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Audiogenic Seizures - Biological Phenomenon and Experimental Model of Human Epilepsies

Inga I. Poletaeva, Irina B. Fedotova,
Natalia M. Sourina and Zoya A. Kostina
Moscow State University
Russia

1. Introduction

Animal models that recapitulate human epilepsies with more or less details are believed to be of importance for clinics – for studies of anticonvulsants (Reigel et al., 1986, Dailey et al., 1996, Fedotova et al., 1996, Kosacheva et al., 1998, Ross, Coleman, 2000 et al.), for dissection of molecular and biochemical pathogenesis of epilepsy, and for the search of epilepsy susceptibility genes. The use of audiogenic epilepsy in rodents as the model for anticovulsant activity of different drugs is popular, the PubMed search for the key words combination "anticonvulsant and audiogenic and model" resulted in about 100 citations. Thus the detailed investigation of this type of seizures has great value for iur knowledge concerning the genesis of seizure (and epileptogenesis) in general and their genetic basis in particular.

Apart of its practical importance, the rodent audiogenic epilepsy is the enigmatic biological and genetic phenomenon. Actually the biological significance of high sound sensitivity for rodent survival was never questioned but at the same time its connection with audiogenic epilepsy (AE) was not analyzed from this point of view either. This chapter aims first to introduce several data items concerning investigations of Russian audiogenic prone rat strain (Krushinsky-Molodkina, KM) as they were not fully represented in English literature and second – to discuss the general biological mechanisms of audiogenic seizure. It is well known that the good theory is the best friend of practice. There is some hope that elucidating the origin of animal audiogenic epilepsies will bring us closer to still unsolved problems of seizure states in general. The methods which were used in studies of audiogenic epilepsies marched along with neurobiology methods starting from the middle of XX century. The same is now – new technologies are going to be applied and will be mobilized in future as these valuable models (seizure states developing in response to loud sound) are of great use for medical practice and clinic in particular.

2. General features of audiogenic epilepsy in KM rat strain and rodents of other genotypes

The data on increased sound sensitivity in audiogenic rats and mice are known for rather long time (Ross, Coleman, 2000, Semiokhina et al., 2006). Although the anomalies in "sensory part" of acoustic impulses in the brain pathway, promoting the acoustic seizure fit is not the single prerequisite for AE development. The abnormal biochemical and

physiological status of central auditory (and other) structures are also the important issues (Garcia-Cairasco, 2002). As several audiogenic rat strains exist, the phenomenon rat AE had been explored in different laboratories.

The audiogenic epileptic fits in rats were noted in Wistar Institute at the beginning of rat breeding program (Ross, Coleman, 2000), while the first observation of mouse audiogenic feature was made by N. Studentsov in I.P. Pavlov laboratory. The instrumental conditioning in mice using loud sound as CS unexpectedly resulted in seizure reaction of animals. In mid-1940-s the AE was noted in DBA/2J strain (Hall, 1947) and was also described in different laboratory mouse strains both inbred (Fuller, Smith, 1953) and outbred. Frings and Frings (1953) selected the albino mouse strain (Frings strains) which further was used later to identify the *mass-1* gene (Skradski et al., 2001). The selection experiment was also performed in mice later (Chen, Fuller, 1976) in order to investigate the relationship between "inborn" AE fits and fits induced by priming. In 1948 L. Krushinsky, L. Molodkina and D. Fless from Moscow State University started the selection of rats for high susceptibility to"sound seizures". The data, describing the seizure pattern in rats, selected for audiogenic epilepsy, were first published in Russia in 1949 in the "Advances of Contemporary Biology" (v 28, p. 108-133). In English they became available in 1962, as the translation of L. Krushinsky monograph had been issued (Krushinsky, 1964), and in Krushinsky et al. (1970) paper. Starting from the mid-50-s this new KM (for Krushinsky-Molodkina) strain had been extensively used as epilepsy model and model of catatonic state in pharmacological studies (Semiokhina et al., 2006). At that time authors avoided to describe the genetic aspect of the problem because scientific genetic investigation had been formally suppressed in Russia up to mid 60-s. Later the genetic study of AE inheritance had been performed (Romanova et al., 1993). In 1986-87 the inbreeding of KM strain was initiated, and up to the present the KM rat strain is maintained as inbred (more than 45 generations of inbreeding).

The marked phenotypic similarity is characteristic for audiogenic seizure fit and concomitant phenomena in rat strains selected in Russia, USA, France and Brazil. This includes the specific pattern of seizure stages, audiogenic kindling and postictal catalepsy, brain metabolite levels and their changes after the seizure fit. The phenomenology of audiogenic fit as well as numerous data on so called "priming" procedures in large number of mouse and rat genotypes were extensively presented in the review of Ross and Coleman (2000, see also below).

The brief description of rat audiogenic seizure fit will follow. It should be noted that the audiogenic seizures in mice have in general the pattern similar to that of rats with relatively larger proportion of animal deaths as the result of breath arrest (Tupal, Faingold, 2006). Mice of DBA/2J strain is most well known as demonstrating the AE phenotype with the peak intensity in the third decade of the first postnatal month and the decline of the trait expressivity at the age 40-45 days. Frings mice which were selected at the early 1950-s demonstrate the adult age AE (Klein et al., 2004). Later the audiogenic seizure proneness was discovered in mice of 101/HY strain carrying the mutant locus *mut-1* which increase their chromosomes sensitivity to the chemical mutagens (Poletaeva et al., 1996).

2.1 The audiogenic epilepsy phenotype

The seizure fit develops according to standard pattern in almost 100% of KM rats with wild run onset in 2-3 s and the clonic-tonic seizures developing in 7-9 s after the sound onset. Audiogenic seizure starts as the wild run stage, consisting of intense running mixed with high jumps of an animal. Wild run stage could stop and the normal waking state of an

animal gradually restores. If an animal display the single wild run bout and stopped, thus displaying the low intensity fit score (KM arbitrary unit "1"). Sound-evoked wild running induced the pattern of c-Fos similar to that of full AS in naive rats, this fact confirming the epileptic nature of this early audiogenic fit component (Simler et al., 1994). The "epileptic" nature of this stage was accepted as the fact by Fehr et al. (2004), who named it "clonic run". At the same time two earlier studies demonstrated that the wild-run stage is of "mixed" nature, which include the intense movements and jumps characteristic for avoidance reaction (fleeing from the fearful stimulus) and the involuntary seizure-like movements. The "avoidance" component in wild run stage was demonstrated when rats were provided with the capacity to escape the box in which the sound was presented, although such escape occurred only in the part of animals (Plotnikov, 1963, Fless, Salimov, 1974). The recent data confirm the relationship between these two behavior manifestations. N. Garcia-Cairasco (2002) made the detailed analysis of this problem basing on chemical stimulation data (injections of drugs into the restricted brain regions and analyzing the seizure pattern induced). He claims, in particular, that audiogenic-like seizures induced by chemical manipulations of specific subnuclei of inferior colliculi suggest overlapping of convulsive and aversive responses. In the review of Garcia-Cairasco the comparison was presented of audiogenic seizure pattern between the animals of selected strain WAR and resistant rats with audiogenic fit induced by chemical injections into inferior colliculli and other midbrain structures. This comparison demonstrated both common fit features and the peculiarities inherent for rats of selected strain (Garcia-Cairasco, 2002). As this author notes: "Obvious discrepancies could be derived from the use of genetic strains versus normal animals with acquired audiogenic responses" (Garcia-Cairasco, 2002).

At the same time all AE susceptible rodent strains demonstrated the phenomenon of the two phases of wild run (or "two waves of motor excitation" in Krushinsky terms). In such cases the wildly running rat could stop, rat remained quiet for several seconds and then the second run phase would resume. Although in many cases the AE fit proceeds and wild run is followed first by clonic and then by clonic-tonic and tonic "full" seizure with extension of extremities. After convulsions developed the normal state gradually returns. The postictal state of an animal could be represented by either the cataleptic state development (see below) or by the prolonged motor excitation, which is locomotion bout, different from wild run and which at least in KM strain was poorly analyzed. This type of motor "after-excitation" could be regarded as the phenotypical equivalent of prolonged abnormally high motor excitability.

2.2 Audiogenic epilepsy prone strains

The marked phenotypic similarity is characteristic for audiogenic seizure fit and concomitant phenomena in rat strains selected in Russia, USA, France and Brazil. This includes the specific pattern of seizure stages, audiogenic kindling and postictal catalepsy, brain metabolite levels and their changes after the seizure fit. The phenomenology of audiogenic fit as well as numerous data on so called "priming" procedures in large number of mouse and rat genotypes were extensively presented in the review of Ross and Coleman (2000). The brief historical notes concerning other AE susceptible rat strains will follow. At late 1940-s-begin of 1950s several papers were published on audiogenic rats sensitivity presumably using Wistar rats. Recent evaluations show that about 20-25 % of Wistar rat population develop the audiogenic fit of low intensity (demonstrating mainly wild run stage). The strains GEPR-3 and GEPR-9 (Genetic audiogenic prone rats) were created by

Albert Picchioni and Lincoln Chin in University of Arizona, USA at late 50-s (see Consroe et al., 1979, Reigel et al., 1988, Jobe et al., 1995). There are also WAS-GAERS rats (Wistar audiogenic epilepsy susceptible rats), selected in Strasbourg (Depaulis et al., 1990) and WAR (Wistar aufiogenic rats), which were bred in San-Paolo, Brazil (Doretto et al., 1996, Garcia-Cairasco 2002 et al.).

The genetic variability in AE propensity was the basis for the successful selection to the high AE seizure intensity and made it possible to create the respective AE susceptible rat strains. These strains were founded using at least three laboratory rat populations (outbred strains). In Wistar rats the successful selection for audogenic epilepsy was performed at least three times. These strains were: KM strain (already mentioned above), Wistar audiogenic sensitive rats (the detailed history not described, Simler et al., 1994) and the WAR strain which was extensively investigated by N. Garcia-Cairasco and his colleagues (Doretto et al., 1994, 2003, 2009, Garsia-Cairasco, 2002). Long-Evans rats served as the basic population for the strain of AE prone rats with about 100% penetrance and high expressivity. This strain had been bred by T. Kalinina and A. Volkova from Moscow Institute of Pharmacology (Russian Academy of Medical Sciences). Unfortunately the strain was lost due to breeding problems and only one paper which describes the experimental data using this strain is available (Surina et al., 2011).. The possibility to breed AE prone rats from Long-Evans population was very informative as this strain previously was reported as being very audiogenic-seizure resistant. The sound-induced seizures in these rats were possible to induce only by means of priming procedure (Ross, Colemann, 1999). The GEPR strains were selected using Sprague-Dawley population (Jobe et al., 1973, Consroe et al., 1979). Rather rapid selection response for this trait was characteristic for each of these experiments. In each case it resulted in creating the viable and long-lasting laboratory population of AE-susceptible rats with high penetrance and expressivity of this trait. In general, it means that the alleles of loci involved in audiogenic seizure propensity are not deleterious to the general neurological and/or somatic state of the animals. Although the oldest strain – KM (which has now more than 45 inbreeding generations and about 150 generations of selection breeding from 1947) demonstrates rather low fertility at present with the delayed start of reproductive age (3.5-4 months).

Audiogenic seizures were also described in the WAG/Rij rat strain which was initially studied as the laboratory model for the "absence" epilepsy (Kuznetzova et al., 1996). Midzyanovskaya et al. (2004) noted that about one third of WAG/Rij rats develop audiogenic seizure fit in response to loud sound stimulation, although these seizures were of low intensity –the tonic seizure stage was demonstrated rarely. GAERS rats also represent the model for "absence" epilepsy although the degree of relatedness between this strain and audiogenic prone strain of Wistar origin in Strasbourg laboratory (Simler et al., 1994) had not been clarified.

Brain structures involved in the development of audiogenic seizures

Audiogenic seizure fit initiates as the excitation arrives into the brain stem structures, namely in inferior colliculli. This fact has been extensively demonstrated in GEPR strains (Millan et al., 1988, N'Gouemo & Faingold, 1998, 1999, Faingold, 1999), as well as in WAR and WAS strains and mice (Willott & Lu, 1980, Garcia-Cairasco, 2002, Garcia-Cairasco & Sabbatini, 1991, Simler et al., 1994). Bilateral lesions of inferior collicculi, lateral lemniscus and the connections between these structures blocked audiogenic seizures expression in rats and mice (Garcia-Cairasco, 2002, Browning et al., 1999 Garcia-Cairasco, Sabbatini, 1991, Kesner, 1966, cited by Garcia-Cairasco, 2002).

The epileptic EEG activity concomitant with AE fit was demonstrated in medulla (Krushinsky et al., 1963, Krushinsky et al., 1970), midbrain, namely PAG and substantia nigra (N'Gouemo & Faingold, 1998, 1999, Doretto et al., 1994), lateral geniculate bodies (Krushinsky, 1963, Ribak et al., 1994), but not in hippocampus or neocortex (Merill et al., 2005, Moraes et al., 2005, Semiokhina et al., 2006). The latter fact was demonstrated both by lack of EEG epileptic pattern during clonic and tonic seizures and by audiogenic fit being unaffected after cortex ablation and during neocortex inactivation in the course of cortical spreading depression (Semiokhina, 1969). Detailed pattern of AE fit development was described in details for GEPR-3 and GEPR-9 by data on EEG and c-fos expression as well by data on brainstem sections and structure ablations (Ribak et al., 1994, Doretto et al., 1994, 2009). The main structures involved in audiogenic fit development are shown on the scheme (Fig.1).
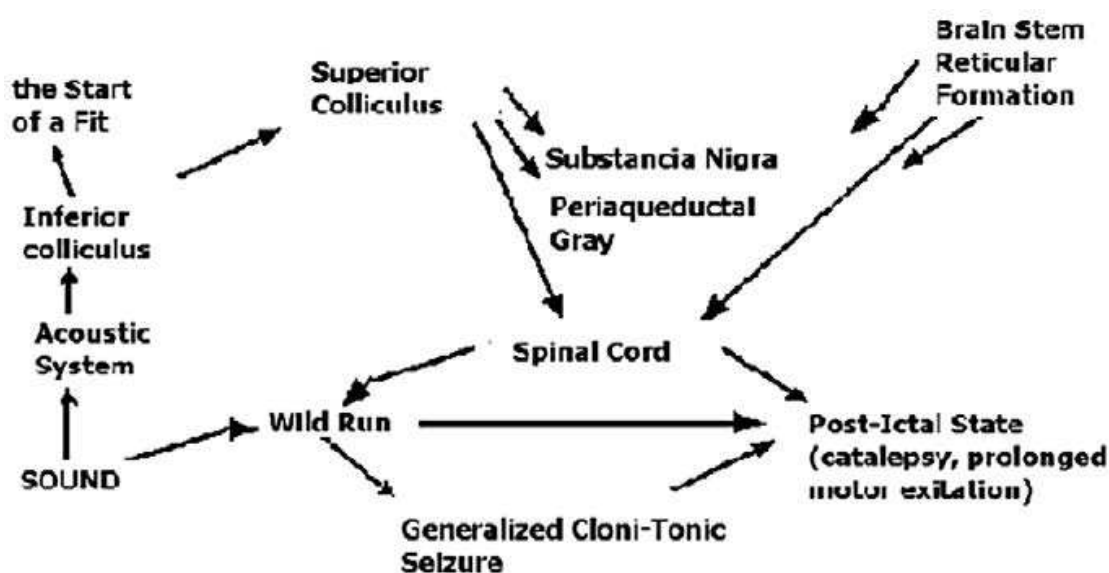

Fig. 1. The schematic representation of audiogenic seizure discharge development involving brain stem structures (see the text)

In several studies of AE, performed on DBA/2J model, the cortical EEG demonstrated the epileptic activity focus (Takao et al., 2006). Although it could be possible that high voltage epileptic potentials could result from electrotonic spread of potentials in the volume conductor, although the active participation of cortical neurons in AE fit development was demonstrated in mice using markers of glia cells activation (Guillaume et al., 1991), demonstrating the cortical catecholamine system activation and suggesting the protective role of neocortex in this process.

Another example of deviations from the commonly accepted view about the lack of EEG activity in the cortex during tonic AE fit was obtained by Zivanovic et al. (1997). The audiogenic seizures induced in non-epileptic Wistar rats by means of metaphit injections (competitive antagonist of NMDA-receptor) manifested the typical epileptic pattern in cortical EEG recordings. Thus the chemically induced AE fits are different by the pattern of pathological discharge propagation from that of "naturally" occurring AE fit in the genetically susceptible rats.

The participation and the key role of inferior colliculi in initiation and development of wild run and motor seizures had been investigated by all techniques available – EEG, activity of

single neurons (Faingold, 1999), 2-deoxiglucose uptake (Clemmesen et al., 1988) and the investigation the c-Fos expression pattern both in mice (Klein et al., 2004) and rat (Eells et al., 2004). The arrival of excitation to the superior colliculus is the first step in the seizure generalization (Ribak et al., 1997). Ribak & Morin (1995) showed (using immunocytochemistry and in situ hybridization) the significant increase in GABA level and the larger number of GABAergic neurons in the central nucleus of the inferior colliculus in GEPR-9 strain in comparison to Sprague-Dawley non-epileptic rats. The number of small cells with diameters less than 15 microns showed the greatest increase. The causal connection of this anatomical trait with AE was proved by the fact that in KM rats (the independent selection experiment from different initial population) the similar increase was recently shown in the number of neurons expressing proteins co-localized with GAD in rat brain of 2, 4 and 6 weeks of age (unpublished data). Ribak & Morin (1995) using the knife cuts through the midbrain indicated that in sound-induced seizure propagation the important stage was the activation of the inferior colliculus external nucleus via projections from the central nucleus.

It was known for rather long time that audiogenic-like seizures could be evoked by microinjections of bicuculline (GABA-A receptors antagonist) into the inferior colliculi, namely into the central nucleus of this structure (Bagri et al., 1989, Terra & Garcia-Cairasco, 1992). The more detailed analysis of morphological substrate of wild run stage in rat by means of stimulation as well as by self-stimulation of collicular structures gave similar results. The "wild run" seizures which follow biccuculine microinjections into inferior colliculus and resemble AE fit were never followed by clonic-tonic stage. The infusion of NMDA in this structure had the similar results. Animals displayed more severe spontaneous audiogenic-like seizures after NMDA injection into central ventral or cortical dorsal inferior colliculus nuclei. which were potentiated by the acoustic stimulus. In general these responses resembled the flight reaction. This reaction could be interrupted by an animal only in cases when electrodes were placed into ventral part of central nucleus (of the inferior colliculus), but not in the cortical region of this structure (Garcia-Cairasco, 2002). Most part of these seizure responses developed prior to sound stimulation and they never ended in tonic-clonic seizures. These audiogenic seizures were blocked by microinjections of 2-amino-7-phosphono-heptanoate (AP7) applied just before NMDA microinjections into central or cortical nuclei (Terra & Garcia-Cairasco, 1994).

The activation of connections between interior and superior colliculli are obligatory for the "sensory-motor transduction in the midbrain", which means that this connection wais activated prior to audiogenic seizure appearance (Garcia-Cairasco, 2002). Thus, the integrity of connections between inferior and superior colliculi projections looks to be the crucial, or "key" point not only for adaptive responses to loud sound (startle, flight) but also for audiogenic seizures (Dutra Moraes et al., 2000). The non-acoustic structures – periaqueductal grey, PAG, and substantia nigra, pars lateralis are also critically involved in the network, activated during audiogenic seizure development. The evoked audiogenic-like seizures (by bicuculline application) could not be modified by lesions in the PAG, which suggest that this structure is not necessary for the senso-motor processing of these seizures (Bagri et al., 1991). In contrast, the ventrolateral portion of this structure is involved in the modulation of audiogenic seizures in GEPRs via a complex mechanism mediated by NMDA, GABA and opiates (N'Gouemo & Faingold, 1998, 1999, Faingold, 1999). In WAR the bilateral microinjections of clobazam into substantia nigra pars reticulata completely blocked mentioned above audiogenic like seizures evoked by unilateral microinjection of

bicuculline into inferior colliculus (Terra, Garcia-Cairasco, 1992). It made possible to suggest that WARs might be genetically deficient in GABA release or GABA receptors number and/or specificity. In another AE model the block of audiogenic seizures in similar situation was not possible, and the non-involvement of nigro-tectal connections in AE had been suggested (Depaulis et al., 1990).

The study of EEG peculiarities (wavelet analysis) in the *striatum – substantia nigra pars reticulate – superior* colliculus in WAR strain demonstrated the active participation of this system in audiogenic fit development. It was suggested that this circuitry could probably participate in active seizure fit termination as well as the participation of cerebellum in such process was not investigated in this model. Although the authors claim that methodology employed cannot answer the question – whether the increase of EEG frequency oscillations means the "desinhibition" of a nucleus, or the decrease of EEG frequency means an "inhibition". These data are of rather big importance as the active nature of seizure cessation is still poorly understood (Doretto et al., 1994, Kryzhanovsky, 2002).

The fact that brain stem nuclei are involved in the audiogenic seizure propagation does not necessarily mean that the wild run and tonic convulsions are mediated by the identical neuronal circuitries. For instance two different kinds of glutamate receptors (NMDA and AMPA) were involved in these two stages of the AE fit (Yasuda et al., 1998). The pattern of EEG and init activity in GEPRs permitted to suggest the way by which the excitation spreads in the brain during seizure fit (Dailey et al., 1996, Deransart et al., 2001). Muscimol intranigral inactivating injections were capable to suppress clonic and absence-like states in audiogenic seizure prone Wistars but were not capable to stop the tonic seizure. The inferior collululi seem to be the critical structure as the increase of neuronal firing there precedes the start of the fit. The excitation spread to the deep structures of the superior colluculus plays the similar role for wild run stage as neuronal firing increase also precedes the start of audiogenic fit. When the excitation reaches the pontine reticular nucleus and PAG the clonic-tonic stage of the fit starts (Molnar et al., 2000). After the end of the seizure fit the electric activity in these structures is depressed (dorsal cortex of inferior colliculus being the exception). The existing evidence in GEPR-9 claims that abnormal epileptic activity is determined by the increase of glutamatergic and decrease of GABAergic brain stem systems (Chakravarty & Faingold, 1999).

2.3 Priming procedure, hearing defects and audiogenic seizure fit

Priming procedures, as well as several other treatments (e.g. methaphit injections, Stanojlović, et al., 2000) could induce AE in non-susceptible rats and mice, this phenomenon in mice being first analyzed by K. Henry (1967).

Innate susceptibility to audiogenic seizures appears and declines with age at varying rates, depending upon genotype and environmental conditions as well (Henry, 1985). Auditory dysfunctions could be experimentally produced which induce susceptibility in otherwise non-susceptible mice or rats. In order to study the correlation between the cochlear functions and audiogenic seizures in genetically susceptible mice, both measures were obtained from LP/J mice, at ages ranging from 8 to 120 days (Henry, 1985). Susceptibility to sound-produced convulsions was first noted at the age of 12 days, was maximal in the period from 18 to 32 days, and declined rapidly by 40 days, disappearing totally by 120 days of age. Cochlear nerve-evoked potential thresholds were very high at 12 days, were lowest between 18 and 32 days and increased thereafter. The correlation between susceptibility and cochlear thresholds was greatest for high frequencies ($r = -.93$), intermediate for

midfrequency (r = -.77), and poorest for low frequencies (r = -.56). It was concluded that either genetic or environmental factors which produce an intermediate level of cochlear damage (for high frequency perception) in the young mouse will produce susceptibility to audiogenic seizures (Henry, 1985).

The detailed analysis of "acoustic" behavior and cochlear functions in albino Frings mice, namely in inbred descendants of them was also performed (Henry, Buzzone, 1986). The cochlear action potential thresholds of the susceptible RB/1bg mice were abnormally high, while the resistant inbred RB/3bg mice had normal audiograms of evoked potentials. The F1 hybrid showed heterosis for cochlear function. This RB/1bg line showed little age-related cochlear loss, which probably accounts for its robust sensitivity to audiogenic seizures over most of its lifespan. Earlier studies had demonstrated that the susceptible RB line had a robust evoked potentials, but little or no cochlear microphonic. The susceptible RB/1bg mice had well-defined potentials and cochlear microphonic (Henry, Buzzone, 1986).

GEPRs cocleas hair cell and electrocochleographic alterations, particularly, were investigated (Faingold et al., 1990) being in accordance with mouse data. Furthermore, several neonatal manipulations such as acoustic trauma (Pierson & Snyder-Keller, 1994) or kanamycin (Pierson & Swann, 1991), perinatal antithyroid treatment (Middlesworth & Norris, 1980) induced audiogenic seizure susceptibility in normal rats.

The detailed reviews of AE after the priming procedure were presented by Ross & Coleman (2000) and Garcia-Cairasco, (2002). In general, priming is thought to be a disruption in the normal development of activity dependent auditory pathways.

When topography of pure-tone responses in Wistar rat inferior colliculus was mapped (using Fos expression), it was demonstrated, that auditory deprivation, starting at the age of 14 days, as well as neonatal exposure to potentially deafening noise (which resulted in hearing losses) change drastically the topographic frequency representation in inferior colliculus (Pierson & Snyder-Keller, 1994). As these treatments are known to result in inducing the audiogenic seizure susceptibility, it was believed that this susceptibility might depend on derangements of hearing due to neonatal auditory deprivation. Pierson & Snyder-Kelly (1994) suggested that the deteriorations in tonotopic organization of inferior colliculi in these cases could be the probable basis of AE. This idea was supported by the fact that the ontogenetic differentiation processes in cochlea and inferior colliculi developed in the similar order – from low to high frequencies. This tonotopic organization was the result of activity-dependent process, and thus the different "priming" treatments which interfere into integrity of normal functional development of inferior colliculus and hearing were effective in AE production.

The hypersensitivity of the inferior colliculus neurons to a high-intensity auditory stimulation and hyperexcitability of these neurons in a stimulation experiment have been reported after priming procedures (Urban & Willott, 1979; Willott & Lu, 1980, Sakamoto & Niki, 2001, cited by Ross, Colemann, 2000). Thus it was more or less established that in majority of cases the AE phenotype could be revealed when inner ear severe damage of different nature took place. Black Swiss mice were audiogenic seizure prone with typical audiogenic fit which peaked in 21 days old animals and declined further (monogenic autocomal-recessive, chromosome 10). The hereditary hearing thresholds increase was found in these mice which were fully developed to the age of 4-5 month. It is interesting to note that this hearing defect was shown not to co-segregate with AE proneness, these two traits being thus independent (Misawa et al., 2002).

The functional and morphological integrity of the peripheral acoustic organ seems to be very important for development of AE fits. The structure of mammal cochlea provides the high auditory sensitivity in the broad frequency range (Dallos, 1992).

The mammalian cochlea contains two types of hair cells – inner hair cells and outer hair cells, embedded in a sensory epithelium, which is organ of Corti. Detailed morphology and function of mammalian cochlea was presented in the instructive paper of Dallos (1992). The organ of Corti is placed on the basilar membrane, which is situated along the whole cochlea length being different in firmness from its base to the apex. Basilar membrane moves as the sound vibrations enter the inner ear. Sound signals in vivo are thought to be enhanced by active mechanisms in outer hair cells – they amplify the sound-induced displacements of the basilar membrane (Dallos, 1992). Thus outer hair cells of the mammalian cochlea besides serving as sensory receptors also generate force to enhance auditory sensitivity and frequency selectivity (Mahendrasingam et al., 2010). Inner hair cells function is to relay auditory signals to acoustic nerve endings (which then travel to the brain). Reciprocally, efferent axonal fibers from the medial olivococholear system innervate sensory cells (Ryan et al., 1990). The function of outer hair cells is based on the voltage-dependent contractility of the outer hair cells, which, in turn, depends on pristine, motile protein specified not long ago (Frolenkov, 2006).Prestin is located in the basolateral wall of outer hair cells, and is thought to alter its conformation in response to changes in membrane potential (Mahendrasingam et al., 2010). Prestin is a member of a gene family, *solute carrie*r (SLC) family 26, which encodes anion transporters and related proteins. In humans three genes of this family (SLC26A2, SLC26A3 and SLC26A4) are associated with different human hereditary diseases (Liu et al., 2003). The details of signal transduction and role of the feedback mechanism in the sensitivity of the peripheral acoustic organ could be very important being the part of presumably pathological mechanism of the AE. The medial olivocochlear efferent system is an important component of an active mechanical outer hair cells system in mammals. It seems that no data on this system functional and/or morphological characteristic in audiogenic prone rats or mice exist at the beginning of 2011, although the protective role of medial olive to cochlea in mammalian ear was well described (Christopher & Smith, 2003).

Morphological and functional changes in auditory path periphery are related to AE in rodents, although this relationship is not simple (Ross & Coleman, 2000). It could be mentioned, for instance, that igf-1 (insulin-like growth factor-1 or somatomedin C) plays the important role in cohlea intrauterine and early post-natal development, although there were no indications that the defects of cochlea development in igf-1 knockouts are accompanied by audiogenic seizures (Camarero et al., 2001). In mouse mutants – Bronx waltzer (bv/bv) – the 75 % loss of inner hair cells cause only moderate elevation of hearing threshold (Schrott et al., 1989). These facts could signify that specific gene-knockout procedure acts selectively inside cochlear cell sparing the neural elements and thus the knockout consequences does not interfere the outer hair cells feedback connections from olive nucleus. At the same time, priming procedures which induced unspecific cochlear damages presumably involving the innervation impairments too, were accompanied by AE. The AE development after priming procedures (early exposure to the loud sound, deafening or toxic kanamicin injections in early postnatal age) does not induce the cochlear damage. So for priming procedure it is necessary and sufficient to change activity in the acoustic neuronal network (e.g. Pierson & Li, 1996).

It should also be mentioned that mapping of fos-like immunoreactive neurons in brain nuclei demonstrated the unexpected decrease of fos expression in the cochlear nuclei and the central nucleus of the inferior colliculi in animals having AE seizures in comparison to controls (Clough et al., 1997)

One of the conclusions which could be drawn on the basis of our present knowledge is that AE develops when acoustic sensitization takes place. Such sensitization could be the result of hereditary inner ear structural (or functional) anomalies of innervation pattern in combination with brain anomalies.

One more source of variability in the function of audiogenic seizure substrate is the level of thyroid hormones, which was reported to influence the AE proneness, although the information was partly controversial. In general the early postnatal onset of hypothyroidism produces audiogenic seizure susceptibility in rodents (Yasuda et al., 1998). These data were supported by developing the audiogenic seizure phenotype in mouse KO mice lacking specifically TR beta (Thrb (tm1/tm1)) (Ng et al., 2001).

In early 1950s Krushinsky and his colleagues found that the artificial increase of thyroxin levels in KM rats increased the audiogenic fit intensity (Semiokhina et al., 2006). The authors suggested that the elevation of thyroid hormone level increased the general level of CNS excitability thus inducing the fit severity.

The opposite data were reported by Mills & Savage (1988), who demonstrated, that GEPRs-9 was hypothyroid from the second week of life up to at least 1 year of age.

Using the battery of seven C57 X DBA (BXD) recombinant inbred mouse strains and the D2.B6-Iasb congenic strain, Seyfried et al. (1984) demonstrated in details that there was no genetic correlation of audiogenic seizure susceptibility and the serum thyroxin levels, although in earlier papers the existence of this relationship was more or less obvious as more simple genetic approach was used (Henry et al., 1981).

2.4 Genetics

Genetic researches of audiogenic seizures in mice and rats have the separate histories. The identification of Asp loci in DBA/2J mouse strain had been possible on the basis of AE susceptibility scores in F2 hybrids of C57BL.6J (resistant) and DBA/2J susceptible strains (Neumann & Collins, 1991). The chromosomal location of three Asp (audiogenic seizure proneness) loci was determined by means of classical genetics approach (Fuller et al., 1950). Later J.Fuller performed the new selection experiment creating 4 strains contrasting by initial AE susceptibility and audiogenic seizures induced by priming. The results of new four lines AE testing permitted to conclude that both traits have the independent genetic determination (Fuller, 1975, Chen & Fuller, 1976).

T. Seyfreid at al. (1980) investigated AE in mice using two parental strains C57BL and DBA mice, their F1 hybrids, backcrosses to both parental strains as well as the battery of 21 recombinant inbred strains. The authors' conclusion was that this physiological trait possessed the hereditary pattern which was characteristic for so called threshold traits. This means that genetic and environmental factors influencing trait in question influence its expressivity but the trait appears as the definite phenotype if the summarized influence of factors exceeds certain "threshold" (Seyfried et al., 1980).

Genetic researches of audiogenic seizures historically bases mainly on data for mouse AE. Three genes were identified on the basis of DBAxC57BL crosses. The first was *asp-1* (a major gene, chromosome 12, between Ah and D12 Nyul), the second - *asp-2* (with smaller effect, chromosome 4), and the third one – *asp-3*, which is located in the proximal region of

chromosome 7 (Neumann & Seyfried, 1990., Neumann & Collins, 1992). The authors ascribe the significant role in trait determination to the genomic imprinting. The model, representing these processes, is presented in which the maternal Asp3 allele is repressed, providing an influence largely from the paternal allele (Banko et al., 1997).

The investigations showed the genetic associations of the *asp-1* locus with the brain stem Ca $^{2(+)}$-ATPase activity level (Neumann & Seyfried, 1991).

The general seizure susceptibility (maximal electroshock seizure threshold) genes were also investigated by QTL technology using C57BL/6 (B6, seizure resistant) and DBA/2 (D2, seizure susceptible) mice. The data obtained demonstrated a significant effect originating from middle region of chromosome 5. Reciprocal congenic strains between B6 and D2 mice were created by a DNA marker-assisted backcross breeding strategy. Comparison of seizure thresholds between congenic strain and that one which contain the parental genetic background genes indicated that mice from strains having chromosome 5 alleles from D2 and B6 genetic background exhibited significantly lower thresholds, than control littermates, and v.v. - congenic mice harboring B6 chromosome 5 alleles on a D2 genetic background exhibit significantly higher thresholds (Ferraro et al., 2007). Thus that was another chromosome locus which could be also responsible for AE proneness differences between DBA/2J and C57BL/6J mice. Similar data were got using chemically induced seizures, demonstrating the plausible connection between audiogenic seizures and seizures induced by the benzodiazepine receptor inverse agonist methyl-beta-carboline-3-carboxylate (beta-CCM). As the injections of this drug induce seizures and the susceptibility for it had the genetic component, both traits were analyzed using recombinant congenic strains of mice bred from B10.D2 and DBA/2J. Although both types of seizures have similar behavioral patterns and might involve GABAergic mechanisms, no correlation was observed between the occurrences of the two types of seizures across the strains, suggesting that these two types of seizures depend on different genetic mechanisms (Martin et al., 1992). These data could be in contrast to the generally increased seizure susceptibility in audiogenic rats (see below).

Another gene had been identified in Black Swiss mice **(**Misawa et al., 2002), which develop the audiogenic seizure with the pick intensity at 21 postnatal day. Genetic mapping and linkage analysis of hybrid mice localized the gene, *jams1* (juvenile audiogenic monogenic seizures), to the region of chromosome 10, delimited by the gene *basigin* (*Bsg*) and marker *D10Mit140*. It is worth to note, that the majority of this critical region is syntenic to a human chromosome 19p13.3 region, which is implicated in a familial form of juvenile febrile convulsions (Klein et al., 2005).

In Frings mice the single gene responsible for AE was mapped on mouse chromosome 13 (Skradski et al., 2001). This locus was named monogenic audiogenic seizure-susceptible (*mass1*). The protein coded by *mass1* (now referred to as Mgr1) is unique in that it is one of only two identified seizure loci that are not associated with an ion channel mutation. This gene codes for *very large G-protein-coupled receptor-1* (vlgr1) which contains about 6300 amino acids, and which is the largest known cell surface protein. It is expressed at high levels within the embryonic nervous system, especially in the ventricular zone. A naturally occurring nonsense mutation in this gene - V2250X, was shown to be linked to susceptibility to audiogenic seizures in mice (McMillan & White, 2004). Vlgr1d and Vlgr1e - alternatively-spliced variants of Vlgr1b/MGR1 - were shown to be transcripts from a locus *mass1*. Experiments performed suggested that Vlgr1d and Vlgr1e are secretory molecules, while Vlgr1b is a receptor. Knockout mice lacking exons 2-4 of Vlgr1 were susceptible to

audiogenic seizures without priming with any apparent histological abnormalities in their brains (Yagi et al., 2005). Mice of other genotypes possessing the Frings Mgr1 allele exhibited a mild to moderate level of hearing impairment which was already present during the days following hearing onset in ontogeny (Klein et al., 2005).

The heritability of audiogenic seizure in rats was no less simple issue. In KM rats the diallelic cross showed that AE heritability is polygenic with additive effects, and alleles determining the resistance to sound induced seizures were dominant (Romanova et al., 1993).

The data on the genetic experiments in other AE rat strains are the following. Audiogenic seizure predisposition in GEPRs was inherited as dominant polygenic autosomal trait (Kurtz et al., 2001). The penetrance and expressivity of the trait was evaluated in 20,373 animals of GEPR strains. The GEPR-3s and GEPR-9s animals both showed incomplete penetrance and variable expressivity of the underlying genetic predisposition to AE. The GEPR-9 strain had more animals with the variable levels of seizure predisposition (as measured by a scoring system that denotes the severity of generalized tonic/clonic seizures) and a greater percentage of animals that exhibited no susceptibility to such seizures induced by sound. Both strains had a number of animals that were not susceptible to sound-induced seizures and that exhibit some variability in seizure severity. The GEPR-9 males show greater differences in expressivity and penetrance compared to GEPR-9 females. The GEPR-3 animals also show sex-associated variable penetrance and expressivity of the epileptic phenotype, although the differences are much smaller. It should be noted that in contrast to GEPRs the trait penetrance and expressivity in rats of KM strain were very high – reaching the level of about 99% (Semiokhina et al.., 2006), probably the different genetic background (Wistar versus Sprague-Dowley) could be responsible. It should be remembered that the KM strain is inbred and display breeding difficulties as well.

Practically no published data could be found concerning the inbreeding used in GEPR strains, while in WAR strain the inbreeding started in parallel with the selection for high AE fit intensity (Garcia-Cairasco, 2002). The selection for high AE predisposition in WAR strain was rather quick (from 3 to 17th generations) the intensity of the fit increasing twice in parallel with fit latencies significant reduction (Doretto et al., 2003). This indicates the additive type of gene action and relative low effect of non-allelic interactions, which resemble the type of AE inheritance in KM strain.

The new experiment is now in progress in which the rats were selected for the lack of audiogenic seizures and the basic population was the F2 and backcross hybrids KM x Wistar. The "0" sensitivity rats which are under selection in this strain share the portion of KM genotype (which is presumably different from the Wistars after more than 100 generations of separate breeding).

The selection success in first ten selection generations of this selection experiment is demonstrated in fig 2. The percentage of rats, demonstrating "0" reaction (which was verified by sound exposure for 2-3 times with no less than one week intervals) was never very high, being about 40% in average. The more thorough analysis performed at the initial stages of selection demonstrated that the distribution of audiogenic sensitivity in F2 and backcrosses corresponds significantly to the two-gene-incomplete penetrance model (Fedotova et al., 2005).

The spontaneous mutation in the rat Wwox gene (Ide/Ide rats) induced dwarfism, postnatal lethality, male hypogonadism, as well as high incidence of epilepsy, typical audiogenic seizures as well, and many structural cell anomalies in the hippocampus and amygdale (Suzuki et al., 2009).
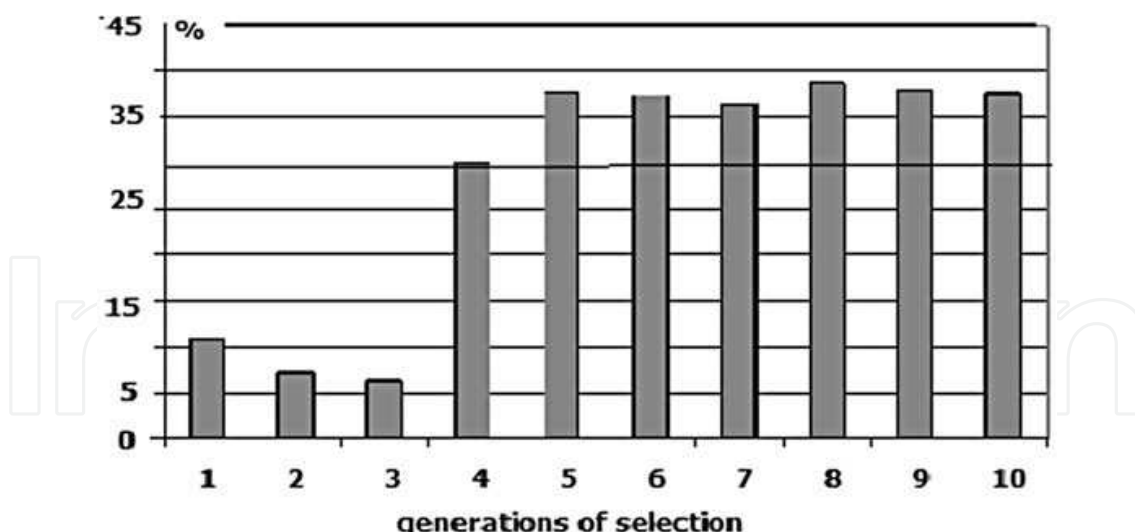
Fig. 2. The percentage of rats, selected for "0" audiogenic seizure susceptibility, starting from hydrids between Wistar rats with "0" susceptibility and KM rats with maximal seizure intensity. Ordinate – the proportion of "0" rats in respectiove generations.

The new data in the field had been brought by new technologies used. KO of several mouse genes resulted in the audiogenic seizure phenotype - fmr-1, interleikin-6, 5-HT2c receptor (Chen, Toth, 2001, Pacey et al., 2009, Brennan et al., 1997, De Luca et al., 2004). Probably these data are only the start point of new discoveries in this area using gene engineering techniques.

2.5 Channelopathies
Seizure states including epilepsy are determined by brain cells pathologies which induce functional changes in neurons. It was demonstrated that in the majority of cases both epileptic neuronal discharges and motor seizures are determined by the deteriorations in ion channels structure and/or function, which were named channelopathies (Mulley et al., 2003, Heron et al., 2007). The changes in the expression of the gene coding for one of the subunits of calcium channel Cav3.2 (as the response to pilocarpin) provoke the anomalous increase of neuronal discharges (Becker et al., 2008). It was demonstrated that in GERPs the dysfunction of voltage-gated Ca^{2+} channels are of primary importance in the development of audiogenic seizures (N'Gouemo & Morad, 2003, N'Gouemo et al., 2009, 2010). In the GEPR strains Ca^{2+} channel blockers (L-type) suppressed the audiogenic fits. The authors demonstrated this dysfunction in neurons of inferior colliculi in GEPRs, while it was unclear whether this "channelopathy" is also characteristic for other brain regions involved in AE. It stayed still unclear whether these Ca^{2+} current properties are inherent to other AE genotypes, although the general similarities between different AE models suggests that this could be the case. Ca^{2+} currents are also known to activate K^+ current that initiate the repolarization of action potential and generate after-hyperpolarization potentials. Such Ca^{2+}-activated K^+ channel may represent an intrinsic inhibitory mechanism that would restore the resting state and maintain normal physiological excitability. The anomalies in this "membrane" trait could be the cause of increased AE susceptibility in rodents. It was demonstrated, that the molecular basis for the enhanced current density of L- and R-type of HVA Ca^{2+} channels in the GEPR inferior colliculli neurons was the upregulation in the expression of Ca^{2+} channel α1D and α1E subunits, and it could contribute to the genetic basis of GEPR enhanced seizure susceptibility. The up-regulation of Ca^{2+} channel α1A subunits

induced by seizures which was demonstrated, could contribute to the increased neuronal excitability in inferior collicullus. This trait developed after repetitive seizures in the GEPR (N'Gouemo, Morad , 2003, N'Guemo et al., 2010).

2.6 Myoclonic seizures induced by repetitive audiogenic seizures

The general notion of brain "kindling" describes the gradual increase of electric responses in limbic system (e.g. hippocampus or amygdala) to the initially subthreshold electrical (or chemical) stimuli (see Galvis-Alonso et al., 2004). Audiogenic kindling (myoclonic seizures, which develop after numerous daily sound exposures) is the result of the spread of seizure discharge to forebrain structures (hippocampus, amygdale, neocortex) after such repetitive stimulation and induces seizure fits of another type. The phenomenology of audiogenic kindling in KM strain was first described by A. Semiokhina in Russian paper (1958, cited by Krushinski, 1963). These seizures are represented by the rhythmic convulsive jerks which involve facial muscles, neck muscles and, as their highest intensity, the musculature of the whole body. In KM rats these seizures appear in response to sound exposure after 10-15 daily sound exposures. These type of seizure (audiogenic kindling) was described and studied extensively in GEPR, WAR and WAS rats (Doretto et al., 2009, Garcia-Cairasco, 2002, N'Gouemo & Faingold, 1996, Dutra Moraes et al., 2000, Ross & Coleman, 2000, Simler et al., 1994). Myoclonic seizure fits severity increases in both GEPR substrains and resulted in prominent cortical epileptiform EEG activity (Feng et al., 2001). The same feature was described in KM rats (Semiokhina et al., 2006).

The audiogenic kindling phenotype in GEPRs seems to be different from that observed in KM strain (N'Gouemo & Faingold, 1996), although War and KM kindling patterns seem to resemble one another (Dutra Moraes et al., 2000). These facts could be ascribed to genetic background similarity/dissimilarity in KMs and Wars from one side and GEPRS – from another.

It appears evident thus, that two factors - the audiogenic seizure proneness and the audiogenic fit "experience" after repetitive sound exposures-form the basis for audiogenic kindling development. The involvement of forebrain structures in the kindling development was demonstrated by EEG techniques as well as by means c-fos expression mapping (Doretto et al., 2009, Garcia-Cairasco, 2002, Eells et al., 2004, Ross & Coleman, 2000, Semiokhina et al., 2006,). The comparison of brain c-fos expression patterns which was characteristic for audiogenic seizure fit and for audiogenic kindling (mioclonic seizures) demonstrated that during kindling procedure the new process takes place - the "transformation" of midbrain seizure fit into forebrain seizure state. The latter involve the structures which initially were not connected directly with overt motor function (Eells et al., 2004). This process was determined by changes in the neuronal excitability in the genetically abnormal brain of AE susceptible rats.

The special interest was paid to the amygdala participation in audiogenic kindling phenomenon. Bilateral microinjection of a GABA(A) agonist, muscimol into amygdale (0.3 nmol/side) significantly reduced the duration of kindling clonic seizures, and they were suppressed by histamine injections. At the same time wild running and tonic components of AE fit were never affected by microinjection of these agents into the amygdala. Thus amygdala becomes critical for seizure development after the expansion of the seizure network (audiogenic kindling), and this type of seizures were negatively modulated by increased GABA function in this structure (Feng et al., 2001). It was also noted that severe brainstem seizures prevent the behavioral expression of forebrain (kindled) seizures in

GEPR-9s, although the EEG spike-wave discharges in the forebrain were present. The authors suggested that it was the high intensity of brainstem seizures which did not allow the forebrain seizure to be manifested (Merrill et al., 2005).

In an effort to identify genes involved in molecular mechanisms underlying acute and kindled audiogenic seizures, the suppression-subtractive hybridization was used in order to construct normalized cDNA library enriched for transcripts expressed in the hippocampus of WARs (Gitai et al., 2010). The most represented gene among the 133 clones sequenced was the ionotropic glutamate receptor subunit II (GluR2), a member of the alpha-amino-3-hydroxy-5-methyl-4-isoxazoleopropionic acid (AMPA) receptor. The hippocampal levels of the GluR2 subunits do not differ between naïve WARs and their Wistar controls, while the transcript encoding the splice-variant GluR2-flip expression was increased in the hippocampus (namely in CA1 region) of WARs submitted to both acute and kindled audiogenic seizures (Gitai et al., 2010).

Audiogenic kindling is the phenomenon inherent to rats with elevated AE predisposition, and for those which are predisposed genetically. Although the special analysis of the genetic basis of audiogenic kindling in KM rats was performed using the genetic selection. L. Romanova selected KM rats for quick and slow audiogenic kindling development. This selection was successful and the maximum selection effect in both new substrains was achieved in 4-5 generations. This made it possible to suggest that the predisposition for audiogenic kindling development is the oligogenic trait (Romanova et al., 1993).

In mouse no data exist about the possibility to induce the audiogenic kindling. Although in C3H male mouse brain, which was kindled by electric stimulation of hippocampus differentially expressed genes were screened in various time intervals after kindling. 50 from about 30,000 bands obtained were displayed differentially. Differential expression of genes identified was demonstrated in hippocampus and forebrain, but not in brainstem or cerebellum (Liang & Seyfried, 2001).

2.7 Audiogenic postical catalepsy

In KM rats as well as in WARs (Garcia-Vairasco, personal communication) the audiogenic seizure fit is followed by the cataleptic state (Semioknina et al., 2006), which was named audiogenic postictal catalepsy. Catalepsy is characterized by the areflexia and drastic changes in the pattern of muscle tone – the so-called waxy flexibility. The duration of postictal audiogenic catalepsy correlated positively with seizure fit intensity (Fedotova et al., 2008). The pharmacological study as well as comparison of catalepsy intensity in rats of different genotypes permitted to conclude that the dopaminergic system was the key structure for this anomaly while glytamate- and GABA-ergic systems participate in its genesis as well playing the roles of modulators. It was possible to "disentangle" audiogenic fit and catalepsy correlation when glutamatergic agents (D-serine and MK-801) were injected (unpublished data). As catatonic syndrome in humans share several features with rat catalepsy we suggest that postictal audiogenic catalepsy could serve as valid laboratory model of this pathology, which would permit to make the preclinical anti-cataleptic drug testing (Fedotova et al., 2008).

2.8 Brain vascular anomalies

Early experiments in L.V. Krushinsky laboratory demonstrated that in cases when the rat was exposed to the sound stimulation for the longer period (e.g. ten minutes or more with special pattern of sound "offs" and "ons") the brain vascular disturbances could be noted in

many cases sometimes with lethal outcome (Krushinsky, 1962, 1963, Krushinsky et al., 1970). The causes of these deaths were the acute brain hemorrhages both epidural and ventricular, which were provoked by drastic changes in the permeability of brain capillary and erythrocyte diapedesis.

In rats which survived the prolonged sound exposure the less serious brain hemorrhages develop as well, which were verified morphologically. These hemorrhages manifested in vivo as hind limbs paresis after sound exposure which restored in several minutes.

The increase in arterial blood pressure was described as the initial phase of audiogenic fit which was followed by its' decrease (up to 87-90 mm Hg) (Krushinsky, 1963). These AP changes are in parallel with capillary permeability anomalies mentioned above. Changes in systemic and regional hemodynamic during sound-induced convulsions were measured in KM rats with microsphere technique. Blood pressure increased from 103 till 178 mm Hg and cardiac index rose from 27.3 to 49.3 ml/min/100 g b. w. during convulsion stage. Blood flow was increased in the brain and in the heart by 140-700%, whereas in most of internal organs it was decreased by 40-94% (Ivashev et al., 1991)...

The venous tone was estimated by means of circulatory filling pressure during a short arrest of circulation by inflating a balloon in the right atrium. It was confirmed that, during audiogenic seizure, AP raised from 104 to 156 mm Hg on the average, while mean circulatory filling pressure decreased from 8.9 to 7.4 mm Hg. The intensity of subdural and subarachnoidal hemorrhages correlated with the raise of AP during seizure. The hemorrhagic area spread over 75 mm^2 when the AP elevated above the 200 mm Hg level, while in lower increment it was only 2.56 mm^2 (Vlasov et al., 1991).

The rates of local cerebral blood flow during audiogenic seizures in Wistar audiogenic seizure rats belonging to a genetic strain selected for AE at the Centre de Neurochimie (Strasbourg, France) were analyzed. During single audiogenic seizures, rates of local cerebral blood flow increased over control values in almost all brain areas, the highest increases being in brain stem (inferior and superior colliculus, reticular formation, and many thalamic and hypothalamic regions). The lowest increases were in forebrain limbic regions and cortical areas. In kindled rats the increase of cerebral blood flow was of lower amplitude, than in controls. Thus the good correlation between the involvement of structures in the AE progress and the increase of blood flow in them was discovered. The circulatory changes in kindled rats consisted in the decrease of blood flow, this fact reflecting the differences in respective mechanisms of brain stem AE seizures and audiogenic kindling (Nehlig et al., 1995).

In KM rats the inhibitor of NO-synthase (L-NNA) increased the severity of seizures, mortality rate and intracranial hemorrhages. In contrast, L-arginine (which is the substrate for NO synthesis) elevated the resistance of animals to acoustic stress. Preliminary exposure of rats to hypoxic conditions (1 hour in hypobaric chamber, simulated altitude of 5000 m above the sea level) decreased the development of dysfunctions induced by acoustic stress. At the same time the protective effect of hypoxic "training" disappeared after the administration of NO-synthase inhibitor (L-NNA). The study demonstrated that nitric oxide (NO) participates in adaptive reactions of cerebral hemodynamics linked with the significant increase of cerebral blood flow (Fadiukova et al., 2005).

2.9 Neurochemical correlates of audiogenic seizure susceptibility and fit development

Brainstem and forebrain neurochemical systems in GERPs and KM rats (to lesser extent) have been characterized. In brief, audiogenic seizure proneness in rats and mice is

accompanied by the changes in the background neurotransmitters levels, including both the background level and seizure aftereffects. The neurotransmitter systems involved in the generation of AE fits include noradrenergic, dopaminergic, serotoninergic systems, as well as glutamatergic and GABA-ergic neurons and neuronal networks (Laird et al., 1984, Jobe et al., 1986, Ribak et al., 1988, Lasley, 1991, Fedotova et al., 1996, Kosacheva et al., 1998). Fig 3 demonstrates the neurotransmitter aminoacid levels in brain regions of KM strain.

Jobe et al. (1986) found the "reciprocal relationship" between both noradrenergic and serotonergic transmissions and the severity of audiogenic seizures, thus indicating the deficit of brain monoamines as one of the concomitant neurochemical features of AE. The serotoninergic brain system participates in AE of DBA/2J mice. Interesting enough was the fact that the number of 5-HT2 binding sites was 20% higher in the cerebral cortex of DBA/2J in comparison to C57 BL/6 mice at the age of "audiogenic" susceptibility of DBA/2J mice but did not differ at other ages. There were no differences in these parameters between the two strains in forebrain, mid-brain, hippocampus and pons-medulla (Jazrawi et al., 1989).

The failure to replicate previously reported significant differences between the susceptible (DBA/2J) and nonsusceptible (C57BL/6J) mice in the brain monoamine levels at the age of peak seizure susceptibility (in DBAs) demonstrated the difficulties of the whole issue, which was probably due to different techniques used (Lints et al., 1980). The cordotomy and brain monoamine levels approach proved, as authors claimed (Willott et al., 1979), that NE and 5-HT are not responsible for attenuation of audiogenic seizures. These data demonstrate that inter species differences (mouse genotypes compared) could be responsible for differences in neurochemical changes during AE fit.

Compared to controls, GEPR-3s and GEPR-9s had a modest and larger increase respectively in Bmax for both high and low affinity GABA sites, with no change in Kd. Chloride-dependent, barbiturate-enhanced GABA binding (increased Bmax) was observed for all conditions and groups. Likewise benzodiazepine binding (Bmax) increased slightly in GEPR-9 animals. There were no observed changes in binding sites for a survey of biogenic amines. Seizure-prone animals appeared to have compensatory denervation-like supersensitivity for their most prominent inhibitory receptor, which may or may not be linked to the seizure event (Booker et al., 1986). This fact was also demonstrated in the direct experiments by chronic depletion of brain 5-HT by i.c.v. administration of 5,7-dihydroxytryptamine. This procedure induced the significant increase in seizure severity, which could be noted in 2, 3 and 4 weeks after drug injections (as compared to vehicle-injected controls) (Statnick et al., 1996).

The thorough comparison of serotoninergic system was performed by Bakhit et al. (1982). Tryptophan hydroxylase activity (the rate limiting enzyme of serotonin synthesis) was significantly lower in brains of Frings mice compared to CF1 control mice probably due to altered kinetic characteristics of this enzyme. However, brain levels of serotonin were similar in both strains, as well as the uptake of tryptophan and accumulation of 5-HT (following MAO-inhibitor pargyline infusion). These data represent the information suggesting that shifts in brain monoamine levels are not the direct cause of AE seizures (Bakhit et al., 1982).

In KM rats the diazepam binding in synaptic membrane of different brain regions was significantly lower than in control non-epileptic Wistars (with highest differences being in cerebellum (Joulin & Pleskacheva, 1991). GABA binding in the cerebellum (but not in the brain stem) was also lower in KM. Presumably the receptor numbers differences but not receptor affinity were the cause of data obtained. Low scores of cerebellum synaptic

membranes binding should be analyzed in the framework of brain anticonvulsive system concept (Kryzhanovskiǐ, 2002), as this structure is suggested to be central in the process of seizure suppression.

Data of the opposite "sign" were obtained in mice by Robertson (1980). The specific binding of 3H-flunitrazepam was higher in the seizure-susceptible DBA/2J strain (at about 22 days of age) when compared to age-matched, seizure-resistant C57BL/6J mice. The DBA/2J strain had higher benzodiazepine binding both in normal state and in seizures. This higher binding in DBA/2J was due to a higher benzodiazepine receptor density (Bmax) in this strain.

The neurochemical studies demonstrated that brain monoamine deficits could be detected in the projection areas of both NA-containing neuronal groups - locus ceruleus and the lateral tegmental area. These deficits existed in GEPRs without seizure experience and were more pronounced in the GEPR-9s as compared to GEPR-3s. GABA and taurine levels were also abnormal (Laird et al., 1984). It was proposed that the NA and 5-HT deficits were the causes of AE proneness, while GABA-taurine anomalies were "the inadequate attempts of the central nervous system to compensate for the seizure-prone state". This statement was proved not to be the case later (see Lasley, 1991).

GABA concentrations were lower in GEPRs compared to non-epileptic controls in several brain regions. Aspartate and taurine content was also elevated although not in all brain areas investigated (Lasley, 1991). Seizure experience induces the changes in this pattern – the increases in aspartate, glutamate and glycine levels took place (as compared to seizure-naive rats) in inferior colliculus and in sensomotor and frontal cortices. Author suggested that the high levels of taurine in GEPR-3s and the elevated content of aspartate in GEPR-9s play certain roles as determinants of seizure severity, as well as low concentrations of GABA did. The seizure-induced changes in brain aspartate and glutamate supported the concept that these excitatory amino acids mediate changes in seizure predisposition (Lasley, 1991, Molnar et al., 2000). In estimating the deviations of brain neurotransmitter levels the main attention was paid to their regional concentrations, inferior colliculi, PAG and substantia nigra being of prime interest. The incomplete seizure suppressant effect of naloxone was moderate, while blockade of NMDA receptors by AP7 or activation of GABA (A) receptors in the PAG really suppressed AE susceptibility. Thus, PAG was viewed as the important link in the chain of structures, necessary for AE fits with GABA (A), opioid peptide and NMDA receptors participating in fit severity regulation (N'Gouemo & Faingold, 1999). The 1,9-fold increase of brain glutamate, 2,3-fold increase in GABA, 2,4-fold increase of taurine in comparison to non-epileptic rats was found in inferior colliculi by Ribak et al. (1988). In the GEPRs bilateral microinjections of NMDA receptor antagonists in substantia nigra blocked or reduced the seizure severity. The technique of brain micro dialysis permitted to measure the reactivity of respective neurotransmitter systems in GEPRs and non-epileptic rats. It was demonstrated that the increases (relative to basal levels) for non-epileptic controls were 35%, 74%, 68%, 847% and 283% for aspartate, glutamate, glycin, taurine and GABA respectively. Corresponding increases for GEPR-9s were less intense - 14%, 10%, 41%, 505% and 123% (Doretto et al., 1994).

Akbar et al. (1998) demonstrated differences in the expression levels of mRNA for three amino acid transporters - glial and neuronal glutamate transporters (GLT-1 and EAAC-1), and the neuronal GABA transporter (GAT-1). Reductions in GAT-1 mRNA were found in genetically epileptic-prone rats in all brain regions examined. Similar reductions in GLT-1 mRNA expression levels were seen in cortex, striatum, and hippocampal CA1 of genetically

epileptic-prone rats; the largest reduction being in the inferior colliculus. Differences in messenger RNA levels for GLT-1 and EAAC-1 were not reflected or were reflected only partially in the expression of the corresponding proteins (Akbar et al., 1998).

The data obtained for KM strain were more or less similar (Raevski et al., 1995, Kosacheva et al., 1998). The baseline content of serotonin and its metabolite (5-oxyindoleacetic acid) in the temporal cortex, hippocampus and medulla as well as the striatal content of dopamine and 3, 4-dihydroxyphenilacetic acid were higher in KMs than in non-epileptic Wistars. The noradrenalin level in striatum was reduced. Audiogenic seizure fit development in KM rats induced the decrease of GABA level in: striatum, hippocampus and temporal cortex, as well as the reduction of striatal and hippocampal glutamate levels (fig.3). In KM rats the histamine levels in the striatum, hippocampus, amygdala, midbrain, thalamus and hypothalamus were significantly lower than in the epilepsy-resistant Wistar rats (Onodera et al., 1992). At the early stage of KM rats selection the caffeine infusions were the experimental technique to increase the audiogenic fit severity (Krushinsky, 1964). Thus the purinergic system could be considered as being involved into generation of the AE fit.
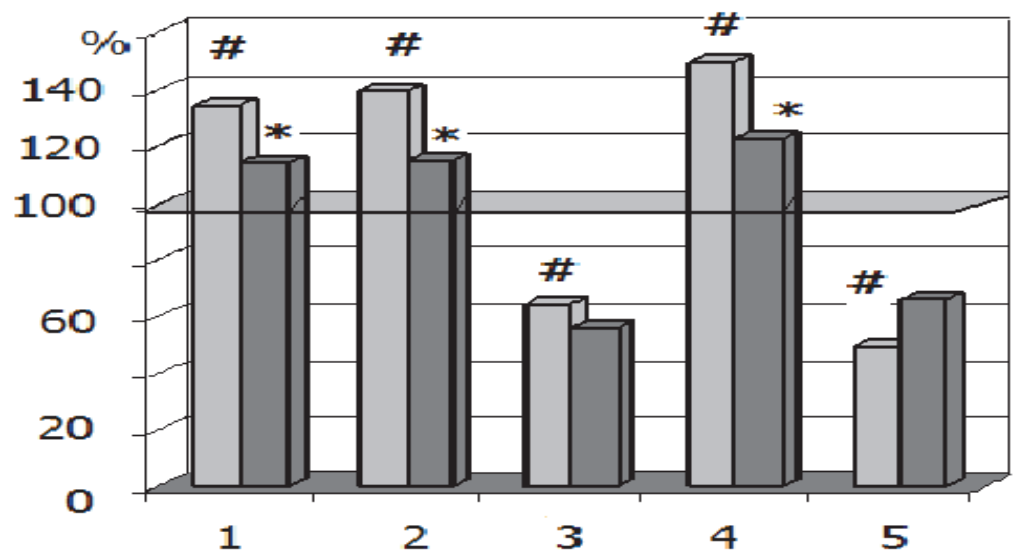

Fig. 3. Medulla levels of excitatory aminoacids (KM rat strain) without seizures (light gray columns) and at the maximum of tonic convulsions in response to sound (dark grey columns) (Raevski et al., 1995). The data presented as the percentage from intact Wistar rats respective level (100%). 1- aspartate, 2-glutamate, 3-GABA, 4-glycine, 5 – taurine. # - significantly different from Wistar rats, $p<0.05$, * - significantly different from the pre-seizure level, $p<0.05$

Brain dopamine system also participates in the complicated pattern of monoamine "audiogenic" pattern (Yu et al., 2000, Sorokin et al., 2004). The combined action of dopaminergic and serotonergic agonists suppressed audiogenic seizures, with local increase in dopamine and reduction in serotonin in the striatum (in rats not selected for AE). The audiogenic seizures which were provoked in rats by the withdrawal from chronic ethanol consumption were associated with increase in striatal dopamine and a reduction in striatal serotonin (Yu et al., 2000). In KM rats and the basal striatal dopamine level measured by in vivo microdialysis was 25% higher that in non-epileptic Wistars. A single amphetamine injection (1 mg/kg body weight, intraperitoneously) caused a significant increase in the

dopamine basal level up to 250-260% in animals of both genotypes. However, in Wistar rats, the dopamine level reached maximum as soon as 20 min after drug infusion, whereas in KM rats, this happened after 120 min. 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%); however, this occurred 20-30 and 100 min after raclopride administration in Wistar and KM rats, respectively. This evidence confirmed that the genetic "defect" in audiogenic seizure prone KM rats is connected with brain monoamines anomalies. At the same time the peculiar scheduling of changes in dopamine increase could be connected with regulatory gene(s) dysfunction (Sorokin et al., 2004).

It is now recognized that neuronal hyperexcitability and excessive production of free radicals have been implicated in the pathogenesis of epilepsy. The high rate of oxidative metabolism, coupled with the low antioxidant defenses and the richness in polyunsaturated fatty acids, makes the brain highly vulnerable to free radical damage (Devi et al., 2008). Prolonged seizures may result in the mitochondrial dysfunction and increased production of reactive oxygen species and nitric oxide, which precede neuronal cell death and cause subsequent epileptogenesis. Emerging evidences also showed that intrinsic mitochondrial apoptotic pathway may contribute to the neuropathology of human epilepsy (Chuang, 2010).

In KM rats the background levels of the some membrane lipid fractions (containing endogenous antioxidants) were higher in comparison to non-epileptic Wistars. The development of audiogenic seizure fit was accompanied by the significant increase in free radicals levels and lipid peroxides while the lipid antioxidative activity decreased. These changes were found in medulla, thalamus and hippocampus but not in the neocortex (Fedotova et al., 1988). The decrease of brain antioxidant levels developed in parallel with the audiogenic fit stages. Thus it was concluded that these oxidative stress mechanism which participated in these processes also play the important role in the brain reaction to sound induced seizures.

The *in vitro* studies (incubation of brain synaptosomes and mitochondria of KM rats with lipid peroxidation inducers) demonstrated the decrease of deamination of serotonin (which is the substrate of MAO-A) in mitochondria, but not in synaptosomes with simultaneous stimulation of GABA deamination process. The latter was apparently due to modification of catalytic properties of brain membrane-bound MAO (Medvedev et al., 1992). The similar parameters of KM brain taken at the height of AE seizures demonstrated the stimulation in brain synaptosomes and mitochondria of lipid peroxidation. This was accompanied by a marked decrease in serotonin deamination, with a simultaneous increase in GABA deamination in both fractions. The data obtained suggested that appearance of GABA-deaminating activity might be the important component in the development of epileptic seizures and it was shown that this deamination was determined by the modification of catalytic properties of MAO (Medvedev et al., 1992).

In DBA/2J mice the combined inhibition of serotonin uptake and oxidative deamination attenuated audiogenic seizures. The administration of MAO-A inhibitor (clorgyline) suppressed these AE seizures and the inhibition of seizures by tryptophan was potentiated by combination with either of the mixed MAO inhibitors (Sparks, Buckholtz, 1985).

Brain cytokine system (interleukins -1, -2, -6) also participate the seizure development and demonstrate differences in mice of different genotypes. In Frings and DBA/2J mice the expression of interleukine-1-alpha transcripts in different brain regions after the AE seizures was elevated in hypothalamus but not in hippocampus presumably by dexamethasone-sensitive pathway (Gahring et al., 1997). Intracerebroventricular administration of

interleukin-2 (both recombinant human and mouse varieties) in DBA/2 mice, increased the incidence of seizures. Since interleukin-2 proconvulsant properties were antagonized by specific monoclonal antibodies, it was suggested that some epileptic phenomena could be linked to stimulation of IL-2 receptors (De Saro et al., 1994). Deficiency in interleukin-6 (IL-6 -/- KO) induce numerous changes in brain metabolism, namely in glutamate, aspartate, GABA, glycine and taurine in different brain structures and these mice developed the audiogenic seizure fits, although no differences between IL-6 WT and KO mice in the susceptibility to maximal electroshock were noted (De Luca et al., 2004).

As mentioned above, brain monoamines levels and metabolism were consistently reported to be different from non-epileptic animals in cases of rodent audiogenic seizures. The biological degradation of monoamines is catalyzed by monoamine oxidase. Tribulin is a fraction of endogenous MAO inhibitors which are detected in human and animal tissues and biological fluids. An investigation of the biological properties of tribulin revealed its heterogeneity and some chemical components were identified. The development of several brain pathologies (epilepsy among them) are accompanied by qualitative changes in catalytic ability of the membrane-bound MAO-A and MAO-B (Medvedev, 1999). Brain tribulin activity in KM rats was studied after audiogenic seizures of different intensity. Moderate and especially maximal audiogenic seizures were accompanied by the increase of both MAO A inhibitory activity (up to 2.5-fold in case of tonic seizures), this increase in sound exposed non-epileptic Wistars was significantly less intense (Medvedev et al., 1991).

Investigation of phosphorylation in homogenates of neocortex and hippocampus, aiming to discover AE proneness influence on Ca(2+)/calmodulin- and cAMP-dependent systems was performed. Non-epilectic Wistar rats, not-pure bred KM audiogenic seizure prone rats and the same rats after being exposed to audiogenic kindling were the subjects of this study. The significant differences in phosphorylation of 270, 58, 54 and 42 kDa proteins in neocortex and hippocampus were found. The activity of PKA was higher both in neocortex and hippocampus in audiogenic sensitive rats. Daily repeated audiogenic seizures induced the decrease of Ca(2+)-independent CAMKII activity in hippocampus and the increase of PKA activity in non-epileptic rat neocortex in comparison to audiogenic rats (Yechikhov et al., 2001). Thus the neurochemical studies demonstrated both the similarity and differences in the shifts of main neurotransmission systems in rats and mice, susceptible to AE. The current problem seems to be to detect which brain chemistry and/or gene expression peculiarities are the primary ones (more close to initial genetic defect) and which – develop as the consequences of primary defects. The high complexity of neuronal signaling pathways permit such suggestion, and could tune researchers to the pessimistic mode. Although the detailed knowledge of gene expression during brain development which is extensively investigated at present could bring the quick and may be unexpected data in this respect.

2.10 Krushinsky's views on AE phenotype: Pure historical interest or the insight with present scientific significance

At the start of audiogenic epilepsy studies (at the beginning of 1950s) L.V. Krushinsky created the hypothesis that this pathology could be explained by the misbalance between brain excitation and inhibition processes. We should remember that Moruzzi and Magoun first published their data on reticular activation system only in 1949, and there were no ways to discuss in the USSR the possible impact of genotype in AE development, although KM data were obtained via the genetic selection. According to L. Krushinsky's hypothesis the following sequence of events took place in AE rat CNS after the sound onset. Strong

sound induces the excitation which "irradiates" along the brain stem structures and wild run stage starts. In response to this start the inhibitory process initiates which could be regarded as the reaction against anomalous excitation. As the result the wild run stage could stop. Then there could be two options of events development: i) the fit stops and no further abnormal reactions take place (that will be the audiogenic fit of low intensity, Krushinsky's arbitrary unit "1"), or ii) there occurs only the "inhibitory pause" in the wild run behavior lasting several seconds. As this pause ends the wild run renews and in majority of cases the motor seizure occurs (arbitrary units 2-4). According to Krushinsky's view the prolongation of sound action during the inhibitory pause leads to the "exhaustion" of inhibition as it is too strong. He hypothesized that the inhibitory pause which inserts into the wild run stage (creating "two waves" of wild locomotion) is the "active" inhibitory process. The finish of motor seizures after the "second wave" of the wild run and clonic-tonic convulsions is the result of "over-limit" inhibition (that is of inhibition which develops as the response to very strong stimulation). Bromide infusions accentuated the "inhibitory pause" in the audiogenic fit sequence, and induce such pause in rats which previously showed the "single wave" pattern of wild run. Caffeine's effect was the reverse – the "inhibitory pause" of wild run dissappeared and the fit intensity increased.

At present some arguments in the favor of that old theoretical consideration could be found, that is arguments for benefit of the postulated brain macro-processes and their interactions. One of them is the well known fact concerning the lack of epileptic EEG discharges in the neocortex and hippocampus during the AE fit. It could be partly ascribed to the "inhibited state" of these structures. Now it was demonstrated that audiogenic fit development is accompanied by the neocortical spreading depression (Vinogradova et al., 2005), which also inhibit both EEG and single unit activity in this structure. The anomalies in the balance of excitatory and inhibitory aminoacid transmitters which are inherent to AE and which are accentuated during and after the AE fit also could be the manifestation of these two processes interactions. The data also exist which concern the induction of c-Fos expression in neocortex as the result of audiogenic seizure fit, which means that the excitation of GABA-ergic interneurons could explain this finding (e.g. Batuev et al., 1997).

3. Conclusion

Many data obtained evidence that the AE susceptibility is associated with the decreased thresholds for evoking seizures of other types (e.g. Scarlatelli-Lima et al., 2003). In WARs the general seizure susceptibility was elevated in comparison to non-epileptic Wistar rats in experiments using other pro-convulsive stimuli (apart from loud sound) - transauricular electroshock, pentylenetetrazole and pilocarpine).

The similar patterns of relationships were found in mouse studies. Audiogenic seizures in mice selectively bred for susceptibility and resistance to ethanol withdrawal (induction of seizures during handling) were investigated. Resistant mice exhibited no AE response at any age, whereas "seizure withdrawal prone" mice were sensitive on several age (days 17, 22, and 28). These data suggested that susceptibility to AE and handling-induced convulsions during EtOH withdrawal may share some common genetic determinants and presumably some common neurochemical systems. This phenomenon could be regarded as the AE susceptibility induced by changes in brain neurochemistry induced by ethanol consumption. Authors suggest that these two types of seizures may share some common genetic determinants and presumably some common neurochemical systems (Feller et al., 1994).

The AE fit pattern in specialized genetic strains of rats and mice is more or less similar and this fact gives the possibility to suggest the existence of the specific "audiogenic epilepsy endophenotype". Gould, Gottesman (2006) introduced the endophenotype notion and described the endophenotypes as "quantifiable components in the genes-to-behaviors pathways". The endophenotype concept has emerged as a strategic tool in neuropsychiatric research, but it has more general applicability. Endophenotypes, as Gould & Gottesman (2006) stated, can be neurophysiological, biochemical, endocrine, neuroanatomical, cognitive or neuropsychological. Such pattern of specific features could be regarded as complex but rather specific trait of given phenomenon. It is evident that the complex relationships between genes and behavior could not be exactly reproduced in different experiments with different objects (namely in different AE models). Although the analysis of whole plethora of AE data obtained from this point of view - that there is hypothetical "common pathway" by which this pathology could be realized in the brain - could help in understanding of this phenomenon. The endophenotype for audiogenic epilepsy could be the specific seizure-provoking constellation of genetic and neurochemical events, which act both at the level of peripheral hearing organ and at the level of brain structures. The development of regional specific channellopathies and/or of the misbalance in GABA and glutamate systems (both central and cochlear) could be the possible links which help in the search of the endogphenotype of interest. The key components of any useful endophenotype are heritability and stability (state independence). Endophenotype approach is useful as "it reduces the complexity of symptoms and multifaceted behaviors" (Gould & Gottesman, 2006) which result in identifying units of analysis that could be explored in animal models.

The data reviewed above demonstrated that apart from phenotypical similarity of AE seizures there are not many traits common for all models explored – these are the disturbances of hearing system and the misbalance of brain glutamate and GABA-ergic system. The malfunction of other traits - brain monoamine, purinergic, histaminergic, cytokine systems dysfunction were also described, although the pattern of changes in cases of AE were not always consistent in different models and vary with different techniques used, animal models and species chosen (rat-mouse).

It looks more or less plausible that the disturbances in gene expression patterns rather early in development could underlie the AE, although these disturbances (mutations) should be still compatible with the fetus survival and future animal viability (although probably reduced). Such mutations are still to be identified, although the examples of genetic elements which could belong to such category are now available.

The simultaneous genetic inactivation of three transcriptional factors connected with circadian rhythmicity (albumin D-site-binding protein proline, hepatic leukemia factor and thyrotrophic embryonic factor) induce the audiogenic epilepsy in young mice (Gachon et al., 2004). The target gene of this transcription factors family is the pyridoxal kinase (*Pdxk*), which catalyses the conversion of vitamin B12 derivatives into pyridoxal-phosphate. The latter is the coenzyme of many enzymes participating in the neurotransmitter metabolism. It was demonstrated that in the triple mouse KOs the levels of brain pyridoxal-phosphate, serotonin and dopamine were decreased (Gachon et al., 2004).

Mutations of other genes which are identified as being involved in the early stages of CNS development could also be the possible candidates for causes of AE development. One example of such mutation could be the *disheveled* genes. The proteins coded by this gene family are the important signaling components of beta-catenin/Wnt pathway, which controls cell proliferation and patterning, and the planar cell polarity pathway. Dvl3 (-/-)

mice died perinatally with several developmental defects, the misorientated stereocilia in the organ of Corti being among them (Etheridge et al., 2008).

The specific pattern of the hypothesized abnormal "developmental" genes expression could be the cause of the CNS disturbances and of the AE in particular. These anomalies presumably could induce the region specific channelopathies in the structures involved in sound-seizure production. As different channellopathies (not yet well understood) are the prominent trait of many human types of epilepsy, the study of genetic/physiological basis of their regional specificity (in AE models) could be of certain clinical value. Although another hypothesis could be tested as well, that such region-specific channelopaties arise in rats and mice as the result of the abnormal pattern of CNS development per se, the rodent brain being especially vulnerable for loud sound as these animals rely on sound sensitivity in avoiding danger in natural habitats.

4. Acknowledgement

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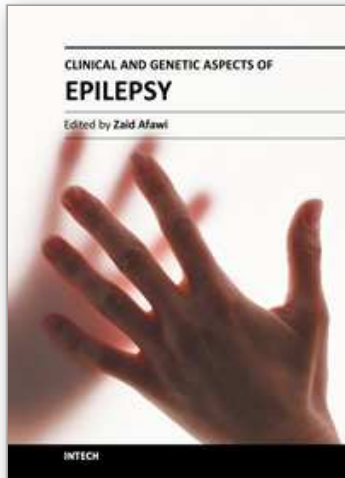
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