Review

Rodent Models of Audiogenic Epilepsy: Genetic Aspects, Advantages, Current Problems and Perspectives

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Abstract: Animal models of epilepsy are of great importance in epileptology. They are used to study the mechanisms of epileptogenesis, and search for new genes and regulatory pathways involved in the development of epilepsy as well as screening new antiepileptic drugs. Today, many methods of modeling epilepsy in animals are used, including electroconvulsive, pharmacological in intact animals, and genetic, with the predisposition for spontaneous or refractory epileptic seizures. Due to the simplicity of manipulation and universality, genetic models of audiogenic epilepsy in rodents stand out among this diversity. We tried to combine data on the genetics of audiogenic epilepsy in rodents, the relevance of various models of audiogenic epilepsy to certain epileptic syndromes in humans, and the advantages of using of rodent strains predisposed to audiogenic epilepsy in current epileptology.

Keywords: audiogenic epilepsy; genetic epilepsy models; epilepsy-associated genes; KM rats; WAR rats; GASH/Sal hamster strain; epileptogenesis

1. Introduction: The Relevance of the Problem

Epilepsy is a heterogeneous group of chronic neurological diseases characterized by recurrent seizure fits. It is one of the most common neurological problems of our time. According to WHO, the incidence of epilepsy varies from 4 to 14 cases per 1000 people in different countries. Being a life-threatening disease, epilepsy leads to a significant reduction in quality of life as well. Severe cases may be accompanied by numerous complications: seizure induced injuries, cerebral ischemia, cardiogenic shock, headaches, intellectual disability, psychosis, hallucinations, depression, and status epilepticus (prolonged seizures or series of seizures without recovery of consciousness between them) [1–6].

Epilepsy can develop as an independent disease or could be a consequence of other pathologies, such as brain developmental disorders, ischemic stroke, neurodegenerative diseases, traumas, infections, etc. [7,8]. Today, the leading role in the pathogenesis of most forms of epilepsy is recognized to have a genetic component. More than 1000 genes are known whose mutations are associated with the development of epilepsy [9,10]. These data, as well as the growing understanding of the molecular mechanisms of various mutations that affect neuronal activity in different brain regions, open up prospects for a targeted impact on the pathogenesis of this disease. A large number of antiepileptic drugs (AEDs) and clinical protocols for epilepsy drug treatment have been developed, but there is also high pharmacoresistance (up to 30% of epilepsy cases) [11]. In addition, many AEDs are characterized by severe side effects as well [12–15], and this requires the search for new, more effective and less toxic anticonvulsants.
The study of epilepsy mechanisms and the development of new methods of its treatment, including the discovery of new pharmacological targets, require adequate animal models. Numerous experimental techniques of epileptic seizures and status epilepticus induction were introduced, including the electrical stimulation of certain brain regions or infusion or application of convulsants, i.e., substances that provoke the development of seizures [16–19]. However, most of these approaches do not allow studying the genetic causes of epilepsy. For this reason, a large number of investigations are focused on deriving animal strains with a genetic predisposition to seizures, which could be either the result of directed genetic knockouts or classical selection experiments [20–25]. Models of inherited audiogenic epilepsy (AE) described in several rodent species stand out favorably among such strains. Their advantages are the stable seizure pattern, easy seizure induction without invasive influences, easily visualized seizure, thus requiring no prolonged observation and/or EEG recording to identify seizure occurrence (procedure inherent for spontaneous seizure models), and high reproducibility of results inherent as well. Based on AE models, it is possible both to search for new genes involved in the development of seizure states and to test new AEDs [26].

In this paper, we attempt to systematize data on the genetic mechanisms associated with AE in rodents and evaluate the possibility of applying the results to human epilepsy science. The applicability of AE models for testing new anticonvulsant compounds as well as for the basic research of epilepsy molecular mechanisms will be assessed.

2. Classification and Etiology of Epilepsy

Epilepsy is a heterogeneous group of syndromes that differ significantly from each other both in the clinical manifestations and in the etiology of the disease. The International Classification of Epilepsy and Epileptic Syndromes was adopted in 1989 and was subsequently revised by The International League Against Epilepsy (ILAE) [27]. Currently, human epilepsy is classified according to the “Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology” [27].

According to the updated version of epilepsy classification, each particular case is considered at several diagnostic levels. The first one is the type of seizure, the second is the type of epilepsy (focal, generalized, combined focal-generalized, and unclassified), followed by the definition of the epileptic syndrome, and finally, the etiology of epilepsy. The main manifestation of epilepsy is seizures that are divided into atonic (loss of consciousness and muscle tone and subsequent rapid recovery), clonic (irregular short-term spasms characterized by a rapid change in periods of contraction and relaxation of skeletal muscles), tonic (prolonged tension of the muscles of the limbs or the entire body, including respiratory muscles), and myoclonic (rapid contraction of various muscle groups). There are also non-convulsive epileptic seizures (absences) in the form of a momentary loss of consciousness [28].

Depending on the degree of brain structure involvement, there are focal, generalized, and combined forms of epilepsy. In focal epilepsy (e.g., temporal lobe epilepsy), a local epileptic focus is formed in one of the hemispheres of the brain, most often as a result of the formation of focal pathology (stroke, tumor) or trauma. In generalized epilepsy, an abnormal excitation spreads widely in the brain; in this case, seizures are associated with the simultaneous activation of many areas of both hemispheres [29,30]. In the case of a combined form of epilepsy (e.g., Dravet syndrome), both focal and generalized seizures may be recorded [31].

The next level of classification identifies the type of epileptic syndrome as a set of characteristics (seizure type, EEG and neuroimaging data, and comorbidity traits) [32]. In some cases, a seizure is provoked by clearly identifiable specific triggers that could be external (visual, vestibular, auditory, or tactile stimuli) or internal stimuli (elementary or higher neural functions such as certain movements, emotions, or calculations). In this
case, one can identify a reflex form of epilepsy. Reflex epileptic seizures could be focal or generalized, and in some cases occur along with spontaneous seizures [33].

The next stage of classification establishes the etiology of the disease. According to the new classification, all cases of epilepsy are divided into structural, genetic, infection-related, metabolic, and immune categories, as well as cases with unknown etiology. Structural epilepsies are determined by a marked defect in brain morphology (due to developmental abnormality, trauma, or stroke) [7,8]. Thus, structural epilepsies can be either genetic (with severe CNS developmental abnormalities due to mutations) or acquired. Genetic epilepsies are caused by mutations that are not accompanied by significant anomalies in CNS development and morphology but cause disruptions in brain cell functions (e.g., mutations of ion channel genes) [34,35]. Metabolic epilepsies are the direct result of a known or suspected metabolic disorder, with epilepsy dominating the clinical picture. They are often well-known inherited metabolic diseases, such as porphyria, amino acid metabolism disorders, creatine disorders, and pyridoxine-dependent seizures. Thus, metabolic epilepsy in most cases can also be determined by genetic factors [36,37]. Infectious epilepsies develop as a consequence of past or chronic neuroinfections, including intrauterine (neurocysticercosis, tuberculosis, HIV, viral encephalitis, toxoplasmosis, Zika fever, and COVID-19) [38–41]. Finally, immune (or autoimmune) epilepsies develop as a direct consequence of autoimmune processes. An example is encephalitis with the detection of autoantibodies to NMDA receptors [42–44]. In some cases, we can run into cases of the combined form of epilepsy. For example, some infectious agents often induce autoimmune processes that lead to structural brain damage with epilepsy as clinical manifestations (in such cases, epilepsy combines infectious, autoimmune, and structural etiologies) [45–47]. Thus, the new classification of epilepsy allows highlighting the main cause of the disease: purely genetic, genetic in combination with structural disorders, structural disorders due to non-genetic causes, etc.

3. Pathophysiological Mechanisms of Epilepsy

At present, the molecular mechanisms of increased neuronal excitability in epilepsy are known in general terms and require further study for picture refinement. The immediate cause of epileptogenesis is the increased excitability of neuronal groups due to the imbalance of excitatory and inhibitory neurotransmitter systems. Such disturbances lead to a prolonged depolarization of the neuronal membrane, which causes a decrease in the threshold for action potentials and massive activation, spreading from the primary epileptic focus to other CNS structures.

The main changes in excitatory systems during epileptogenesis affect the glutamatergic system. The excessive activation of ionotropic NMDA and AMPA glutamate receptors is the one of most common causes of epileptogenesis, which occurs during and after an epileptic seizure. A quantitative increase in ionotropic NMDA receptors in the brain of epileptic patients and in many epilepsy animal models has been demonstrated. This change could also be accompanied by a shift in the subunit composition of receptor proteins, mainly due to an increase in calcium-permeable subunits [48,49]. The characteristics of type II metabotropic glutamate receptors (mGluRII) located on the presynaptic membrane and controlling the activity of glutamatergic synapses could also be affected [50–52]. Quantitative and qualitative rearrangements of ionotropic and metabotropic glutamate receptors lead to higher intensity of glutamatergic signaling, increasing seizure readiness.

The dopaminergic system is involved in the regulation of glutamatergic synaptic transmission activity through modulation of mitogen-activated kinase (ERK1/2) activity (part of MAPK signaling pathway) [53–55]. ERK1/2 stimulates the expression of NMDA receptors and some other synaptic proteins, which increases synaptic excitability [56,57]. In addition, ERK1/2 phosphorylates synapsin I, promoting the release of glutamate from presynaptic vesicles [58]. The stimulation of D1 receptors causes the phosphorylation and activation of ERK1/2, whereas the activation of the D2/D3-dependent pathway has the opposite effect [59–61]. Thus, a shift in the balance of dopamine receptors toward an increase in D1 receptors leads to increased neuronal excitability, which has been observed.
in epileptic patients and model animals [62–64]. In addition to the glutamatergic and
dopaminergic systems, the other neurotransmitter systems were also shown to be affected
in epileptogenesis development [65–71].

The decrease in neuronal excitability that has antiepileptic effects is based mainly on
the GABAergic system function. In cases of epilepsy development, the decrease in the
number of GABA \(_A\) receptors as well as changes in their subunit composition, including
those involving ERK1/2, has been demonstrated both in humans and in animal models [72].
In some cases, decreased GABA production and/or increased GABA reuptake in synapses
have been shown [73–78].

In addition to the imbalance of neurotransmitter systems, changes in the activity
and/or amount of potential-dependent ion channels, in particular, Na-, K- and Ca channels,
play an important role in epileptogenesis, leading to the increased entry of Na\(^+\) and Ca\(^{2+}\)
ions into the cell and K\(^+\) ions exiting from the cell [35,79–81]. These changes decrease
the voltage of membrane potential and the threshold of neuronal excitation, leading to
the generation of the action potential. Increased intracellular Ca\(^{2+}\) concentration could
also lead to the activation of glutamate release, decreased GABA levels, and activation of
proinflammatory signaling cascades [81,82]. Together with neuronal excitation changes,
an important role in epileptogenesis is now ascribed to glia. Reactivated astrocytes, in
particular, increase the concentration of glutamate and K\(^+\) ions in the nervous system, con-
tributing to the spread of neuronal excitation [83]. Unfortunately, even a brief description
of this issue is beyond the scope of this review. To get acquainted with the problem, we can
recommend other reviews [84,85].

Thus, we can summarize that one of the main causes of epilepsy is disturbance in the
normal activity of ion channels (both receptor- and potential-dependent). These disorders
may result from mutations in the genes encoding the respective ion channels, changes in the
signal cascades activity, affecting their expression, metabolic disorders (as a result of muta-
tions in enzyme genes), mutations leading to the abnormal development of the nervous
system resulting in the abnormally high activity of “excitatory” neurons and decreased
activity of “inhibitory” ones, and/or in excessive astrogliosis [86]. Neuroinflammation
leading to astrocyte activation may also play an important role in the development of
epilepsy [87,88]. The changes described initiate the development of an epileptic focus,
i.e., a pool of neurons with prolonged membrane depolarization. Due to the diffusion of
glutamate and potassium ions into the intercellular space, the excitation thresholds of the
adjacent neurons also decrease, and the excitation of such neuronal pool synchronizes. The
excitation, born in the primary epileptogenic focus, spreads to other parts of the brain,
and the dynamic epileptic system with the development of secondary epileptogenic foci
emerges, which in turn can acquire determinant properties [89].

Below, several genetic causes are analyzed concerning the changes in neuronal ex-
citability that may lead to the development of epilepsy.

4. Genetic Aspects of Human Epilepsy: Brief Review

A significant number of epilepsy cases could be considered inherited diseases with the
possibility of identifying mutations responsible for the development of seizures [9,10,90].
Genetic variants sometimes could be identified, which influence the likelihood of epileptic
seizures emergence in cases of focal brain lesions (strokes, tumors) [10].

Broad-scale epidemiological studies provide convincing evidence for the important
role of the genetic factor: the risk of developing epilepsy in patients with a family history
of seizure disorders in close relatives is 8 to 12%, which is significantly higher than the
general population’s respective average risk (approximately 0.5 to 1%) [91–94]. To date,
about 1000 genes associated with the development of various forms of epilepsy have been
identified [9,10]. Some forms of hereditary epilepsy are monogenic, being inherited both
by autosomal dominant (e.g., sodium channel alpha-subunit SCN1A gene mutations in
Dravet syndrome or familial febrile seizures) [95] and autosomal recessive types (in case
of TBC1D24 gene mutation in familial infantile myoclonic epilepsy) [96]. There are forms
of epilepsy and complex diseases that include seizures as one of the symptoms that are inherited as X-linked in a dominant or recessive type (CDKL5 gene mutations in early infantile epileptic encephalopathy or SYN1 in X-linked epilepsy with variable learning disabilities and behavior disorders and some forms of refractory epilepsy) [97–99]. However, most cases of epilepsy appear to have a polygenic basis and are determined by a combination of many specific alleles of certain genes associated with CNS development in the prenatal and early postnatal periods [9,10,100–103]. Even in cases of the monogenic inheritance of epilepsy, the severity and the pattern of epileptic seizures may depend largely on the genetic background [9]. Individual cases, diagnosed as the same form of epilepsy, very often happen to be caused by different single mutations or combinations of many “unfortunate” alleles. For example, in early infantile epileptic encephalopathy (EIEE), more than 40 genes may be associated with the development of the disease [9]. On the other hand, mutations in the same gene could be found in different epilepsy phenotypes; for example, mutations in the GABRA1 gene are associated with EIEE, childhood absence epilepsy (CAE) and juvenile myoclonic epilepsy (JME) [104–106]. Finally, many genetic variants do not lead to epilepsy in 100% of cases but are expressed in cases of combination with adverse external conditions and/or traumatic influences (stress, sleep deprivation, stroke, and infections) [107]. In some cases, mutations leading to the development of epilepsy occur de novo, i.e., they were absent in parents but found in a child, sometimes in the form of chimerism (due to a somatic mutation that occurred early in embryogenesis) [108]. Thus, it is extremely difficult to systematize the genetic causes of epilepsy, both because of the diversity of its clinical manifestations and because of the many combinations of genetic variants that can lead to different results in terms of certain forms of epilepsy development.

In general, the diversity of genes associated with epilepsy can be divided into several large functional groups [9,10,109]. A significant percentage of epilepsy cases with autosomal dominant inheritance are due to mutations in genes encoding various subunits of potential-dependent and receptor ion channels: sodium, potassium, calcium, chloride, GABA_A-receptor subunits, NMDA-receptors and acetylcholine receptors. Sometimes, such cases are grouped under the general name “channelopathies”. Mutations of these genes directly lead to excitation/inhibition imbalance in the central nervous system and, as a consequence, to the development of epileptic seizures. The next groups of genes associated with the development of epilepsy are those encoding enzymes and enzyme activity-regulating proteins [110–113]. Finally, the less-represented groups include genes responsible for cell adhesion, signal transduction proteins, membrane trafficking proteins, and cytoskeletal proteins. In addition, in some cases, mtDNA mutations that disrupt the functions of mitochondrial proteins and tRNAs can lead to the development of epilepsy [114,115].

Disruption in these gene functions can lead to the development of epilepsy in different ways (Figure 1). Mutations in genes encoding subunits of potential-dependent and receptor ion channels directly lead to the persistent depolarization of neuronal membranes and, consequently, to their epileptization. Such disorders (channelopathies) are responsible for approximately 15% of epilepsy cases [83,116]. Disorders in the functions of receptor genes, signal transduction proteins and membrane trafficking proteins, cytoskeleton proteins, and mitochondrial enzymes initiate a more complex chain of events. Such disorders can lead to a shift in the balance of neurotransmitters, or indirectly lead to the development of structural or metabolic epilepsy, which could be the consequences of developmental anomalies of the brain, metabolic syndromes, or neurodegeneration [113]. A direct cause of these types of epilepsy could lie, particularly, in changes of signaling cascades activity, including those regulating neurotransmitter release and ion channel gene expression (e.g., MAPK and mTOR) [10,57,117–120]. The imbalance in signaling cascades activity can lead, also, to cell cycle deteriorations during neuronal proliferation; the development of mitochondriopathy; excessive apoptosis, affecting definite types of neurons; the development of neuroinflammation; and other mechanisms of epileptogenesis, which has been mainly studied in animal models [121–126]. Thus, some cases of genetically determined epilepsy
are the result of disturbances in the complex networks regulating the development and homeostasis of the nervous system.

**Figure 1.** Mutations leading to the development of epilepsy may affect genes directly involved in the generation and transmission of nerve impulses (group I), or genes responsible for the development and metabolism of the nervous system (group II). In the second case, violations of the functions of ion channels and specific synaptic proteins occur indirectly.

5. Animal Models of Epilepsy

Creating experimental models of epilepsy in animals (mainly in rodents) is the main way to study the pathophysiological mechanisms of seizure development and to search for new targets of new AEDs. There are many such models available today, but no single model can fully capture all the features of epilepsy and describe all the variety of symptoms observed in humans [127].

Traditionally, the most widely used models are those in which epileptic seizures in mice or rats are induced either by repeated stimulation of various brain structures with an electric current or by administration of pharmacological drugs that decrease the seizure barrier. Such exposure has been called “kindling”. Kindling is a phenomenon in which, in response to repeated epileptogenic stimuli of subthreshold intensity, the convulsive threshold of the brain decreases, and spontaneous convulsions consistently develop. The kindling process suggests that it starts with a limited number of neural circuits and subsequently recruits additional circuits as the behavioral component of the seizure progresses to seizures [128]. The classical variant of electrical kindling is the repeated subliminal electrical stimulation of limbic structures of the brain, which results in the development of epileptic seizures. Pharmacological kindling involves repeated exposure to subthreshold doses of convulsants, such as pentylentetrazole (PTZ) or kainate, resulting
in the development of spontaneous seizures. Kindling models allow the induction of spontaneously recurrent seizure development, as commonly seen in patients with temporal lobe epilepsy [129]. The historically more “old” chronic epilepsy model is cobalt-induced epilepsy [130,131]. The rocking of the epileptic system also occurs after a powerful single epileptogenic exposure, such as pilocarpine or kainate, inducing status epilepticus (post-status models). Post-status patterns are most consistent with refractory forms of epilepsy because they are accompanied by neuronal death, aberrant neurogenesis, development of encephalopathy, etc. [132].

The “gold standard” in the search for new potentially active (AEDs) are simple models of acute seizures: the maximal electroshock test (MES) and subcutaneous injection of PTZ in mice and rats. These models have been used for the testing and discovery of most potential AEDs [133,134]. The advantage of these epilepsy models is that they do not require special strains of laboratory animals. Their disadvantage is that they do not reflect such an important aspect as the contribution of genetic factors in epilepsy development.

Therefore, genetic models of seizures, i.e., animal strains with an innate predisposition to epilepsy, are widely used in laboratory practice. These models make it possible to study the contribution of individual genes, groups of genes, and related signaling cascades in epilepsy development, which is necessary to find new AEDs targets. Today, there are genetic strains derived from several animal species (baboons, chickens, rats, mice, hamsters, and felines) that are seizure-prone (both spontaneous and refractory convulsions). For example, the seizure response in Papio papio baboons and Fepe chicken strains could be induced by rhythmic flashes of light, and in cats and many rodent strains by a sudden loud sound (audiogenic epilepsy, AE) [26]. Photosensitive epilepsy is quite common in epileptic patients, whereas audiogenic seizures in humans are very rare; their closest analogs in humans are startle-induced seizures [26]. Nevertheless, it is the AE-prone rodents that are commonly used as epilepsy models in laboratory practice because their reaction to a seizure-provoking stimulus (sound) is easily reproduced, and they display the standard type of seizure fit. Standard and experimental AEDs reduce the intensity of seizures in AE-prone rodents, and thus these strains could be used for the search for new AEDs and analysis of their anticonvulsive mechanisms [26,135]. Therefore, rodent AE-prone strains can generally be considered to be sufficiently fit for these studies, not only for human reflex epilepsy.

Genetic abnormalities in rodent AE-prone strains and in human epilepsy may coincide, but in some cases, they demonstrate differences as well (see below). On the other hand, as mentioned earlier, even in epilepsy clinics, a huge variety of both symptomatic manifestations and their genetic causes could be found in different patients.

Historically, work on genetic models of epilepsy in rodents began in the early 1900s, when the outbred strain of albino Wistar rats (existing till now) was derived in the Wistar Institute (Philadelphia, PA, USA). A certain percentage of these animals developed epileptiform seizures in response to loud sounds [21]. Different sources indicate different percentages of Wistar rats sensitive to sound, from 15 to 50%; apparently, sensitivity varies considerably in different Wistar substrains maintained in isolation in different catteries for many years [121,136]. Subsequently, a similar phenomenon of AE-proneness was found in mice [137,138]. In general, one may conclude that many laboratory rodent strains are generally characterized by increased sensitivity to loud sounds, which rodents do not encounter in a natural habitat, and which is presumably the hypertrophied startle reaction in response to alarming stimuli [139]. Therefore, the selection of strains predisposed to AE in rodents is rather quick, as rodent CNS has presumably the “stereotyped pattern” of reaction to strong sound. Thus, mutation events, affecting different genes in such a cascade, enhance the reaction up to the pathological level. A wide set of rodent strains (including rats, mice, and hamsters) with genetically determined AE were obtained. Animals of these strains respond to loud sounds by displaying generalized seizures. In all AE-prone strains, seizures proceed according to a similar pattern. In response to 100–120 dB sound onset, the first phase of a seizure develops (it is the so-called “wild run stage”), during which
the animals rush around the cage or sound chamber. In essence, it is the defense reaction as an attempt to avoid sound, although with an admixture of involuntary movements, indicating the start of convulsions proper (sometimes this stage is called the “clonic run phase”) [139]. The next stages of the seizure proceed: clonic and tonic convulsions, followed by a post-convulsive state (catalepsy, or prolonged excitation) [137,140,141].

The first strain of rats 100% predisposed to audiogenic epilepsy was obtained at Moscow State University by L.V. Krushinsky, L.N. Molodkina and D.A. Fless, which was derived in the late 1940s from the Wistar strain (Krushinsky-Molodkina, abbreviated KM strain) [142]. Independently the WAR (Wistar audiogenic rat) strain was developed at the University of São Paulo, Brazil in the 1990s [25]. In the late 1950s, two GEPR (genetically epilepsy-prone rat) strains, GEPR-3 and GEPR-9, were bred at the University of Arizona based on the Sprague Dawley outbred rat strain, maintained further as independent strains with different levels of AE intensity [143]. The strain of AE-prone rats (P77PMC) also was selected in China [144,145]. The AE-prone hamster strain GASH/Sal (genetic audiogenic seizure hamster, Salamanca) was obtained in the University of Salamanca [146]. There are also several AE-prone mouse strains that were obtained as a result of spontaneous mutations: Frings, DBA/2, Black Swiss, 101/HY and BALB/c [137,138,147,148]. It has now become a rather common practice to derive AE models by the knockout of genes, presumably associated with epilepsy—they are Lgi1 mice, Fmr1 strain, etc. [20,26]. Thus, there is the set of strains with a similar AE phenotype, but with different genetic backgrounds and different genetic causes of this pathology.

Analysis of gene expression profiles and localization of respective mutations as well as the comparisons with each other and with the original AE-non-prone strains could allow revealing both common genetic patterns characteristic of AE and individual strain characteristics, leading to the same result: the development of AE. Using AE-prone strains, it is also possible to compare genetic changes with already established genetic causes of human epilepsy in order to find common mutations and molecular mechanisms leading to seizure proneness. Thus, rodent AE-prone strains increase the scientists’ potential for searching for mutations leading to epilepsy development.

6. Pathophysiology of Audiogenic Seizures

Studies of the biochemical peculiarities of AE-prone animals performed in many studies demonstrate numerous “deviations” from the AE-non-prone phenotype practically in all brain neurotransmitter systems tested: glutamatergic, GABAergic, monoaminergic, and purinergic [149]. Numerous studies show that, at the level of biochemical changes, the mechanisms of epileptic seizure in rodents with AE (as in other epilepsy models) and in human epilepsy, in general, are reduced to an imbalance between the glutamatergic and GABAergic systems. In AE-prone rodents, impaired mitochondrial functions, neuroinflammatory processes and increased levels of MAPK signaling cascade activity have also been demonstrated [66,150–152].

The well-known similarity of audiogenic seizure fit is based on the similar pattern of brain excitation spreading from the cochlear nuclei up to the corpora quadrigemina (in the case of generalized clonic–tonic seizures) and up to the forebrain structures in the case of audiogenic kindling phenomena, developing after repetitive sound exposures. The AE seizure initiates as the abnormal acoustic impulsion arrives in the inferior colliculi (IC). The details of the IC structures’ involvement in seizure initiation have been described in detail with the GEPRs AE model [153,154], as well as in WARs and in mice [155–158]. Bilateral lesions of the IC, lateral lemniscus and the connections between these structures blocked audiogenic seizures expression in rats and mice [156,157,159]. Further, the superior colliculi (SC) activated with the spread of abnormal excitation into brain stem nuclei and further into spinal projections [160]. Rybak and Morin (1995) showed [161] (using immunocytochemistry and in situ hybridization) a significant increase in GABA level and a larger number of GABAergic neurons in the central nucleus of the IC in GEPR-9 strain in comparison to Sprague Dawley AE-non-prone rats. In GEPRs IC, the number of small
cells (<15 mcm) was also increased. The IC structure was also affected similarly in KM rats (derived independently from GEPRs). In general, the marked phenotypic similarity in brain structure involved during AE fit is characteristic of rat strains selected in Russia, USA, France and Brazil. The phenomenology of AE seizures as well as numerous data on so-called “priming” procedures in several mouse and rat genotypes were extensively presented in [21]. The role of the acoustic system of AE-prone mouse and rat strains was described in detail earlier [149]. Recently, the signs of acoustic system peculiarities were also demonstrated in GASH/Sal as well [162].

Rodents (rats, mice and Guinea pigs) could be made AE-prone with the injections of metaphit, the drug, which is the ligand of phencyclidine receptors [163,164]. This is another confirmation of the general AE-proneness pattern, and the prevalence of brain excitation circuits. There is experimental evidence suggesting that delta sleep inducing peptide (DSIP) reduced audiogenic seizures, induced by metaphit injections [165]. In general, the effects of this peptide on brain functions are numerous [166,167]. However, the most interesting for the problem of audiogenic seizures mechanism is the evidence of the DSIP influence on the brain antioxidant and glucocorticoid systems [168,169]. It is worth mentioning that the neuronal membrane lipid content in rats of KM strain changed significantly (both quantitatively and qualitatively, in striatum and brain-stem tissues) as the result of audiogenic seizure fit [170]. The data may suggest that the anticonvulsant effect of DSIP was realized via the regulation of membrane processes shifted by metaphit action.

7. Different Models of Audiogenic Epilepsy in Rodents

7.1. Overview of AE Strains Type

Among AE-prone rodents already described, there are strains with a monogenic inheritance of this trait, and several strains with a presumably polygenic inheritance of the predisposition to AE are now maintained [26]. The new rodent AE strains demonstrate the AE monogenic autosomal dominant or recessive inheritance. They were derived either by targeted genetic knockout or N-ethyl-N-nitrosourea mutagenesis followed by screening for mutations of the target gene [171]. This approach allows the unambiguous association of certain mutations with epilepsy in parallel with data on the sequencing of large epilepsy patient cohorts in search for orthologous gene mutations. There are also rodent strains with monogenic epilepsy derived by subsequent selection after the discovery of respective spontaneous mutations. Strains with a polygenic type of epilepsy inheritance were also obtained independently in different laboratories. These are considered to be the more preferable models of human seizure states since a significant part of epilepsy clinical cases is caused by a combination of multiple “unfortunate” alleles of different genes. At the same time, the localization of specific mutations leading to the development of AE in these strains is a much more difficult task. Brief information about the AE models described in this review is given in Table 1.

7.2. Monogenic Models

AE in the mouse strain derived from the Fmr1 gene knockout was found as a model of human Martin–Bell syndrome (fragile X chromosome syndrome). In patients, this pathology develops as the result of CGG trinucleotide expansion in the X chromosome, which leads to hypermethylation of the promoter region of the FMR1 gene and a decrease in its expression [172]. The protein product of this gene (fragile X mental retardation protein, FMRP) is responsible for the transport of mRNAs along dendrites and the regulation of the local translation of mRNAs in synapses. The loss of function of this protein leads to the overexpression of glutamate receptors and impaired synaptic plasticity, which in turn results in intellectual disability and autism, macroorchidism, sensory hypersensitivity, and with up to 15% of male and 5% of female patients displaying seizures [173]. Mice with Fmr1 gene knockout show a phenotype with several similarities to humans: enlarged testes, hyperactivity and mild spatial learning impairment in the Morris water maze, as well as AE [20,174]. The manifestation of audiogenic seizures in fragile X mice is age-
dependent. The peak of susceptibility to auditory stimuli in homozygous Fmr1-/ females was observed at 22 days of age, after which the intensity of seizures decreased [175]. In another study [176], males of the same genotype showed no convulsions before the age of 10 weeks. At the age of 10–12 weeks, 57% of the fragile X KO mice displayed audiogenic seizures. After the injection of the Fmr1 transgene, the susceptibility to audiogenic seizures in this strain was reduced [174]. In Fmr1-/ mice, seizures were shown to be the result of excitatory metabotropic glutamate receptors and inhibitory GABA_B receptors signaling imbalance [177].

In the Frings mice strain, AE is caused by one base deletion at nucleotide 7009 of the Vlgr1 gene (also known as GPR98, MASS1, Neurepin1 and ADGRV1), resulting from spontaneous mutation when the truncated protein variant expresses [22–24]. The deletion of exons 2 to 4 of the Vlgr1 gene also leads to the development of AE in mice [23]. The Vlgr1 gene encodes very large G-protein coupled receptor 1, a member of the adhesion-GPCR (G protein-coupled receptors) family, highly expressed in the embryonic central nervous system [178]. Mutations of the ADGRV1 (VLRG1) gene in humans are associated with the development of myoclonic epilepsy and Usher syndrome [24]. The Vlgr1 protein (referred to by the authors as MASS1) inhibits ubiquitinylation of the myelin-associated glycoprotein (MAG) involving the PKA and PKC signaling cascades [179]. Presumably, the Vlgr1 protein dysfunction (inducing epileptogenesis) is associated with impaired axon myelination. At 3 weeks of age, about 90% of Vlgr1-/- mice responded to sound exposure with wild-type running and seizures. By the age of 8 weeks, this percentage of AE-proneness decreased to 40%, with less than 20% of animals displaying seizures [180].

Vlgr1-mutated mice represent a “monogenic” model in which the manifestation of AE was highly dependent on genetic background [180]. Vlgr1-mutated mice backcrossed with C57BL/6 and 129S1/SvImJ strains were obtained. The 129-backcrossed Vlgr1-mutated mice showed a higher incidence of wild running than C57BL/6-backcrossed mice, and C57BL/6-backcrossed Vlgr1-mutated mice demonstrated significantly higher mortality after sound exposure than 129-backcrossed mice.

The genetic variant of the Vlgr1 gene with 14198T > C substitution was also confirmed in the WAR AE model, evidencing the causal connection of this gene with AE proneness [181]. Another gene with Mendelian inheritance associated with multiple central nervous system pathologies including epilepsy in humans is WWOX (WW domain-containing oxidoreductase), previously described as a tumor suppressor [182]. Bi-allelic mutations in this gene cause a syndrome called WWOX-related epileptic encephalopathy (WOREE) with epilepsy, severe developmental delay, ataxia and premature mortality in childhood [183,184]. To date, the role of the WWOX gene in CNS development is not known in detail. A spontaneous Wwox mutation in inbred Wistar-Imamichi rats leads to dwarfism, postnatal lethality, male hypogonadism and a high incidence of epilepsy (lethal dwarfism with epilepsy, LDE rats) [185]. Homozygous Wwox-null mutated rats display hippocampal region vacuolization and AE in 95% of animals. The tissue-specific deletion of the Wwox gene in mouse CNS led to a significant decrease in the transcript levels of genes involved in myelination, decreased axon myelination and reduced maturation of oligodendrocytes. There is a known association between myelination disorders and epilepsy [186]. Wwox-null mutared mice were predisposed to brain hyperexcitability, intractable epilepsy, ataxia and postnatal lethality [183]. The restoration of Wwox expression by neonatal gene therapy using an adenoviral vector carrying Wwox cDNA under the control of the synapsin I gene promoter reduced premature mortality and predisposition to AE, as well as promoting partial normalization of the development of Wwox-mutated mice [187].

Predisposition to AE and spontaneous death after seizures was shown in serotonin 5-HT2c receptor mutant mice [188]. Audiogenic seizures in this strain started to develop at 60–75 days of age, and by day 120, 100% of animals tested were AE-prone. Data on the role of the serotonergic system in epilepsy development are inconsistent and depend on the epilepsy form (in humans) or animal model [189–193].
One more gene of interest in terms of inherited causes of epilepsy is GABRB2, which encodes the β2-subunit of the gamma-aminobutyric acid receptor—GABA_A. In humans, various mutant alleles of this gene determine the development of a wide range of epilepsy forms [194–196]. A Gabrb2-/− knockout mouse strain with a characteristic schizophrenia-like phenotype and AE was obtained [197]. Interestingly, this strain showed signs of neuroinflammation indicated by increased brain levels of the oxidative stress markers, malondialdehyde and proinflammatory cytokines.

The dysfunction of the Lgi1 (leucine-rich repeat glioma-inactivated) protein, originally described as a suppressor of tumor growth and metastasis [198] is associated with epilepsy in humans. Unlike most proteins whose gene mutations are associated with the development of epilepsy, Lgi1 is a secreted protein, the ligand of ADAM22 and ADAM23 (disintegrin and metalloproteinase domain-containing proteins). Lgi1 binds to ADAM22 at the postsynaptic membrane and ADAM23 at the presynaptic membrane, mediating AMPA receptor and potassium channels activity, and thus participating in the regulation of synaptic activity [199,200]. The increased expression of Lgi1 can also inhibit ERK1/2-cascade activity [201]. Finally, Lgi1 regulates the activity of inwardly rectifying K+ (Kir) channels, which contain astrocyte Kir4.1 subunits (Kir4.1 channels) involved in the K+ homeostasis in the CNS [200]. In humans, at least 43 mutations in the LGI1 gene are known to be associated with autosomal dominant lateral temporal lobe epilepsy (ADLTE) [202]. The autoimmune reaction with the development of autoantibodies to Lgi1 causes a form of autoimmune epilepsy [42,43]. Finally, loss-of-function mutations in the KCNJ10 gene encoding Kir4.1 cause the epileptic disorders known as “EAST” (epilepsy, ataxia, sensorineural deafness, and tubulopathy) [200]. Mutations in the Lgi1 gene leading to epilepsy cause impaired secretion of the Lgi1 protein [200,203]. Rats carrying a missense mutation (L385R) in the Lgi1 gene were obtained. Homozygous Lgi1-mutant rats were predisposed to early-onset spontaneous epileptic seizures and died prematurely. Heterozygous Lgi1-mutant rats were more susceptible to audiogenic generalized tonic–clonic seizures than wild-type rats. Lgi1 knockout mice with a similar phenotype were also obtained [204]. The seizure threshold in Lgi1 heterozygotes decreased with age (13% sensitive animals at 21 days of age, and 52% at 28 days of age) [204].

Recently, a rat strain with a homozygous knockout of the Kcnj16 encoding K-channel Kir5.1 gene, leading to the development of AE, was obtained as one more model of channelopathy, leading to epilepsy. Mutations in the KCNJ16 gene were previously found in patients with epilepsy [205,206].

The Black Swiss mouse strain is characterized by partial hearing loss and susceptibility to AE, which reaches a maximum at 2 to 3 weeks of age and then gradually decreases so that by 6 weeks of age, the mice become resistant to loud sounds. A locus within chromosome 10 responsible for the predisposition to AE in Black Swiss mice (juvenile audiogenic monogenic seizure 1, jams1) was identified [207]. Originally, two loci designated as age-related hearing loss (ahl5 at chromosome 10) and ahl6 (at chromosome 18) were hypothesized to be responsible for hearing loss, and it was believed that the ahl5 locus made the major contribution to deafness inheritance [208,209]. It was further shown that the ahl5 and jams1 loci partially overlap. A mutation in the Gipc3 (GAIP-interacting protein C terminus) gene, responsible for both progressive hearing loss and juvenile audiogenic epilepsy in Black Swiss mice, was identified [209]. The encoded protein, Gipc3, contains the PDZ domain, which plays a key role in the anchoring of the receptor proteins to the cytoskeletal components. The Gipc3 protein was shown to be co-localized with vesicular glutamate transporter 3 (VGLUT3) and myosin VI, which regulate glutamate release from presynaptic terminals in the inner hair cells, suggesting its possible involvement in excitation transfer by glutamatergic neurons at the level of vesicular transport [209]. Mutations in the GIPC3 gene are thought to induce autosomal recessive deafness (DFNB) but, according to the data available, are not related to human epilepsy [209].

In general, physiological and morphological abnormalities of the auditory system have been described in many rodent strains with AE, but the direct link between hearing
impairment and AE has not been confirmed. This suggests that both hearing system abnormalities and AE-proneness could have some common source, i.e., genetic changes leading to abnormal prenatal CNS development [149].

The strain of mice with the tremor phenotype was obtained as a result of a spontaneous mutation found in the Swiss-Webster mouse colony (University of São Paulo, Brazil). This strain is characterized not only by audiogenic generalized clonic seizures, but also by body tremor, ataxia, and decreased exploratory behavior. The tremor strain is characterized by increased expression (in comparison to wild type) of the Egr3 (early growth response protein 3) gene, which encodes a transcription factor controlling the expression of GABA_A and NMDA receptors [83,210,211]. To date, we have been unable to find data on the association of mutations in this gene with human epilepsy.

A knockout of eukaryotic elongation factor 1Bδ (eEF1Bδ) long isoform encoded by the Eef1d gene was obtained from the AE-non-prone C57BL/6J mouse strain. In the knockout mice, the sound-induced seizures were significantly more pronounced and observed in a higher percentage of animals [212]. This factor (eEF1Bδ) is a heat-shock-responsive transcription factor [213]. Mutation of this gene in humans leads to severe intellectual disability and microcephaly [214], whereas no significant developmental or behavioral disorders were identified in knockout mice [212]. Thus, not all genes with mutations leading to AE-proneness are associated with epilepsy in humans.

7.3. Models of Pyridoxine-Dependent Epilepsy and Angelman Syndrome

Mouse knockout of three genes from the family, encoding the proline and acidic amino acid-rich basic leucine zipper (PAR bZip) transcription factor, develops spontaneous and audiogenic seizures. The expression of these genes in most tissues obeys circadian rhythmicity, but in brain tissues they are expressed at almost invariable levels. The authors attribute the knockout effect of these transcription factors to the fact that one of their targets is the Pdxk gene encoding pyridoxal kinase, which converts vitamin B6 derivatives into pyridoxal phosphate, involved in amino acid and neurotransmitter metabolism. It was further shown that the resulting effect was mainly due to the knockout of one of the three PAR bZip coding genes, Tef (thyrotrrophic embryonic factor), as the strain with only the Tef gene knockout showed a similar convulsive phenotype [215]. The authors believed that this mouse strain could be a model of pyridoxine-dependent human epilepsy. However, in humans, this epilepsy is caused by other gene mutations that are also involved in vitamin B6 metabolism. They are ALDH7A1 gene (coding alpha-aminoadipic-semialdehyde dehydrogenase) and PROSC gene (pyridoxal-5′-phosphate binding protein). Perhaps the mouse model described could be closer to epilepsy caused by a mutation in the gene encoding the pyridoxal-5′-phosphate oxidase (PNPO) responsive to pyridoxal-5-phosphate administration, not to pyridoxine administration [216].

Human Angelman syndrome (AS) manifests as defects in intellectual and speech development, emotional retardation, general motor deficits, and epilepsy in 80% of cases. It is caused by a partial deletion of the 15q11.2-q13.3 region in the maternal chromosome, which leads to either loss or mutation of the UBE3A gene encoding the ubiquitin–protein ligase E3A (UBE3A) also known as E6AP ubiquitin–protein ligase (E6AP). This enzyme is involved in targeting proteins for degradation within the proteasome. Inheriting paternal allele mutation in the same locus leads to the development of Prader–Willi syndrome with more mild neurological manifestations. The molecular mechanisms of the pathophysiology and inheritance of this syndrome were previously described [217]. Mutations specifically affecting the UBE3A gene occur in 5 to 10% of AS. In more than 75% of cases, large-size deletions within the maternally inherited chromosome 15 appear, herewith the deletion includes not only the UBE3A gene, but surrounding sequences containing additional genes (namely GABRB3, GABRA5 and GABRG3, encoding different GABA_A receptor subunits) [218,219]. To date, several mouse models of AS with a characteristic phenotype have been obtained. The most commonly used model was generated by the deletion of the Ube3a exon 5 with a frameshift mutation [220]. Subsequently, several additional
Ube3a knockout models with different mutations of this gene were obtained (reviewed in [217]). The deletion of the GABRB3-GABRA5-GABRG3 gene cluster as a cause of AS was modeled by 1.6 Mb deletion of the region containing Ube3a, Atp10a and Gabrb3 genes or by deletion involving the Ube3a, Atp10a, Gabrb3-Gabra5-Gabrg3 cluster (and several other closely located mouse genes). Detailed phenotypic descriptions are not available for all these strains obtained, but all AS mouse models available showed audiogenic seizures which could be treated with AEDs [217,221].

7.4. Models with Polygenic or Unknown Inheritance

The first example of a putatively polygenic type of inheritance of AE in rodents is DBA/2J mice. Three loci presumably related to AE in this strain were identified: audiogenic seizure prone 1 (Asp1), Asp2, and Asp3 on chromosomes 12, 4, and 7, respectively [26,222]. Subsequently, evidence was obtained that the Asp1 and Asp2 loci were mainly responsible for the manifestations of AE [222]. Variations in the coding sequence of the Kcnj10 gene (localized on chromosome 1) leading to amino acid substitutions in the Kir4.1 potassium channel in DBA/2J relative to the C57BL/6B seizure-insensitive mice were also shown [223]. As cited above, mutations in the KCNJ10 gene cause epileptic disorders in humans [200]. It is assumed that the functions of the genes localized in the Asp1 and Asp2 regions are related to the regulation of Ca\(^{2+}\)-ATPase activity, which is important for synaptic function, in particular affecting the amount of calcium within the synapse, which, in turn, influences the neurotransmitter release from synaptic vesicles [26,224]. To date, these genes have not been identified. Impaired potassium channel activity and glutamate reuptake, in particular, reduced activity of Kir4.1 in astrocytes of DBA/2J mice in comparison with AE-non-prone C57BL/6, was demonstrated [225]. This observation supports the idea that Kcnj10 gene polymorphism could play a leading role in DBA/2J-C57BL/6 seizure threshold differences in connection with AE [223].

| № | Species | Strain | Gene | Protein Function | References |
|---|---------|--------|------|------------------|------------|
| 1 | Mouse   | Fmr1 knockout, model of Martin-Bell (fragile X chromosome) syndrome | Fmr1 | FMRP (fragile X mental retardation protein), mRNA transport | [161–164] |
| 2 | mouse   | Frings | Vlgr1 | Very large G-protein coupled receptor 1, cellular adhesion | [22–24,165–167] |
| 3 | rat     | LDE, lethal dwarfism with epilepsy rats | Wwox | WW domain-containing oxidoreductase | [172] |
| 4 | mouse   | CNS-specific Wwox knockout mice | Wwox | WW domain-containing oxidoreductase | [173] |
| 5 | mouse   | 5-HT2c receptor mutant mice | Htr2c | Serotonin receptor | [175] |
| 6 | mouse   | Gabrb2/- knockout | Gabrb2 | β2-subunit of the gamma-aminobutyric acid receptor | [184] |
| 7 | rat     | Lgi1-mutant rats | Lgi1 | Secreted protein, modulator of disintegrin and metalloproteinase domain-containing proteins and K-channel activity | [191] |
| 8 | mouse   | Lgi1-mutant mice | Lgi1 | Secreted protein, modulator of disintegrin and metalloproteinase domain-containing proteins and K-channel activity | [191] |
| №  | Species       | Strain                        | Gene       | Protein Function                                                                 | References                  |
|----|---------------|-------------------------------|------------|----------------------------------------------------------------------------------|-----------------------------|
| 9  | rat           | Kcnj16-knockout               | Kcnj16     | Kir5.1 potassium channel                                                         [192, 193]                |
| 10 | mouse         | Black Swiss *                 | Gipc3      | GAIP-interacting protein C terminus, anchoring of the receptor proteins to the cytoskeleton | [194–196]                   |
| 11 | mouse         | Tremor                        | Egr3       | Early growth response protein 3, transcription factor                             [197]                       |
| 12 | mouse         | Knockout of eukaryotic elongation factor 1Bδ (eEF1Bδ) long isoform | Eef1d      | Eukaryotic elongation factor 1Bδ (eEF1Bδ) long isoform                           [199]                       |
| 13 | mouse         | Tef knockout mouse strain     | Tef        | Proline and acidic amino acid-rich basic leucine zipper (PAR bZip) transcription factor | [202]                       |
| 14 | mouse         | Ube3a mutated mice, model of Angelman syndrome | Ube3a      | Ubiquitin–protein ligase E3A                                                      [204, 207]                 |
|    |               |                               |            | **Polygenic or putatively polygenic inheritance**                                 |                             |
| 15 | mouse         | DBA/2J                        | Kcnj10     | Kir4.1 potassium channel                                                         [209, 210]                |
| 16 | mouse         | 101/HY                        | unknown    | Unknown                                                                         [213]                       |
| 17 | rat           | GEPR, genetically epilepsy-prone rats | unknown    | Unknown                                                                         [137, 214, 215]             |
| 18 | rat           | WAR, Wistar audiogenic rats   | Hypothetically: | Vlgr1 | Very large G-protein coupled receptor 1, cellular adhesion                        | 83, 168, 198, 217, 218, 222 |
|    |               |                               |            | Chrna4 | Glutamate (NMDA) receptor subunit                                                |                             |
|    |               |                               |            | Grin2a | Glutamate (NMDA) receptor subunit                                                |                             |
|    |               |                               |            | Grin2b | Glutamate (NMDA) receptor subunit                                                |                             |
|    |               |                               |            | Kcnq3 | Voltage-gated potassium channel                                                  |                             |
|    |               |                               |            | Egr3 | Early growth response protein, transcription factor                              |                             |
|    |               |                               |            | Ttr | Transthyretin, transport protein                                                 |                             |
| 19 | rat           | KM, Krushinsky-Molodkina      | Hypothetically: | Ttr | MutS Homolog 3, DNA mismatch repair                                               | 115                         |
|    |               |                               |            | Msh3 | Glutathione S-transferase Mu 1, sulfur metabolism, detoxification                |                             |
|    |               |                               |            | Gstm1 |                                           |                             |
| 20 | hamster       | GASH/Sal, genetic audiogenic seizure hamster, Salamanca | Hypothetically: | Cacna1a | Calcium voltage-gated channel subunit                                            | 217, 219, 221               |
|    |               |                               |            | Cacna2d3 | Calcium voltage-gated channel subunit                                            |                             |
|    |               |                               |            | Grik1 | Glutamate ionotropic receptor kainate type subunit 1                           |                             |
|    |               |                               |            | Grin2c | Glutamate (NMDA) receptor subunit ε-3                                             | 217, 219, 221               |
|    |               |                               |            | Zeb2 | Zinc finger E-box-binding homeobox 2, transcription factor                      |                             |
|    |               |                               |            | Egr3 | Early growth response protein, transcription factor                              |                             |
|    |               |                               |            | Ttr | Transthyretin, transport protein                                                 |                             |
|    |               |                               |            | Msh3 | MutS Homolog 3, DNA mismatch repair                                               |                             |
| 21 | mouse         | Ube3a-deleted mice, model of Angelman syndrome | Ube3a      | Ubiquitin–protein ligase E3A                                                      [204]                       |
|    |               |                               | Atp10a     | Phospholipid-transporting ATPase VA (aminophospholipid translocase VA) β3-subunit of the gamma-aminobutyric acid receptor | 204                         |
|    |               |                               | Gabrb3     |                                           |                             |
Table 1. Cont.

| № | Species | Strain | Gene       | Protein Function                                                                 | References |
|---|---------|--------|------------|----------------------------------------------------------------------------------|------------|
| 22| mouse   | Del(7Gabrb3-Ube3A), model of Angelman syndrome | Ube3a      | Ubiquitin-protein ligase E3A                                                     |            |
|   |         |        | Atp10a     | Phospholipid-transporting ATPase VA                                              |            |
|   |         |        | Gabrb3     | β3-subunit of the gamma-aminobutyric acid receptor                               |            |
|   |         |        | Gabra5     | α5-subunit of the gamma-aminobutyric acid receptor                               | [204]      |
|   |         |        | Gabrg3     | γ3-subunit of the gamma-aminobutyric acid receptor                               |            |
|   |         |        | Oca2       | Melanocyte-specific transporter protein, membrane transport                      |            |
|   |         |        | Herc2      | Giant E3 ubiquitin protein ligase                                                |            |

* Was previously considered as a strain with polygenic inheritance.

There are other strains of mice with presumably polygenic inheritance of AE, such as 101/HY [226], but it is unknown which mutations are responsible for AE-proneness in these strains.

Two substrains were selected for AE based on the Sprague Dowely population: GEPR-3, displaying moderate seizure intensity, and GEPR-9 with severe AE seizures [26]. Sound-induced seizures appear in GEPR-9 at the age of 25–35 days, with a further increase in intensity and decrease in fit latency [227]. Genetic studies indicate a polygenic inheritance of AE-proneness in GEPRs, while genes responsible for AE are still unknown [143,228]. At the same time, GEPRs’ GABAergic system anomalies were described in detail [26,229].

The genetics of AE development in three rodent strains obtained by classical selection with presumably polygenic inheritance of this trait, WAR, KM and GASH/Sal, were described in detail. In KM rats, the audiogenic phenotype appears at 1 month of age, and by the age of 3 months, 100% of animals are AE-prone [25]. In the GASH/Sal strain, the age of AE expression start was not indicated. In WAR, the stable AE phenotype is present at the age of 70–78 days [25]. The cDNA microarray and RNA-seq methods identified the genetic abnormalities in connection with AE-proneness in these strains, followed by mutations in exon sequences, determining the expression of a wide range of genes and differences in the activity of key signaling pathways, demonstrated by the comparison of AE-prone and control strains [121,230–233]. In WAR and GASH/Sal, the transcriptome of the IC, the structure, determining the start of AE seizure, was analyzed for both groups—animals not exposed to sound (naïve) and for animals after a seizure [230,234]. In KM rats, the transcriptome of the IC and SC of naïve animals was analyzed [121]. It is the profile of the transcriptome in naïve animals that is of maximal interest, as it allows to evaluate the contribution of various genes and signaling pathways to the AE-proneness. On the other hand, changes in the genes expression levels after seizures may include those involved in the compensatory mechanisms of seizure consequences [121]. However, the identification of specific genes with mutations and/or changes in expression levels that lead to seizure development in epilepsy models with polygenic or unknown nature of inheritance using whole-genome analysis methods faces a fundamental issue which complicates the whole problem. The thing is that most “classical” AE-prone strains (KM, GEPRs, WAR, and GASH/Sal) were bred by selection several decades ago, and after this, they were maintained in isolation from the original populations for a long time. This isolated breeding makes the direct comparison between AE-prone and AE-non-prone strains not very informative, as many genetic events could occur (both in initial and selected strains). The majority of such events should be neutral, i.e., not associated with the trait investigated—AE-proneness. Thus, 71 differential-expressing genes (DEGs) for the WAR model and 64 DEGs for GASH/Sal (in AE vs. non-AE comparison) were detected [130]. A comparison of the transcriptomes of KM and Wistar rats revealed 1488 DEGs [121]. Finding the genes responsible for AE in this dataset is a challenging goal. A plausible method of analysis is
the search for orthologous genes associated with human epilepsy among the DEGs found in AE-prone rat strains. However, this may not be sufficient, as not all genes causing human epilepsy are discovered. Moreover, several mutations were described that have different effects in rodents and humans. For instance, mutations in the \textit{Eef1d} gene (see above) do not influence development and behavior, but cause AE in mice, while in humans, similar mutations induce severe intellectual disability and microcephaly [212].

The search for genetic and biochemical peculiarities common to various AE-prone strains resulting from spontaneous mutations with further selection could be informative for revealing mechanisms of AE. Since, as mentioned above, some predisposition to AE is characteristic of rodents in general, we can assume the existence of some genetic pattern leading to this phenotype common to different strains and species. In this regard, it is of interest to compare different models for which RNA-seq data are available, i.e., WAR, KM, and GASH/Sal. Analysis of the IC transcriptome of the GASH/Sal hamster and WAR strains revealed several DEGs common to these strains in comparison to the original AE-non-prone strains—this list of genes includes \textit{Egr3}, \textit{Rgs2}, \textit{Ttr} and \textit{Npy} in both AE models [230,234]. A study of the IC and SC transcriptome in KM rats showed the significantly increased expression of the \textit{Ttr} gene compared with that in naïve Wistar rats. This trait appears to be common for three genotypes—GASH/Sal, WAR and KM [121,230,234]. In addition, the expression of the \textit{Msh3} gene was significantly (5 to 10-fold) reduced in KM rats compared with the Wistar strain. Another list of DEGs for KM and Wistar pair did not overlap with those found for WAR and GASH/Sal. Thus, KM rats (compared with Wistar) demonstrated a decrease in the expression of several mitochondrial enzymes genes (in particular, \textit{Acsm5} encoding acyl-CoA synthetase medium-chain family member 5), several respiratory chain components, the \textit{Cacng4} gene (Voltage-dependent calcium channel gamma-4 subunit), \textit{Igfbp5} (insulin-like growth factor-binding protein 5) and \textit{Gstm1} (glutathione S-transferase Mu 1) genes. The involvement of most of the DEGs detected in the epileptogenesis has not been proven yet.

The \textit{Egr3} gene overexpressed in WAR and GASH/Sal encodes a transcriptional regulator that belongs to the EGR (early growth response proteins) family of C2H2-type zinc-finger proteins and regulates NMDA receptor 1 and GABA\textsubscript{A} receptor \textalpha{}4 subunit via the BDNF-PKC/MAPK signaling pathway [83,211,235]. Increased expression of GABA\textsubscript{A} receptor \textalpha{}4 subunit and, conversely, decreased expression of \textalpha{}1 subunit of this receptor plays an important role in human \textit{temporal lobe epilepsy} and in a mouse model of pilocarpine-induced seizures [83,235,236]. Thus, increased expression levels of \textit{Egr3} may play a causative role in the development of AE in WAR and GASH/Sal as well. The AE-prone \textit{tremor} mouse strain is also characterized by increased expression of the \textit{Egr3} gene [210]. On the other hand, we were unable to find data on the association of the \textit{Egr3} gene with human epilepsy. Mutations in the \textit{Ttr} gene in humans cause family amyloid polyneuropathy but not epilepsy [237,238]. It is the only gene for which overexpression was found in WAR, KM and GASH/Sal, compared with the original AE-non-prone strains [121]. Transthyretin encoded by the \textit{Ttr} gene regulates the activity of GABA\textsubscript{A} receptors, which play an important role in the control of predisposition to seizures [239]. Deficiencies of GABA\textsubscript{A} receptor-mediated neurotransmission were previously shown in GASH/Sal hamster and WAR rat models. In KM rats, the imbalance of glutamate-GABA content was noted at a neurochemical level as well [66,142,230,232]. On the other hand, several studies reported the neuroprotective role of transthyretin in Alzheimer’s disease and in cases of cobalt-induced seizures in animals [240–242]. Therefore, overexpression of the \textit{Ttr} gene in AE-prone models may be regarded as a compensatory mechanism. The \textit{Rgs2} gene encodes a protein that modulates G protein-coupled receptor signaling cascades (GPCRs), the so-called G protein signaling regulator 2 (RGS2) [243]. An increase in this gene expression occurred after electroconvulsive stimulation, and this change could be also of adaptive significance [244]. In humans, the decreased expression of the \textit{Rgs2} gene is associated with mild cognitive impairment and several neurodegenerative diseases [245]. Neuropeptide Y, encoded by the \textit{Npy} gene, is characterized by anticonvulsant function. Its
increase in WAR and GASH/Sal in comparison with AE-non-prone animals also looks like an adaptive change [40,246]. Among the DEGs found in KM and Wistar transcriptomes compared, the association with human epilepsy was found for the orthologue of the Gstm1 gene only [121,247,248].

In addition to DEGs, sequencing of the transcriptome of GASH/Sal animals in comparison with the control AE-non-prone strain revealed several mutations in genes’ coding regions, and several of these genes were described as being associated with human epilepsy. In this list, mutations in the Cacna1a and Cacna2d3 genes encoding subunits of the calcium voltage-gated channel are of the most interest [232]. In humans, mutations in the CACNA1A induced developmental epileptic encephalopathies (DEEs) [249]. Grik1 (glutamate ionotropic receptor kainate type subunit 1) gene polymorphism was found in hamsters, while the human ortholog is associated with epilepsy development, including juvenile absence epilepsy (JAE) [232,250]. Cacna1a and Grik1, together with Grin2c, in which a substitution was also found in GASH/Sal, are parts of the glutamatergic synapse pathway, which is enhanced in GASH/Sal [232]. The Grin2c gene encodes the glutamate (NMDA) receptor subunit ε-3 [251]. Mutations in genes encoding glutamate receptor subunits ε-1 (GRIN2A) [252] and ε-2, i.e., genes related to previously mentioned (GRIN2B) [253], are also associated with human epilepsy. One more GASH/Sal gene Zeb2 (encoding Zinc finger E-box-binding homeobox 2) carries the substitution (in comparison to the control strain) and is possibly associated with seizure development. The encoded protein is the transcription factor, which participates in the transforming growth factor β (TGFβ) signaling pathway and is essential for early fetal development. Mutations in the ZEB2 gene in humans are associated with Mowat–Wilson syndrome, a complex disease with epilepsy and severe CNS developmental abnormalities [232,254,255]. Mutations in several other genes found in GASH/Sal are probably neutral.

WAR transcriptome analysis revealed mutations in Chrna4, Grin2a, Grin2b, Kcnq3, Vlgr1 and several other genes [181]. Chrna4 encodes a subunit of the nicotinic acetylcholine receptor, and its mutations are associated with nocturnal frontal lobe epilepsy. Kcnq3 encodes a subunit of the voltage-gated potassium channel with mutations associated with benign familial neonatal seizures [256]. Mutations in the Vlgr1 gene are associated with human epilepsy and with AE in the Frings mice (see above) [181]. Thus, mutations found in GASH/Sal and WAR and absent in AE-non-prone strains affect mainly voltage-gated ion channels and glutamatergic system. In addition, several thousands of apparently neutral polymorphisms between WAR and Wistar strains were detected using RNA-seq [181].

One should note that no mutations in exon regions of any genes, associated with the development of epilepsy in humans, were found in the KM rat transcriptome analysis [121]. At the same time, GASH/Sal mutations in the Msh3 and Ttr genes were found in addition to those listed above. The Msh3 gene encodes a homolog of the bacterial protein mutS, which forms a heterodimer with the Msh2 protein responsible for DNA mismatch repair [257]. In the case of the Msh3 gene, one of the two mutations found in the GASH/Sal strain apparently prevents the interaction of the Msh3 protein with Msh2 [232]. No association with epilepsy in humans had been described for the MSH3 and TTR genes, although human TTR gene mutations cause family amyloid polyneuropathy [237,238]. The level of the Msh3 gene expression is significantly higher in GASH/Sal (in comparison with the control strain), and those plausibly could be a compensatory mechanism for the inactivity of the mutant Msh3 protein [232].

No mutations in the coding region of the Msh3 gene were found in KM rats, but a significant decrease in the transcription level of this gene (in comparison to Wistars) was noted [121]. It has previously been shown that decreased levels of the Msh3 partner protein, Msh2, in mice lead to increased susceptibility to kainic acid (KA)-induced seizures due to mitochondrial dysfunction [258]. Signs of mitochondriopathy in the form of reduced ATP production and increased H2O2 levels in brain and liver tissues compared with Wistar rats were also found in KM rats [122]. As mentioned above, transcriptomic analysis shows a decrease in Acsm5 gene expression, as well as in several genes encoding components of the
respiratory complexes and \( F_0 \)-ATP synthase in KM rats, which could indicate the mitochondriopathy in these animals \[121\]. In humans, no association of \( Msh3 \) gene mutations with epilepsy has been found, although mitochondriopathies (induced by mutations in several genes encoding mitochondrial proteins) are known to be associated with epilepsy in 40% of cases \[259\]. Thus, a leading role of abnormalities in the function or in the expression level of the \( Msh3 \) gene in rodent AE development seems probable. In addition, disorders of the DNA repair system may increase the general frequency of mutations and thus facilitate the selection for the AE phenotype. Interestingly, the 101/HY mouse strain which carries a mutation in the gene locus controlling DNA repair after chemical mutagenesis was found to be AE-prone \[226\].

The comparison of signaling pathways, involved in synaptic regulation mechanisms, could reveal the common pattern of deviations that are specific to the “epileptic brain” both in AE models and in humans. This pattern could be found despite the differences described in the mutation “list” for AE strains and for that associated with human epilepsy. From this point of view, the KM rat strain \[121\] was investigated in more detail. In the KM rats’ brain, increased activity of the MAPK signaling cascade was found which has direct pro-epileptogenic effects in the corpora quadrigemina, as well as proapoptotic and proinflammatory signaling pathways differences from Wistar \[121\]. MAPK/ERK1/2 activity presumably contributes to seizure threshold decrease via the upregulation of glutamatergic synaptic transmission and suppression of GABA\(_A\) receptors functions \[53–56,64,260,261\].

It is interesting to note that the cDNA expression array performed using the Chinese AE-prone P77PMC rat strain showed a significant increase in ERK2 expression in the cerebral cortex relative to the original AE-non-prone strain \[145\].

As already mentioned above, in the selection and maintenance of rodent AE strains (and control non-AE strains as well), neutral as well as AE-provoking mutations could be accumulated in the genomes. This makes the correct comparison between AE and control animals a rather problematic one. To facilitate the search for genes associated with AE, the new strain was selected based on F2 (KM x Wistar) hybrids with two back-crosses to the KM strain. As the result, the strain obtained is phenotypically intermediate (in respect to AE phenotype expression) between KM (100% AE-prone) and Wistar (10–15% AE-prone). This strain was named “0”, with 30–60% of AE-prone animals with a fit intensity of a low level, with only AE-non-prone animals being used in the study \[121,142,262,263\]. Transcriptome sequencing in animals of this “0” strain shows a gene expression profile also intermediate between KMs and Wistars. In AE-non-prone animals of this strain, the expression level of \( Msh3 \), \( Ttr \), \( Ascm5 \), \( Gstm1 \) and several other genes is close to the norm, i.e., to the expression level close to that in AE-non-prone Wistar rats. The activity of MAPK/ERK1/2 cascade and proapoptotic signaling pathways \[121\] is also normalized in the “0” animals in comparison to KM. Thus, the data available suggest the participation of these genes and signaling pathways in AE development.

Summarizing the data displayed above, one may conclude that the participation of certain genes in polygenic AE strains could be confirmed by their direct knockouts only, thus confirming (or rejecting) the respective hypothesis.

8. The Use of Rodent Strains with AE in AEDs Screening

All AEDs currently used in clinics are characterized by a wide range of side effects, including rather severe ones, and they are not effective in all cases of epilepsy. For this reason, the search for new AEDs continues in order to find drugs with high efficacy and a smaller spectrum of side effects than those currently used. The development of new AEDs mainly includes studies of modified analogs of conventional drugs, possessing fewer side effects \[264\]. In addition, research continues on the mechanisms of epileptic seizures and on the search for new target proteins, such as cholesterol metabolism enzymes \[265\].

As mentioned above, the “gold standard” models in AEDs testing are the maximal electroshock technique and the PTZ-induced seizure model \[266–268\]. At the same time, the use of PTZ models proved to be sometimes ineffective, e.g., the absence of the anticon-
vulsant effect of levetiracetam using this type of seizure [269], whereas in both AE and other types of seizure induction, this drug was effective [270,271]. Numerous investigations proved that clinically approved AEDs reduce effectively the seizure intensity in AE-prone rodents. Numerous data, obtained in this field, confirm the applicability of AE-prone rodents for new AEDs generation testing [135,272,273].

In general, there are probably too many AE-prone rodent strains available today for screening new anticonvulsants and for analyzing the mechanisms of their efficiency. Actually, several strains have rather explicit neurophysiological and biochemical characteristics to be used for this purpose. They are DBA/2 mice, WAR, GEPRs, KM rats and GASH/Sal. Appropriate genetic models described earlier are now used to develop specific treatments for some definite human pathologies, such as fragile X syndrome, Angelman syndrome, etc. [177,274,275].

The DBA/2 mouse strain was used to reveal the anticonvulsant effects of clobazam [276], benzodiazepine drugs [277]; adenosine (Ado) type 1 receptors (A1Rs) and their ligands [278,279]; effects of serotoninergic system enhancing substances [280]; and structurally diverse GABAergic positive allosteric modulators [281]. The DBA/2 strain was also used to study the synergism of carbamoxalone (the succinyl ester of glycyrrhetinic acid, an inhibitor of 11beta-hydroxy steroid dehydrogenase) and conventional antiepileptic drugs (carbamazepine, diazepam, felbamate, gabapentin, lamotrigine, phenytoin, phenobarbital and valproate) [282] as well as the pharmacodynamic potentiation of antiepileptic drugs’ effects by HMG-CoA reductase inhibitors [283]. In Frings mice, the effects of a new analog of topiramate [264], the anticonvulsive properties of soticlestat, a novel cholesterol 24-hydroxylase inhibitor [265], and the effects of synaptic and extrasynaptic GABA transporters inhibitors were investigated [284]. Fmr-/- mice were used to analyze the possibility of mGluRs and GABA receptors’ activity modulation in fragile X syndrome therapy [177,275]. The anticonvulsant properties of lovastatin were investigated in fragile X and Angelman syndrome models [274]. In GEPR-3 and GEPR-9 strains, the anticonvulsant effect of several ion-exchange transporter inhibitors [285] and the ability of liraglutide to reduce tolerance to diazepam [286] were studied. The KM strain was used in studies of the ability of vigabatrin (a GABA decay inhibitor) to reduce the clonic component of audiogenic seizures [287]. Additionally, KM rats were used in studies of the antiepileptic potential of ERK1/2 inhibitors [59,64]. In WAR, the anticonvulsant effects of carisbamate, a novel neuromodulator for the treatment of epilepsy [288], nifedipine (calcium channel inhibitor) [289] and cannabidiol [290] were studied. Finally, pharmacological and neuroethological studies of the acute and chronic effects of lamotrigine, phenobarbital and valproic acid were performed using the GASH/Sal model [291,292].

In general, one may conclude that along with standard models of seizures induced by maximal electroshock and PTZ, the AE-prone rodents could be widely used in the testing of old and new AEDs.

9. Near-Term Prospects and Conclusions

There is currently a rapidly expanding set of new epilepsy models with monogenic inheritance obtained by directed mutagenesis, due to the amazing success of genetic engineering. These achievements have promoted an understanding of the molecular mechanisms of epileptogenesis. In monogenic models, it is possible to establish an unambiguous causal relationship between a known mutation and the development of epileptic events. One may assume that large collections of knockout and transgenic mice (such as Jackson Laboratory), may possess several mutant strains that are predisposed to AE, but this trait has not yet been revealed. This assumption seems legitimate, given that in rodents the AE trait (in some cases) could be determined by mutations in genes for which no association with human epilepsy has been discovered [215,293]. An example of such incidental finding of gene knockout association with a predisposition to AE was mentioned previously [215]. Interestingly, the lethal audiogenic seizures in mice with knockout of three PAR bZip genes occurred on definite days of the week. Subsequently, it turned out that the staff
was cleaning the lab using a noisy vacuum cleaner on these particular days. Thus, some unobvious relationships between genes with a not-described association with epilepsy and the development of AE could be found by testing for AE of a wide set of mutant rodent strains available.

The available set of rodent AE-prone strains with a monogenic type of inheritance demonstrates a significant diversity of genes involved in various regulatory processes. These are mutations of genes that control the expression of AE: transcription factors (Egr3, Tef), enzymes (Wwox), receptors (5-HT2c, Vlgr1, Gabrb2), anchor proteins (Gipc3), regulators of mRNA translation and transport (Fmr1), etc.

Thus, the models of various forms of epilepsy are available for epilepsy syndromes with different etiologies and in which definite CNS mechanisms are involved, including action potential generation and early developmental events. In several AE models, the altered function of signaling cascades was also described (e.g., MAPK in KM rats) as well as the development of neuroinflammation. Thus, the AE models available provide an opportunity to test a wide range of potential AEDs targeting different proteins involved in various cellular processes, the disruption of which could induce epileptogenesis. Moreover, knockout mouse strains represent an obligatory model system for the development of epilepsy gene therapy methods based on CRISPR/Cas or adenoviral systems targeting, i.e., the development of the individual (associated with epilepsy) mutations “corrections”.

Rodent AE models with polygenic inheritance (KM, GEPRs, WAR and GASH/Sal) were developed as the result of numerous spontaneous mutations’ accumulation. Only part of these mutations is responsible for AE-proneness, while others are neutral or even exert compensatory effects for the AE phenotype (having been involuntarily selected for during selection generations). On the one hand, the identification of the genes responsible for audiogenic seizures in these models faces rather serious problems. It is known that several mouse knockouts of genes, whose human orthologs are associated with epilepsy, do not display neither AE nor spontaneous seizures in mice [293]. As an example, Tsc1 and Tsc2 (Tuberous sclerosis complex) knockouts do not lead to the development of seizures in mice, unlike tuberous sclerosis cases in humans [293,294]. On the other hand, the opposite is also true, i.e., several mutations were described that induce seizures in rodents, and definite disorders in humans [83,210,211]. Pathological deviations that lead to epileptogenesis in AE-prone strains obtained by selection in independent experiments obviously do not coincide with one another because they could be determined by different mutations. Nevertheless, they could lead to similar results, demonstrating violations of glutamate and GABAergic systems, which provoke seizures. Polygenic AE animal models could be indispensable for studying human epilepsy with a complex type of inheritance. The role of genetic pathology patterns when mutations of different alleles of multiple genes combine with genetic background characteristics (which is observed, in particular, in the KM model), should be analyzed in more details to understand the nature of many complicated forms of epilepsy [9,295,296].

Most monogenic mouse models of epilepsy were obtained by introducing mutations into the coding regions of target genes (reading frame shifts or substitutions). Many epilepsy cases in humans also describe mutations in the coding regions of certain genes, leading to the loss of functions of the protein encoded. At the same time, a lot of human epilepsy cases were described with mutations affecting not the coding, but the regulatory region of genes [297,298]. In such cases, functional disturbances occur due to changes in expression levels relative to the normal ones. In this aspect, the KM rat strain is indicated (in comparison to other rodent models), in which no mutations were found in candidate genes for association with epilepsy, but a wide range of candidate genes could be indicated in which the expression is significantly increased or decreased relative to the conditional norm of Wistar rats [121].

Gene expression could be also affected by the methylation status of gene promoters, as was demonstrated for epilepsy-associated genes FMR1 and BRD2 (bromodomain-
containing transcriptional activator 2) in humans [172,299]. The expression level of many genes could also be regulated by the RNA interference mechanism involving miRNAs (small non-coding RNAs that regulate post-transcriptional gene expression) [300]. It was found that in some cases, miRNAs as well as long non-coding RNAs can act as biomarkers and therapeutic targets in human epilepsy [301–306]. Thus, in the case of some rodent models with polygenic inheritance obtained by the selection, the search for mutations in the regulatory regions of some genes, for epigenetic changes, and changes in the expression of interfering RNAs represent a mandatory field for future research.

Transcriptomic studies in WAR, KM strains and GASH/Sal were carried out using adult animals 3 months of age, after the full development of the AE phenotype [121,230]. At the same time, it is also important to analyze CNS disorders during pre- and postnatal development in these animals, which could lead to subsequent AE development [149]. It is plausible that the important changes in gene expression, leading to future epileptic events emergence, could occur at the early stages of ontogeny which should also be investigated by RNA-seq methods in the future.

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**Abbreviations**

| Acronym | Definition |
|---------|------------|
| AE | audiogenic epilepsy |
| AEDs | antiepileptic drugs |
| AMPA | α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid |
| AS | Angelman syndrome |
| CAE | childhood absence epilepsy |
| CNS | central nervous system |
| DEEs | developmental epileptic encephalopathies |
| DEGs | differential-expressing genes |
| EAST | epilepsy, ataxia, sensorineural deafness, and tubulopathy |
| EEG | electroencephalography |
| EIEE | early infantile epileptic encephalopathy |
| ERK | extracellular signal-regulated kinase |
| GABA | gamma-aminobutyric acid |
| GASH/Sal | genetic audiogenic seizure hamster from Salamanca |
| GEPR | genetically epilepsy-prone rat |
| IC | inferior colliculi |
| ILAE | The International League Against Epilepsy |
| JAE | including juvenile absence epilepsy |
| JME | juvenile myoclonic epilepsy |
| KM | Krushinsky–Molodkina |
| MAG | myelin-associated glycoprotein |
| MAPK | mitogen-activated protein kinase |
| MES | maximal electroshock test |
| Msh3 | MutS Homolog 3 |
| mtDNA | mitochondrial DNA |
| mTOR | mammalian target of rapamycin |
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NMDA receptors: N-methyl-D-aspartate receptor
PAR bZIP: proline and acidic amino acid-rich basic leucine zipper
PTZ: pentylenetetrazole
SC: superior colliculi
TGFβ: transforming growth factor β
tRNA: transfer RNA
Trr: transhyretin
WAR: Wistar audiogenic rat
WHO: World Health Organization
WOREE: WWOX-related epileptic encephalopathy
WWOX: WW-domain-containing oxidoreductase

WWOX WW-domain-containing oxidoreductase
WOREE WWOX-related epileptic encephalopathy
WHO World Health Organization
WAR Wistar audiogenic rat
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