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Audiogenic Seizures and Their Importance in Experimental Behavioral Studies: A Review

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The aim of this review is to explain and detail the role of audiogenic seizures (ASs) in neurobiological events occurring in the central nervous system (CNS) and their importance in experimental models in light of the current literature. Audiogenic seizures are a model of generalized tonic-clonic seizures, which are brainstem-generated. The rodent audiogenic seizure is a biological and genetic phenomenon. In this review, general features of audiogenic seizures in different rat and mouse strains are discussed, and we try to explain the neurotransmitter systems that are involved in audiogenic seizures and brain structures involved in the development of audiogenic seizures. We also address audiogenic seizure behavior and the relationship between neural plasticity and audiogenic kindling, as well as explaining audiogenic kindling, experimental studies in different drug groups, and the genetics involved.

MeSH Keywords: Epilepsy, Reflex • Models, Animal • Neuropharmacology

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4039 — — 82

Background

Audiogenic seizures (AS) are generalized, self-sustained convulsive seizures in which acoustic stimulations evoke wild-running tonic flexion and extension [1]. Following intense sound stimulation, generalized seizures occur as AS (loss of consciousness accompanied by rhythmic muscle spasms and rigid muscle stiffness) [2]. AS can be induced in susceptible animals by 110 dB (high-intensity) acoustic stimulation and can be used as a rodent model of generalized tonic-clonic seizures. AS can result from hyper-synchronized firing of neurons and mostly occur without structural abnormalities. They vary substantially with regard to the age of maximum risk, severity, and duration [3].

AS may be triggered in normal rodents and in adult animals. There are genetically-based audiogenic seizures that are inherited in origin; different in-bred mouse strains are used, such as DBA/2J and Frings mice. The specific genes responsible for the AS susceptibility remain unidentified. Genetically epilepsy-prone rats (GEPRs) are a widely studied form to determine the susceptibility to AS. GEPR-9s and GEPR-3s are the 2 substrains of the genetically epilepsy-prone rats that can be used to differ the severity of convulsive behavior [4].

Neonatal thyroid deficiency model, intense acoustic stimulation model, administration of ototoxic drugs such as kanamycin [5], and ethanol withdrawal syndrome (EWS) model [6] are different models used to induce AS. AS may also be triggered by developing magnesium deficiency and systemic administration of pharmacological agents, including metaphit (a phencyclidine analog), which act on glutamate receptors [7].

Another prominent and classical way to trigger AS in rodents is to establish "withdrawal syndromes". AS may be observed after the continued administration of alcohol, as well as barbiturates and benzodiazepines (depressant drugs). If ethanol is repeatedly given for a sufficient duration by self- or experimenter-initiated means, the rodent will have convulsive seizures in the withdrawal period. During the EWS, "generalized audiogenic seizures" in rats may be triggered by intense acoustic stimulation [8].

From another point of view, AS may also be an indicator of EWS. The basic pharmacological mechanisms underlying AS that are triggered by EWS are unknown. Also, AS can be used as a marker to explain the effects of the drugs in experimental studies. The intensity and latency parameters of AS can be recorded in experiments. Significant changes have been found in the "intensity" and "latency" of audiogenic seizures due to the atypical antipsychotic treatment (e.g., quetiapine, ziprasidone, and risperidone) on EWS in rats [9–11].

The main purpose of this review is to explicate and detail the role of ASs in neurobiological events occurring in the CNS, and its importance in experimental models in light of the current literature.

Neurotransmitter Systems that are Involved in Audiogenic Seizures

Glutamate, serotonin, dopamine, glycine, GABA, nitric oxide (NO), and agmatine are the neurotransmitters that have been most studied related to monoaminergic changes in audiogenic seizures. Alterations in striatal dopamine and serotonin levels are necessary but not sufficient to predispose audiogenic seizure susceptibility in ethanol-dependent rats. An increase in striatal dopamine and a decrease in striatal serotonin were found to be associated with ethanol withdrawal seizures in ethanol-dependent rats [12].

Glutamate

Glutamate is the main excitatory neurotransmitter in the brain. There are 3 types of ionotropic glutamate receptors (ligand-gated ion channels) named according to their prototypic agonists: NMDA (N-methyl-D-aspartate) receptor, AMPA (α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainate (KA). Ionotropic glutamate receptors mediate the majority of excitatory neurotransmission. These glutamate receptors are named after the agonists that activate them: NMDA (N-methyl-d-aspartate), AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionate), and kainic acid. Ionotropic glutamate receptors are nonselective cation channels. This means that they allow the passage of Na+ and K+, and in some cases small amounts of Ca^{2+}. AMPA/kainate and NMDA receptors are formed from the association of several protein subunits. The NMDA subfamily of glutamate receptors have interesting properties. 1. NMDA receptor ion channels allow the entry of Ca^{2+} in addition to monovalent cations such as Na+ and K+. As a result, EPSPs produced by NMDA receptors can increase the concentration of Ca2+ within the postsynaptic neuron; the Ca^{2+} concentration change can then act as a second messenger to activate intracellular signaling cascades. 2. Opening the channel requires the presence of a co-agonist (the amino acid glycine), and that extracellular Mg^{2+} blocks the channel at hyperpolarized, but not depolarized, voltages. There are at least 5 forms of NMDA receptor subunits (NMDA-R1, and NMDA-R2A through NMDA-R2D); different synapses have distinct combinations of these subunits, producing a variety of NMDA receptor-mediated postsynaptic responses [13].

Glutamatergic mechanisms play crucial roles in AS. It has been reported that the glutamate system within the inferior colliculus plays a crucial role in AS activity. Glutamate is implicated in the aberrant processing of acoustic information in the inferior colliculus that may lead to development of audiogenic seizures. It is already reported that increasing glutamatergic

transmission intensifies AS and decreasing glutamate transmission reduces AS severity or abolishes it [1].

NMDA receptors may be involved in the molecular mechanisms of seizures of different etiologies. Krushinsky-Molodkina (KM) rats exhibit inherited susceptibility to audiogenic seizures and auditory stimuli induce generalized tonic-clonic seizures that resemble human epilepsy [14].

The intraperitoneal administration of N-methyl-D-aspartate (NMDA) elicited epileptic motor seizures in developing rats (aged from 7 to 25 days) and in young adult rats. A study of NMDA-induced seizures in developing rats showed that manipulating the glutamate system is also effective in producing seizures in other models of generalized tonic-clonic epilepsy [15].

The reduced number of dopamine and glutamate receptors in the striatum can be associated with neurological peculiarities of KM rat strain (audiogenic seizures and post-ictal catalepsy) [16]. There may be an involvement of activation of NMDA and calcium-permeable AMPA/kainate receptors in the pathogenesis of audiogenic seizures [17].

Serotonin

To identify whether serotonergic drugs are an adequate and suitable target in controlling audiogenic seizures, the effects of drugs on AS, which affects mainly the *serotonergic activity* on the central nervous system, were investigated previously, such as olanzapine, escitalopram, venlafaxine, and fluoxetine [9]. In previous studies, olanzapine and escitalopram were found to be ineffective in controlling audiogenic seizures [18,19]. Venlafaxine has been found to reduce the incidence of audiogenic seizures at the 6th hour of EWS [20].

GABA

GABA is the major inhibitory neurotransmitter of the brain. GABA can be directly related to AS activity. The microinjection of baclofen (a GABA-B receptor agonist) into Ic protects against AS, and blockade of the breakdown of endogenous GABA by gabaculine (a GABA transaminase inhibitor) increased GABA levels and blocked AS susceptibility in the GEPR-9 [21].

It has been previously reported that GABA and glutamate are the neurotransmitters that play a critical role in the control of audiogenic seizures and seizure initiation in the inferior colliculus [21,22]; GABA-mediated inhibition causes excessive acoustically-evoked neuronal firing in the formation of audiogenic seizures.

Periaqueductal gray (PAG) is a requisite nucleus in the neuronal network for audiogenic seizures and GABA-A, opioid peptide, and NMDA receptors in the PAG modulate AS propagation [23]. IL-6 mice show a range of biochemical and behavioral changes correlated with a higher AS susceptibility [24].

Glycine

Glycine acts as a co-agonist together with glutamate and is an absolute requirement for NMDA channel activation [25]. Glycine plays an important role as a major inhibitory neurotransmitter in the central nervous system, mainly in the spinal cord and brainstem, where it acts via the strychnine-sensitive glycine receptor (GlyR) chloride channels to control spinal reflexes and locomotor behavior [26]. Thus, glycine can affect both excitatory and inhibitory neurotransmission. The concentration of glycine within synapses is effectively regulated by a rapid reuptake mechanism consisting primarily of glycine transporters (GlyT). Two types of GlyTs have been identified – GlyT type 1 (GlyT1) and GlyT type 2 (GlyT2) – which differ in their pharmacological properties and anatomical distribution [27].

Inhibition of GlyT1 by sarcosine and subsequent accumulation of glycine were discussed as a mechanism not only for seizure inhibition but also for tonic activation of GlyRs in the hippocampus [28], suggesting that GlyT1 inhibitors may be helpful in treatment of disorders associated with neuronal hyper-excitability, such as epilepsy. Recent studies showed that sarcosine may act not only as a GlyT1 inhibitor, but also may directly act as a co-agonist of NMDA receptors at the glycine-binding site.

Glycine receptors are well established as playing important roles in controlling motor functions and sensory signaling in vision and audition [29]. Changes resulting from seizure-experience consisted of increases in aspartate, glutamate, and glycine compared to seizure-naive groups in inferior colliculus and in motor-sensory and frontal cortices [30].

The mechanism of the anticonvulsant effect of glycine is similar to that of some of the anticonvulsant drugs such as Dilantin; this mechanism is not effective in all seizure models [31].

Intragastric glycine protected DBA/2 mice (young audiogenic seizure-susceptible mice) against all 3 phases of sound-induced convulsions (wild-running, clonic, and tonic seizure). With increase of glycine, the cerebral levels of glutamine and serine also increased, but that of glutamic acid decreased. The endogenous glutamic and glycine levels were slightly higher in the brains of the audiogenic seizure-susceptible DBA/2 mice than in the resistant BALB/Cy strain [32].

It has been reported that the oral administration of glycine and polyamine receptor antagonists blocks ethanol withdrawal seizures [33] and glycine potentiates the action of some anticonvulsant drugs in some seizure models [31]. Glycine B

antagonists reported to attenuate the expression of the withdrawal syndrome. Audiogenic seizures associated with alcohol withdrawal after 7-day treatment in rats are inhibited by L-701,324 at 5 mg/kg [33]. MDL-100,458 and MDL-102,288 are equipotent as glycine B antagonists *in vitro* but exhibit strikingly different *in vivo* profiles for audiogenic seizures in DBA/2 mice and for separation-induced ultrasonic vocalizations in rat pups (a model of anxiolytic activity) [34].

Dopamine

It is already known that dopamine plays an important role in the protection against audiogenic seizures in mice [35]. It has been reported that in the sensitive mice, developmental differences in mechanisms of monoamine storage and/or synthesis may exist that could contribute to deficient amounts of physiologically releasable transmitter [36]. The brain dopamine system is involved in the abnormal pattern of monoamines in the "audiogenic" brain [12,37]. The audiogenic seizures provoked in rats by the withdrawal of chronic ethanol consumption were associated with an increase in striatal dopamine and a reduction in striatal serotonin. In Krushinsky-Molodkina (KM) rats, the basal striatal dopamine level measured by *in vivo* microdialysis was 25% higher than that in non-epileptic Wistar rats. A single amphetamine injection (1 mg/kg body weight, intraperitoneally) caused a significant increase in the dopamine basal level of up to 250–260% in animals of both genotypes. The increase in the dopamine level after a single injection of raclopride (antagonist of D2 and D3 receptors) was also similar in amplitude in rats of both genotypes (up to about 210%). As mentioned above, these changes occurred in KM rats after much longer time intervals (after more than 100 min *vs.* 20–25 min in Wistar rats). It was suggested that this peculiar timing of changes in dopamine increase could be connected with dysfunction of 1 or more regulatory genes [37].

In audiogenic seizure-susceptible (AGS) mice, evidence suggests a role for dopamine as well as GABA and possibly serotonin [38]. Pharmacological studies demonstrated a reciprocal relationship between both noradrenergic and serotonergic transmission and audiogenic seizure severity and susceptibility in genetically epilepsy-prone rats (GEPR).

The deficit of brain monoamines as one of the concomitant neurochemical features of AS proneness has been identified as the "reciprocal relationship" between both noradrenergic and serotonergic transmissions and the severity of audiogenic seizure was found [39]. The reduced number of dopamine and glutamate receptors in the striatum can be associated with neurological peculiarities of the Krushinsky-Molodkina rat strain (audiogenic seizures and post-ictal catalepsy) [16].

A brief exposure to an aversive sound produces 5HT activation in the corticothalamic loop and the hypothalamus. The epileptic rats displayed a higher 5HTergic activation of the thalamus by the sound stress as compared to the non-epileptic rats, whereas the latter animals exhibited a larger cortical response [40].

Nitric oxide (NO)

There is extensive data to support the possible relationship between nitric oxide and audiogenic seizures. It has been reported that NG-nitro arginine methyl ester (L-NAME) and 7-nitroindazole (7-NI) significantly decreased audiogenic seizures in rats [41].

Experiments on the models of epileptiform seizure and hemorrhagic stroke (KM rats) showed that selective inhibitors of inducible and neuronal NO synthases (aminoguanidine and 7-nitroindazole) significantly decrease the mortality rate, reduce the severity of motor disorders, and prevent the development of intracranial hemorrhages under conditions of audiogenic stress [42]. The role of nitric oxide and lipid peroxidation were evaluated in genetically epilepsy-prone (GEP) rats and DBA/2 mice (with genetically determined audiogenic epilepsy). In rats and mice, acoustic stimulation led to locomotor activation followed by clonic-tonic seizures. It has been shown that the contents of nitric oxide and lipid peroxidation products at the peak of seizures markedly surpassed the control level [43].

Agmatine

Agmatine is synthesized in the brain and stored in synaptic vesicles in regionally selective neurons. It is accumulated by uptake, released by depolarization, and inactivated by agmatinase. The role of agmatine on the EWS has been investigated in rats [44]. Agmatine is a novel neurotransmitter that may be related with AS. Agmatine is an amine that is formed by the decarboxylation of L-arginine by the enzyme arginine decarboxylase (ADC) and hydrolyzed by the enzyme agmatinase to putrescine [45]. The biological role of agmatine on audiogenic seizures needs to be further investigated.

Brain Structures Involved in the Development of Audiogenic Seizures

The main structures involved in audiogenic seizure development are the brain stem structures. Lesions of the inferior colliculi (bilaterally) and lateral lemniscus and the connections between these structures blocked audiogenic seizure expression in rats and mice.

Superior colliculus (SC) deep layers are involved in the expression of acute and kindled audiogenic seizure. The cerebral

cortex is an important brain structure essential for audiogenic kindling development [46]. It has been reported that the pathway between the central amygdala and ventrolateral periaqueductal gray is implicated in the network of audiogenic seizures in GEPRs [47].

The effects of intense audiogenic stimulation (AGS) on rats treated with the antibiotic imipenem and dipeptidase inhibitor cilastatin (Imi/Cil) were investigated. Imi/Cil-induced and Imi/Cil-audio-induced seizures differed behaviorally and electroencephalographically. It has been suggested that different neuronal pathways are responsible for these 2 types of seizures: neuronal networks in the cortex are involved in Imi/Cil-induced seizures, whereas audiogenic seizures use networks residing primarily in the brainstem [48].

Audiogenic Seizure Behavior

Audiogenic seizure behavior can be divided into 3 phases: wild-running, clonus, and tonus. Audiogenic seizure (AGS) involve a phase of wild-running ending in convulsions of tonic-clonic/tonic. The WAR strain [49], the GEPR strain [50], and the AGSR strain [51] were used to produce audiogenic seizure-susceptible rats.

In the wild-running phase, at some time after acoustic stimulation begins, rats run uncontrollably at full speed in the testing chamber [1]. Threshold and duration of wild-running had been studied to distinguish between the normal and audiogenic seizure-susceptible animals [51].

There is experimental data on the effects of neuromodulators such as carisbamate (RWJ-333369) in 2 models of genetically determined generalized epilepsy (the GAERS and the audiogenic Wistar AS). Carisbamate increased the latency to the first running episode and induced the occurrence of a second running episode in 3 of 8 rats in Wistar AS [52].

It has been reported that the antiepileptic drug levetiracetam dose-dependently lengthened the latency and reduced the duration of audiogenic seizures in both non-kindled and kindled rats. The “latency and duration of audiogenic seizures” and the “duration of running, tonic, post-tonic-clonic phases” were measured [53].

Clonic convulsions are characterized by flexion of the dorsal surface, neck, forelimbs, and hindlimbs and occurs after the wild-running phase, accompanied by full body muscle spasms and rocking motions [1].

In a tonic seizure, the body assumes an arched shape. Tonus involves sustained rigid extension of the dorsal surface, neck, forelimbs, and hindlimbs, in contrast to the fleeting tonus of a tonic-clonic seizure [1]. The post-ictal period includes immobility and vocalization [54,55].

Neuronal Plasticity and Audiogenic Kindling

Mechanisms of neuronal plasticity involved in audiogenic kindling have been investigated by several researchers [56]. The brain undergoes changes in its basic structure and function (e.g., neural plasticity with an increased susceptibility in neuronal synchronization and network circuit alterations). Some of these changes are transient, while others are permanent.

The neuronal network for audiogenic seizures was explained by Faingold (Jaspers Basic Mechanisms of Epilepsies, 4th edition) as: (1) the inferior colliculus as the initiation site (GABA mechanisms), because GABA is the major inhibitory neurotransmitter in the inferior colliculus, mediating several different normal forms of acoustically-evoked inhibition in IC; (2) the superior colliculus; (3) periaqueductal gray, (4) substantia nigra; and (5) the brainstem reticular formation in the audiogenic seizure network.

It has been reported that repeated generalized audiogenic seizures induce plastic changes in acoustically-evoked neuronal firing in the amygdala [57]. It has also been suggested that audiogenic kindling induces plastic changes in the neuronal firing patterns in periaqueductal gray [56]. Also, synaptic plasticity in the pathway from the medial geniculate body to the lateral amygdala is induced by audiogenic seizure repetition [57].

Repetition of Audiogenic Seizures (AGS Kindling)

Audiogenic seizures are a model for generalized tonic-clonic brainstem-generated seizures.

Audiogenic kindling can activate limbic networks in an epileptogenic way. Audiogenic seizure epilepsy models do not show epileptiform EEG activity in the cortex during seizures. AGS kindling in several strains of AGS-susceptible rats does result in the appearance of epileptiform cortical EEG [58]. It has been reported that amygdala neurons may play a critical role in AGS kindling in GEPR-3s [59].

It has been reported that permanent audiogenic kindling-induced limbic epileptogenicity is mainly associated to gluzinergic terminal reorganization in the amygdala but not in the hippocampus, and with no hippocampal cell loss [60]. Cortical epileptiform activity and additional seizure behaviors are seen in repetitive generalized audiogenic seizures (AGS kindling) in AGS-susceptible rodents [61].

Experimental Studies with Different Drug Groups and Audiogenic Seizures

Atypical antipsychotic drugs

Previous experimental studies (audiogenic seizures induced by the EWS in rodents) showed the effects of atypical antipsychotic drugs on ethanol withdrawal audiogenic seizures. Clozapine [62] did not produce any significant effect on audiogenic seizures. Olanzapine was found to be ineffective in controlling the intensity and latency of audiogenic seizures [18]. In contrast to previous studies with clozapine and olanzapine, marked inhibition of audiogenic seizures was observed by risperidone, quetiapine, and ziprasidone treatments on EWS in rats [11].

Antiepileptic drugs

Levetiracetam (LVT) has showed an anticonvulsant effect on all the parameters of audiogenic epileptiform seizures (AES) in Krushinsky-Molodkina (KM) rats [63]. Pro-epileptic effects of the cannabinoid receptor antagonist SR141716 have been shown in a model of audiogenic epilepsy [64]. The remote effects of neonatal injections of caffeine and piracetam on audiogenic seizure susceptibility in neonatal DBA/2J, 101/HY and CBA/Lac/Sto mice genotypes has been reported [65].

Antidepressant drugs

Venlafaxine has been shown to reduce the incidence of audiogenic seizures at the 6th hour of ethanol withdrawal. Venlafaxine (20 mg/kg) has been shown to significantly prolong the latency of the seizures [20]. Both short-term and long-term tianeptine treatment produced some significant inhibitory effects on audiogenic seizures during the EWS [66]. Serotonergic drugs (fluoxetine, tianeptine, hypericum perforatum, escitalopram, and venlafaxine; especially fluoxetine and tianeptine) [9] have been found to be effective therapeutic agents for audiogenic seizures in ethanol withdrawal.

Escitalopram was found ineffective on AS during the EWS [20]. Hypericum perforatum (HPE) produced some significant inhibitory effects on audiogenic seizures during the withdrawal period [67]. Beneficial effects of fluoxetine, tianeptine, HPE, escitalopram, and venlafaxine on ethanol withdrawal signs, including audiogenic seizures, were observed [9].

HMG-CoA reductase inhibitors (Statins)

Statins, in addition to their beneficial cardiovascular effects, may be able to affect brain areas that might participate in regulation of seizure susceptibility. The effects of lovastatin, simvastatin, atorvastatin, fluvastatin, and pravastatin in DBA/2 mice (an ideal genetic model for generalized tonic-clonic seizures) have been investigated, and the co-administration of these compounds with some antiepileptic drugs were studied to identify possible positive pharmacological interactions. It has been found that simvastatin only was active against both the tonic and clonic phase of audiogenic seizures. Other statins tested were found to be partially effective against the tonic phase, with the following order of potency: lovastatin >fluvastatin >atorvastatin; pravastatin was completely ineffective up to the dose of 150 mg/kg [68].

Cannabidivarin (CBDV)

CBDV has been reported to be an effective anticonvulsant in a broad range of seizure models. CBDV was effective in 3 models of generalized seizure: maximal electroshock, audiogenic, and PTZ-induced seizures in rats. CBDV (200 $mg \cdot kg^{-1}$) completely prevented tonic-clonic convulsions in the audiogenic seizure model [69].

Genetic studies

There are 3 main rat strains that are genetically susceptible to audiogenic seizures: GEPR, WAR (Wistar audiogenic rat), and DBA. There are also GEPR-3 and GEPR-9 strains. Wild-running, tonic convulsions, tonic hindlimb extension, and post-ictal depression of consciousness are seen in AS in GEPR-9s [6]. Genetically epilepsy-prone rats (GEPR-9s) are a well-studied genetic model of generalized convulsive epilepsy [70].

GEPR-9s exhibit a greater than normal susceptibility to seizures induced by convulsant drugs and metabolic conditions, and they are also susceptible to sound-induced seizures or AS. DBA/1 mice exhibit susceptibility to audiogenic seizures followed by sudden death associated with respiratory arrest [71].

The strong genetic component of audiogenic seizures was highlighted by Misawa et al., who identified a monogenic locus causing juvenile audiogenic seizures in mice. They reported that cloning the gene for audiogenic seizures in black Swiss mice may provide important insight into the fundamental mechanisms for developmentally regulated human epilepsy syndromes [72].

Electroencephalographic profiles of the audiogenic seizures of the hamster strain GASH: Sal are parallel to EEG patterns of other animal models of generalized tonic-clonic seizures [73]. It is reported that the antiepileptic drugs hamster (GASH: Sal) is a reliable model for genetic audiogenic seizures [74].

The susceptibility subject to audiogenic seizures is still an open question and it has been found that Vlgr1 knockout mice show audiogenic seizure susceptibility [3]. It is known that audiogenic seizures are reflex seizures that are provoked by loud noises

and can be induced in rodents by acoustic priming, accomplished by exposing animals to strong auditory stimuli at an early developmental stage. DBA/2 and Frings strains of mice are susceptible to audiogenic seizures without priming, and in those strains seizures may be provoked by auditory stimuli [75]. A mouse with mutated 5-hydroxytryptamine type 2C receptor (5-HT_{2C}) also exhibits susceptibility to audiogenic seizures [76]. Mass-1 was also found to be related to audiogenic seizures [77].

The lde/lde rat is a new model of genetic audiogenic seizure and the central conducting pathway of audition in these animals may be involved in the occurrence of seizures [78]. In a previous study, it was reported that the mice lacking selenoprotein p and selenocysteine lyase exhibit severe neurological dysfunction, neurodegeneration, and audiogenic seizures [79].

Conclusions

Acute audiogenic seizure pathways include inferior colliculus, superior colliculus, substantia nigra, reticular formation, and other brainstem areas such as periaqueductal gray. In kindled audiogenic seizures, however, in addition to those brainstem structures critical for acute audiogenic seizures, the amygdala, hippocampus, and neocortex are some of the more critical substrates of limbic recruitment [80]. GEPRs represent an important animal model to evaluate pharmacological treatments and other therapies associated with seizure propensity [81].

Thus, the information from neurochemical studies, although fragmentary, demonstrates the definite shifts in the function of the main neurotransmission systems in audiogenic seizure-prone rats. However, these data do show which brain chemical cascade and/or gene expression peculiarities are the primary events that cause audiogenic epilepsy or which ones develop as the secondary processes as the consequences of the primary defect. The neuronal signaling pathways delineated at present are very complicated and the precise role of their definite links (and definite compounds that could be identified) is still not known [82].

In summary, the evidence reviewed here shows the role of the main neurotransmission systems in different brain structures in audiogenic behavior and kindling.

Finally, determining how these neurotransmitter circuits are involved in the modulation of seizures and whether they can be activated by a seizure itself may help to understand the mechanisms regulating the occurrence of seizures, as well as helping to develop future therapies using the physiologic basis of neurotransmitter circuits and the pathophysiologic basis of audiogenic seizures. Further investigations using neurochemical approaches are necessary to understand the mechanisms of audiogenic seizures and to develop a new therapy.

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