, Jobe and coworkers [58] postulated that a CNS monoaminergic deficit causes the appearance of the epilepsy-prone state in rats which carry some other genetic seizure factor. A deficit in monoaminergic transmission was considered insufficient to cause susceptibility in rats not carrying this other factor. Whether deficits in noradrenergic transmission are more critical than those in dopaminergic or 5-hydroxytryptaminergic activity in the etiology of the seizure prone state could not be determined from the study.

In addition to these few observations related to seizure susceptibility, a substantial number of experiments consistently support the concept that a reciprocal relationship exists between noradrenergic activity and seizure intensity in the epileptic rat [9, 10, 59]. In some of these studies, reserpine and Ro 4-1284 were used to reduce brain monoamine levels in the epileptic rat. These manipulations caused an increase in seizure severity which was temporally correlated with changes in the levels of norepinephrine but not of dopamine [10, 32, 59]. Further support for the seizure modulatory action of norepinephrine has been provided through use of electrolytic lesions and 6-hydroxydopamine (an agent that destroys catecholamine nerve terminals). Using these techniques, Bourn *et al.* [60–63] provided additional evidence that selective decrements in brain norepinephrine, but not dopamine, markedly increase seizure intensity.

Another approach used to evaluate the role of norepinephrine in modifying convulsions in the epileptic rat has been to selectively elevate central norepinephrine levels. Such studies have uniformly shown that increments in synaptic concentrations of norepinephrine, but not dopamine, decrease seizure severity in the epileptic rat [32, 64, 65].

Observations also support the concept that a noradrenergic deficit might contribute to the genetically determined seizure-prone state in mice. However, these data are open to other interpretations [10]. Schlesinger *et al.* [66] showed that DBA/2J mice have significantly lower levels of CNS norepinephrine than do seizure resistant C57BL/6J mice. In contrast, other findings of Schlesinger *et al.* [66, 67] appear to provide no support for a noradrenergic deficit as a cause of audiogenic susceptibility. For example, at 14 days of age, B6D2F1 mice are completely nonsusceptible to sound-induced seizure and their brain norepinephrine levels are very low. By 21 days of age, these animals develop a high degree

* GABA = γ-aminobutyric acid.

of susceptibility and a marked increase in brain norepinephrine levels.

Another indication that brain norepinephrine levels may not be involved in regulation of seizures in audiogenic mice is provided in the work of Lints *et al.* [68]. These workers were unable to replicate the earlier study (described above) of Schlesinger *et al.* [66] using DBA/2J mice.

Other investigators have reported lower activity of catechol-*o*-methyltransferase, an enzyme which causes degradation of catecholamines, in brains of DBA/2J mice as compared to seizure resistant C57BL/6J mice [69]. Furthermore, DBA/2J subjects have abnormally high central tyrosine hydroxylase activity [70]. Whether these differences in enzyme activities are causally related to the epileptic state remains to be shown.

Recently, Horton *et al.* [71] showed that drugs which activate α-2-adrenergic receptors reduce seizure activity in the epileptic mouse (DBA/2J). This is an interesting observation since activation of α-2-receptors is thought to reduce release of norepinephrine into the synapse [72, 73]. However, the agonists and doses used in this study may have acted on the α-1-receptors (postsynaptic) [74, 75].

With regard to E1 mice, whole brain norepinephrine levels are lower than in some seizure resistant mice [76]. Other studies are necessary to confirm these findings.

Epileptic gerbils were studied for responses to several drugs which alter noradrenergic parameters. DL-Threodihydroxyphenylserine (DOPS) significantly reduces seizure intensity [77]. This observation is instructive because DOPS is converted directly to norepinephrine by aromatic amino acid decarboxylase. Thus, the anticonvulsant effect of DOPS may result from an increase in noradrenergic activity. However, a complicating factor in this interpretation is that relatively large doses of α-methyl-*p*-tyrosine (α-mpt) and diethyldithiocarbamate (DEDTC), drugs which reduce endogenous norepinephrine levels, also cause inhibition of seizure intensity. One possible interpretation of these data is that both of these enzyme inhibitors have intrinsic anticonvulsant activity that is independent of their capacity to alter brain norepinephrine and/or dopamine content. In this regard, Jobe [78] observed that disulfiram (an *in vivo* precursor to DEDTC) in large doses is anticonvulsant in the epileptic rat with and without intact dopamine and norepinephrine stores. Furthermore, smaller doses, which are sufficient to inhibit synthesis of norepinephrine, prolong the seizure-enhancing and norepinephrine-depleting effects of Ro 4-1284 in the epileptic rat. With regard to α-mpt, this analog of the norepinephrine precursor tyrosine, is converted to α-methylnorepinephrine, which accumulates in noradrenergic vesicles as a false transmitter and assumes functions of norepinephrine [79, 80]. Thus, it appears reasonable to discount the possibility that anticonvulsant effects of large doses of DEDTC and α-mpt are due to depletion of norepinephrine in the epileptic gerbil.

A role for norepinephrine in seizure proneness in the epileptic baboon is supported by a limited number of observations [20]. In these animals, intracerebroventricular norepinephrine produces a dose-related suppression or abolition of photically-induced seizures [81]. Conversely, seizure resistant baboons become susceptible to photic seizures upon chronic but not acute administration of reserpine. The possibility that these neuropharmacologic effects in the epileptic baboon are due to induced alterations in noradrenergic transmission is intriguing. Also, it would be important to determine whether epileptic baboons have innate noradrenergic deficits.

In the px chicken, norepinephrine levels are abnormally low in the cerebellum [82]. This may represent a decrease in noradrenergic function within the cerebellum which removes inhibitory effects on descending excitatory tracts leading to convulsions [82].

Norepinephrine concentrations in FD epileptic chickens are slightly higher in the cerebral hemispheres when compared to non-epileptic controls [25]. Also α- and β-adrenergic receptor antagonists do not effect seizures in epileptic chickens [25]. Thus, the noradrenergic system may not regulate seizures in these animals.

A cryptic report by Edmonds *et al.* [27] indicates that epileptic beagles do not have abnormal brain norpinephrine levels. Other indicators of noradrenergic abnormalities were not reported. Also, the parietal cortex was the only area of the brain analyzed. This may not be the area where the molecular abnormality exists even though it shows an abnormal electroencephalogram. Whether experimentally-induced noradrenergic deficits cause non-epileptic beagles to develop a seizure-prone state is not known.

In summary, the seizure-prone state in the epileptic rat, audiogenic mouse, E1 mouse, epileptic baboon, px chicken and the epileptic gerbil may be under noradrenergic influence. The most consistent evidence for this exists in the epileptic rat. However, even in this species, it has not been proven. Thus, much work remains to be done to elucidate the molecular basis for the noradrenergic control of the seizure-prone state in all of these species, as well as in the FD chicken and the epileptic beagle.

Dopamine. In sharp contrast to the major role that noradrenergic transmission appears to play in determining seizure susceptibility and/or intensity in the epileptic rat, dopaminergic activity in this model has little if any influence in seizure regulation. Selective increases in dopamine content produced by L-DOPA in iproniazid-pretreated animals cause no change in seizure susceptibility [65] or intensity. In this regard, L-DOPA-induced decreases in seizure susceptibility and intensity are obviated when dopamine-β-hydroxylase, the enzyme responsible for converting dopamine to norepinephrine, is inhibited since the accumulation of dopamine but not norepinephrine occurs under these conditions. Apparently, L-DOPA inhibits seizures in the epileptic rat only as a result of increases in norepinephrine. With regard to seizure enhancement, several studies indicate that drug-induced decrements in dopaminergic transmission are devoid of effects on seizure intensity [32, 62, 63] in the epileptic rat.

In epileptic mice, evidence indicates that dopamine modulates seizure activity. For example, Bog-

gan and Seiden [83] attributed the anticonvulsant effects of L-DOPA to its conversion to dopamine in the brain of DBA/2J mice. Furthermore, Kellogg [70] found that apomorphine (a dopaminergic receptor agonist) decreases the incidence of clonic-tonic convulsions and death in DBA/2J mice. Anlezark *et al.* [84] showed that, in this same strain of mice, the potencies of various dopamine receptor agonists to suppress sound-induced seizures are similar to their potencies in behavioral tests of dopaminergic function. Finally, Shaywitz *et al.* [46] reported that the turnover rate of dopamine in DBA/2J mice progressively increases from 3 weeks of age (when 94 per cent of the animals are susceptible to audiogenic seizures) to 6 weeks (when only 30 per cent are susceptible) and finally to 12 weeks (when none of the animals exhibit seizures). In contrast, norepinephrine turnover rate increased between 3 and 6 weeks of age and remained stable thereafter. These observations support the concept that initially the reduction in seizure susceptibility is caused by an increase in both dopaminergic and noradrenergic activity between the third and sixth week of age with the seizure resistant state being caused by an increase in dopaminergic transmission thereafter [46].

In E1 mice, brain dopamine levels do not appear to be abnormally low when compared with ten other strains of mice [76]. Other experiments defining the central dopaminergic system in these animals remain to be reported.

Three experiments indicate that dopaminergic systems may be capable of modulating seizures in the epileptic gerbil. First, dopamine-β-hydroxylase inhibition appears to suppress seizures if these animals are treated with DOPS to prevent a decline in norepinephrine levels which normally occurs when the enzyme is inhibited [77]. A decline in norepinephrine levels appears to offset some of the anticonvulsant effect of dopamine-β-hydroxylase inhibition. Conceptually, this anticonvulsant effect may occur because of the accumulation of dopamine after enzyme inhibition. This hypothesis still awaits experimental verification since these neurochemical endpoints were not measured in the epileptic gerbil. Second, amphetamine and apomorphine both cause an anticonvulsant effect in epileptic gerbils [77, 85]. These observations are compatible with the possibility that increases in dopaminergic transmission suppress seizures because both drugs increase dopaminergic activity. Third, haloperidol, a dopamine-receptor blocking agent, enhances seizure intensity in the gerbil [85].

In epileptic baboons, neither high intracerebral doses of dopamine nor chronic peripheral administration of L-DOPA had an effect on photically-induced seizures [81]. Interestingly, dopamine failed to influence seizures in these animals despite the fact that it was administered in a dose that was approximately six times larger than an effective anticonvulsant dose of norepinephrine.

In contrast to these studies with dopamine and L-DOPA , nomifensine, an antidepressant which may directly or indirectly activate dopamine receptors, protects against seizures in epileptic baboons [86]. However, this drug also is a potent inhibitor of norepinephrine re-uptake [87]. Thus, the anticonvulsant effect of nomifensine might occur because it activates both noradrenergic and dopaminergic receptors. If this is a valid point of view, L-DOPA or dopamine administration might be expected to produce a similar result since they would each augment both dopamine and norepinephrine concentrations in the CNS.

Further support for the concept that dopaminergic neurons exert an anticonvulsant effect in the epileptic baboon is provided by studies of two dopamine-receptor agonists, apomorphine and *N-n*-propylnorapomorphine. Both of these drugs suppress seizures in this epilepsy model [88]. Two other drugs, ergocornine and ergometrine, also reportedly act as dopamine receptor agonists and they too suppress seizures in the epileptic baboon [84].

Dopamine levels in the FD epileptic chicken are abnormally low in the cerebral hemispheres but not in the midbrain-pons-medulla [25]. However, treatment with L-DOPA increases brain dopamine content without affecting seizure susceptibility. Whether this dopamine increase is neuronal or extraneuronal was not determined.

Dopamine levels have been measured in one area of the epileptic beagle brain, namely, the parietal cortex, and they appear to be normal [27]. Systematic studies of dopaminergic function have not been undertaken in this epilepsy model.

In summary, evidence indicates that dopaminergic neurons do not determine seizure intensity or susceptibility in the epileptic rat. Whether these neurons are also devoid of such activity in the epileptic baboon is not established. In contrast, dopaminergic transmission appears to exert strong modulatory effects on seizure activity in at least one type of epileptic mouse, namely, the DBA/2J strain. Dopaminergic transmission in this genetic model may regulate both seizure susceptibility and intensity. An innate deficit may actually exist in synaptic dopamine content during the time that these animals are developmentally seizure susceptible. Neuropharmacologic studies indicate that dopaminergic neurons may be capable of exerting a similar influence in the epileptic gerbil. However, whether an innate dopaminergic deficit exists in this model is not established. The current data on the role of dopamine in epileptic chickens and beagles are too cryptic to formulate a meaningful hypothesis regarding its significance in seizure regulation.

Serotonin. In the epileptic rat, depeletion of central serotonin stores by *p*-chlorophenylalanine [89, 90] or *p*-chloromethamphetamine [91] causes a marked increase in sound-induced seizure intensity. In contrast, elevation of brain serotonin by peripherally administered 5-hydroxytryptophan plus a monoamine oxidase inhibitor reduces audiogenic seizure intensity and susceptibility [89]. These data support the hypothesis that the central serotonergic system inhibits seizure intensity and perhaps susceptibility. In this regard, Laird *et al.* [56] reported an abnormally low serotonin content in the cerebral hemispheres and midbrain of epileptic rats. These decrements may represent a deficit of serotonergic inhibitory function. Studies comparing tryptophan hydroxylase and 5-hydroxytryptophan decarboxylase in epileptic rats and seizure resistant rats remain

to be done. Monoamine oxidase activity in the epileptic rat appears to be normal in the telencephalon, hypothalamus-thalamus, midbrain, pons-medulla and spinal cord [57].

In the E1 mouse, a deficit in serotonergic transmission is correlated with seizure activity [92]. Audiogenic mice reportedly have abnormally low brain serotonin levels when comparisons are made to controls [66, 93]. Recently, other workers [68] have conducted similar experiments but found no abnormalities in brain serotonin content in audiogenic mice.

Kellogg [70, 93] showed that the rate of serotonin synthesis is slower in the forebrain and faster in the hindbrain of audiogenic mice (DBA/2J) than in control mice. The activity of monoamine oxidase is lower, while 5-hydroxytryptophan decarboxylase activity is normal in audiogenic mice [93]. These data, if confirmed, show a defective serotonergic system in audiogenic mice and suggest that this defect may play a role in the epilepsy-prone state of these animals. Other work with audiogenic mice lends credence to this hypothesis since experimental manipulations which cause central serotonergic decrements or increments yield a corresponding enhancement or a reduction in audiogenic seizure susceptibility or intensity [30, 83, 94].

In contrast, other data in the epileptic mouse do not appear to support this hypothesis. A few reports suggest that *p*-chlorophenylalanine produces a distinct inhibition of audiogenic seizure intensity [95–99] and that this effect is accompanied by a marked reduction in brain serotonin levels. Furthermore, drugs which reportedly block serotonin receptors also suppress sound-induced seizures in mice [99].

The literature on serotonin and seizure activity in the epileptic gerbil is scanty. In fact, the only report shows no difference in endogenous serotonin content in brains of seizure-prone and resistant gerbils [77].

The function of the serotonergic systems in regulating photomyoclonic seizures in epileptic baboons remains to be elucidated. There are no comparative reports in the literature characterizing the endogenous content or the enzymes of synthesis and degradation for serotonin in seizure-prone and resistant baboons. Furthermore, the results of the few pharmacological studies in the literature are equivocal. For example, Wada *et al.* [100] and Trimble *et al.* [86] showed that 5-hydroxytryptophan produces protection against photically-induced seizures in the epileptic baboon. Along these same lines, Meldrum and Naquet [101] showed that agents which interact with serotonin receptors inhibit the myoclonic and electroencephalographic effects of intermittent light stimulation. On the other hand, Altshuler *et al.* [81] found that intracerebroventricular serotonin and intraperitoneal *l*-tryptophan did not produce any change in seizure susceptibility or intensity.

Evidence is insufficient to implicate a defect in central serotonergic transmission as the basis for the epilepsy-prone state in either px or FD epileptic chickens [25, 38]. For example, the FD epileptic chicken has slightly lower endogenous brain serotonin levels; however, pharmacological elevation of central serotonin content does not change seizure activity.

No differences in serotonin content of biopsy samples from the parietal cortex of epileptic and control beagles have been identified [27]. Other experiments on the serotonergic system in this model have not been reported.

From this discussion, it is apparent that more evidence supports a role for serotonin in the epileptic rat and mouse than in the other models. However, characterization of the function of serotonergic systems in the epileptic process is grossly incomplete in all of these models.

Acetylcholine. The role of acetylcholinergic neurons in the genetic models of epilepsy has received little attention. Observations of Jobe [10] show that young epileptic rats killed in liquid nitrogen exhibit a reduction in central levels of this neurotransmitter during audiogenic convulsions.

With regard to epileptic mice, Aronstam *et al.* [102] observed that, in the hippocampus, DBA/2J mice have a higher cholinergic receptor density than do seizure resistant C57BL/6J mice. Whether this represents a decrease in cholinergic transmission in the DBA/2J mouse is open to speculation. If a deficiency exists, it might be hypothesized that seizure proneness in this epilepsy model is caused by insufficient cholinergic activity. This idea is compatible with an earlier observation by Kellogg [103] that the muscarinic agonist oxotremorine depressed seizure susceptibility, and that the muscarinic blocking agent scopolamine prevents the anticonvulsant effect of oxotremorine.

In the E1 mouse, the concentration of brain acetylcholine is abnormally high [104]. When exposed to postural stimulation, a decline in acetylcholine levels occurs both before and during convulsions.

Killam [20] believes that acetylcholine is probably not involved in the regulation of seizures in the epileptic baboon. Both the antimuscarinic agent atropine and the acetylcholine esterase inhibitor eserine have failed to modify seizure responses [105].

Acetylcholinesterase activity may be abnormally high in FD epileptic chickens [25]. Also, choline acetyltransferase activity is decreased in cerebral hemispheres of epileptic chickens. The role of these abnormalities in seizure proneness in these animals is unknown. However, FD epileptic chickens are more sensitive to the convulsant effects of physostigmine than are seizure resistant chickens [25].

Thus, cholinergic activity may influence seizures in the epileptic rat, mouse, and FD chicken. The role of cholinergic abnormalities in genetically determined epilepsy states in these models has not been determined. Also, whether these abnormalities are expressed as excessive or deficient transmission is not established. The influence of acetylcholinergic activity in the epileptic gerbil and beagle is unknown. Limited data indicate that acetylcholine does not play a significant role in the seizure-prone state of the epileptic baboon.

Amino acid neurotransmitters. Laird and Huxtable [106] showed that four amino acids—taurine, GABA, glycine and aminoisobutyric acid—exert a dose-dependent anticonvulsant action against audiogenic seizures in the epileptic rat. In addition, taurine injected into the inferior colliculi elevates intracerebral electroshock thresholds in the epileptic rat

but causes no change in thresholds in non-epileptic rats [33].

Further studies were made to search for a defect in free amino acid patterns as ratios of their concentrations in the brains of epileptic rats. However, no abnormalities were found when measurements were made in the cerebral hemispheres and inferior colliculi of these animals [107]. Nevertheless, the function of an amino acid neurotransmitter system may be compromised at other sites (e.g. synthesis or receptor binding). Yet, no differences were found in the ability of the epileptic rat to synthesize GABA [108].

Many pharmacological actions of the benzodiazepines may be mediated by the GABA-ergic system [109]. Receptor binding studies with benzodiazepines show that the affinity of these drugs for binding sites can be increased by GABA [110]. Interestingly, Mimaki and coworkers [111] have shown that the numbers of benzodiazepine binding sites are abnormally high in the brains of epileptic rats, although receptor affinity appears normal. It is tempting to suggest that a defect exists in the "endogenous benzodiazepine system" as it interacts with the GABA system. However, much work remains to be done in characterizing the GABA receptor and its modulation by the endogenous benzodiazepine-like ligands in the epileptic rat.

In the audiogenic mouse, pharmacological treatments which elevate central GABA levels uniformly reduce susceptibility to and severity of audiogenic seizures [67, 112–114]. In addition, audiogenic mice release less GABA in response to K^+ stimulation of brain slices [115], and exhibit a reduced capacity for synthesis of GABA from glucose in the cortex [116]. Although receptors for GABA are present in abnormally low numbers, they have a higher affinity for binding that do receptors from seizure resistant mice [117]. Also, benzodiazepine receptor density is abnormally high in audiogenic mice [118].

The only published study on amino acid transmitters in the E1 mouse suggests that the levels of glutamine and glutamate are lower than in controls, whereas GABA content is abnormally elevated [104]. This may be a compensatory response to the epileptic state of the animals rather than the cause of the epilepsy [104].

Two studies of amino acid transmitters in the epileptic gerbil and chicken have been reported. These investigations show that the GABA content is abnormally low in the brains of both types of epileptic animals [77, 119].

In the epileptic baboon, drug-induced decrements in synaptic GABA enhance light-induced seizures, whereas experimentally-induced increments in functional GABA levels are anticonvulsant [21]. Nevertheless, an innate GABA-ergic defect may not exist in the epileptic baboon [120].

In the epileptic beagle, no abnormalities in absolute concentrations in amino acids are seen in brain, cerebrospinal fluid or serum [121]. However, the concentration of glutamate + aspartate + glycine is lower in the serum of epileptic beagles. Furthermore, there is a greater number of amino acid correlations (i.e. level of one amino acid influencing level of another) in cerebrospinal fluid of epileptic beagles. These correlations may indicate a subtle defect in CNS sodium homeostasis [121]. This concept is based on the fact that the correlated amino acids are transported by a sodium-dependent carrier.

Peptide neurotransmitters. Recently Elomaa *et al.* [122, 123] proposed that epileptogenesis may be the result of the action of somatostatin or vasoactive intestinal peptide (VIP). This postulate is an indication of the growing awareness of peptides as important compounds in neurobiology. Indeed, several of these substances are suggested as neurotransmitter candidates within the CNS (e.g. somatostatin, substance P, and endorphins) [53, 124]. However, their significance in regulating the seizure-prone state has not been reported in any of the genetic models of epilepsy.

Conclusions

At this time, evidence is insufficient to identify a common neurotransmitter defect in the genetic epilepsy models, although a growing body of evidence supports a pivotal role for norepinephrine and possibly serotonin and GABA in regulating seizure genesis. However, it is doubtful that there is a *common* neurotransmitter defect underlying *all* genetic seizure disorders in man or other animals. Despite this complicating possibility, the search for the relationships between neurotransmitter abnormalities and the genetic epileptic state may ultimately reveal the molecular bases of epileptogenesis. We suggest that, as the process proceeds, it will become increasingly apparent that different neurochemical abnormalities underlie different types of epilepsy. If this concept is validated, specific genetic animal models of epilepsy should provide valuable neurochemical (and perhaps behavioral) analogues of corresponding genetically determined human disorders.

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