1st Congress
Audiogenic epilepsy
Salamanca, Spain
September 9th – 12th, 2014

“From Models to the Clinic”

Organized by

PROGRAMME BOOK
Welcome

On behalf of the Organizing Committee it is our honour to welcome you to the First International Conference “Audiogenic Epilepsy: from Animal Models to the Clinic”.

The Congress held at the Neuroscience Institute of Castilla y León (INCyL), Salamanca, Spain, from September 9th – 12th, 2014 is focused on a broad spectrum of cutting-edge epilepsy research and technologies. This Congress is intended to be a consolidated forum for multidisciplinary interaction between basic research and clinical scientists, working at the genetic-molecular, cellular, and behaviour levels. Of special interest are the main topics of the Congress: reflex epilepsies, audiogenic seizure models, genetic models of epilepsy, antiepileptic drugs, and human epilepsies.

Your participation, through the presentation of latest research results, developments, and applications in Epilepsy is instrumental for the success of this congress as well as future editions.

We are looking forward to share a memorable time at Salamanca.

Dolores E. López García & Norberto García-Cairasco.
Audiogenic Epilepsy: From Models to the Clinic

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Norberto García-Cairasco

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Norberto García-Cairasco (University of São Paulo, Brazil).
Inga I. Poletaeva (Lomonosov Moscow State University, Russia).

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Fax: +34 923 294549
Email: audiogenic@usal.es
<table>
<thead>
<tr>
<th>Time</th>
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<tbody>
<tr>
<td>16:30</td>
<td><strong>Registration</strong></td>
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<tr>
<td></td>
<td>Venue: Neuroscience Institute of Castilla y León (INCyL), Calle</td>
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<td>Pintor Fernando Gallego, 1, 37007, Salamanca, Spain.</td>
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<td>Entrance hall INCYL</td>
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<td>18:00</td>
<td><strong>Inauguration</strong></td>
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<td><strong>Vice-chancellor for Research (USAL):</strong> Juan Manuel Corchado</td>
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<td>Rodríguez</td>
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<td><strong>Health councillor of Salamanca:</strong> Mª José Fresnadillo</td>
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<td><strong>Director-General for Healthcare Planning and Innovation of</strong></td>
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<td>Castilla y León: Rafael Sánchez Herrero</td>
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<td><strong>Director of the IBSAL:</strong> Rogelio González Sarmiento</td>
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<td><strong>Chairs:</strong> Dolores E. López García and Norberto García-Cairasco</td>
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<td>Auditorium INCYL (Second floor)</td>
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<td>19:00</td>
<td><strong>Ramón Areces Conference</strong> (Opening lecture)**</td>
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<td><strong>Analysis of the brain: technological innovation and</strong></td>
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<td><strong>interdisciplinary approach</strong></td>
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<td>Javier De Felipe Orqueta (Cajal Institute, Madrid, Spain)</td>
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<td>Auditorium INCYL (Second floor)</td>
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<td>20:00</td>
<td><strong>Welcome cocktail</strong></td>
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<td>First floor and roof terrace of the INCYL</td>
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<td>Time</td>
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| 8:00  | **Registration**  
Venue: Neuroscience Institute of Castilla y León (INCyL), Calle Pintor Fernando Gallego, 1, 37007, Salamanca, Spain.  
http://www-incyl.usal.es/  
Entrance hall INCYL |
| 8:45  | **Session I: Human epilepsies**  
1- *Reflex epilepsies in humans*  
Antonio Gil-Nagel Rein (Neurology, Hospital Ruber International Hospital, Madrid, Spain) |
|       | 2- *Reflex epileptic mechanisms in humans: lessons about natural ictogenesis*  
Peter Wolf (Danish Epilepsy Centre Filadelfia, Dianalund, Denmark) |
|       | 3- *Human genetic epilepsies*  
Jose M. Serratosa (Neurology, Fundación Jiménez Diaz, Madrid, Spain)  
Auditorium INCYL (Second floor) |
| 10:15 | **Coffee break**  
First floor and roof terrace of the INCYL |
Session II: Audiogenic seizures strains

4- *AGS-induced rat model including viral transfec* *t application and the work with seizure-sensitive mice*

James R. Coleman (Department of Psychology, University of South Carolina, Columbia, South Carolina, USA)

5- *The Wistar Audiogenic Rat (WAR) Strain: Contributions to Neuroscience and Epilepsy Studies*

Norberto Garcia-Cairasco (Neurophysiology and Experimental Neuroethology Laboratory, Physiology Department, Ribeirão Preto School of Medicine, University of São Paulo, Ribeirão Preto, São Paulo, Brazil)

6- *The rats of Krushinsky-Molodkina strain. Study of audiogenic epilepsy during 65 years*

Inga I. Poletaeva (Laboratory of Behavioral Physiology and Genetics, Department of Higher Nervous Activity, Biological Faculty, M.V. Lomonosov Moscow State University, Moscow, Russia)

Auditorium INCYL (Second floor)

Lunch

Colegio Mayor Tomas Luis de Victoria.

Resumed session II

7- *The GASH:Sal. Where do we stand and where we're going?*

Melissa Carballosa-Gautan (University of Salamanca. Salamanca, Spain)
8- **Audiogenic Seizures and Sudden Unexpected Death in Epilepsy**
Huajun Feng (Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA)

9- **The C57/Bl10 SPS/sps (audiogenic seizure) mouse; Neurochemical correlates**
José G. Ortiz (Department of Pharmacology, University of Puerto Rico School of Medicine, San Juan, Puerto Rico)

Auditorium INCYL (Second floor)

16:30

**Poster session**
Entrance Hall INCYL (Ground floor)

18:00

**Tourist guided visit to the city's historical center of Salamanca.**
With local guides – Spanish and English speaking
Starting from: Under the archway clock of the Plaza Mayor de Salamanca.
(Address: Plaza Mayor, 1, Salamanca)
Congress Program

11th September 2014
Thursday

8:00
Registration
Venue: Neuroscience Institute of Castilla y León (INCyL), Calle Pintor Fernando Gallego, 1, 37007, Salamanca, Spain.
http://www-incyl.usal.es/
Entrance hall INCYL

8:45
Session III. Audiogenic seizure models: behavior and biological substrates
10- Audiogenic kindling as a valuable model for studying cortical hyperexcitability and epileptogenesis
Liudmila Vinogradova (Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, Moscow, Russia)

11- Untwining the concepts of excitability and synchronicity using animal models of epilepsy
Marcio F.D. Moraes (Universidade Federal de Minas Gerais, Instituto de Ciências Biológicas, Departamento de Fisiologia e Biofísica, Belo Horizonte, MG, Brazil)
Auditorium INCYL (Second floor)

9:45
Session IV: Molecular and neurochemical substrates of the audiogenic seizures strains
12- Molecular and neurochemical substrates of the audiogenic strains
Carlos de Cabo (Complejo Hospitalario Universitario de Albacete, Unidad de Neuropsicofarmacología, Albacete, Spain).
Coffee break
First floor and roof terrace of the INCYL

Resumed session IV
13- Increased numbers of GABAergic collicular neurons provide a basis for audiogenic seizures in Genetically Epilepsy-Prone Rats
Charles E. Ribak (Department of Anatomy and Neurobiology, University of California, Irvine, CA, USA)

14- Audiogenic Epilepsy and Auditory pathways: from Animals Models to the Otorhinolaryngology Clinical Practice
Miguel Hyppolito (Otorrinolaringology. Hospital das Clínicas de Ribeirão Preto, Universidade de São Paulo, Brazil)

Tourist guided visit to old library of the University of Salamanca
Starting from: Facade of the University of Salamanca
(Address: Patio de escuelas, 1, Salamanca)

Lunch
Colegio Mayor Tomas Luis de Victoria.
<table>
<thead>
<tr>
<th>Time</th>
<th>Session/Event</th>
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<tbody>
<tr>
<td>15:00</td>
<td><strong>Session V: Audiogenic seizure models and the antiepileptic drugs</strong></td>
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<td>15- <em>Molecular and neurochemical substrates of the audiogenic strains</em></td>
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<td>Felix-Martin Werner (Euro-Schulen Poeessneck, Poeessneck, Germany)</td>
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<td>16- <em>GEPRs and DBA/2 mice, two audiogenic models of seizures, able to evaluate anticonvulsant and proconvulsant drugs</em></td>
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<td>Giovambattista De Sarro (Department of Experimental and Clinical Medicine, Faculty of Medicine and Surgery, University of Catanzaro, School of Medicine, Catanzaro, Italy)</td>
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<td>17- <em>Pharmacological validation of the genetic audiogenic seizure hamster (GASH:Sal) using several antiepileptics</em></td>
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<td>Consuelo Sancho (Departamento de Fisiología y Farmacología, University of Salamanca, Salamanca, Spain)</td>
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<td>Auditorium INCYL (Second floor)</td>
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<td>16:30</td>
<td><strong>Poster session</strong></td>
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<td>Entrance Hall INCYL (Ground floor)</td>
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<td>18:00</td>
<td><strong>Tourist guided visit to the Casa Lis (Museum of Art Nouveau and Art Deco)</strong></td>
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<td>The museum has 19 different collections from the late 19th century and early 20th century. The museum also shows the &quot;Gaudí y su entorno&quot; special exhibition.</td>
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<td>Starting from: Casa Lis</td>
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### Congress Program

**12th September 2014**

**Friday**

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<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker(s)</th>
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<tr>
<td>8:00</td>
<td>Registration</td>
<td>Venue: Neuroscience Institute of Castilla y León (INCYL), Calle Pintor Fernando Gallego, 1, 37007, Salamanca, Spain. <a href="http://www-incyl.usal.es/">http://www-incyl.usal.es</a>. Entrance hall INCYL</td>
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<tr>
<td>9:00</td>
<td>Session VI: Genetic animal models of epilepsy</td>
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<td>18- <em>A Genetic Context for the Study of Audiogenic Seizures</em></td>
<td>Stephen C. Maxson (Department of Biobehavioral Sciences, University of Connecticut, Storrs, CT, USA)</td>
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<td>19- <em>The role of Egr2 and Egr3 in audiogenic seizures</em></td>
<td>Dolores E. López (Neuroscience Institute of Castilla y León, University of Salamanca, Salamanca, Spain)</td>
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<td>20- <em>Mouse models of genetic epilepsies</em></td>
<td>Kazuhiro Yamakawa (Laboratory for Neurogenetics, RIKEN Brain Science Institute, Hirosawa, Wako-shi, Saitama, Japan).</td>
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<td>Auditorium INCYL (Second floor)</td>
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<tr>
<td>10:15</td>
<td>Coffee break</td>
<td>First floor and roof terrace of the INCYL</td>
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**Registration**

Venue: Neuroscience Institute of Castilla y León (INCYL), Calle Pintor Fernando Gallego, 1, 37007, Salamanca, Spain.

[http://www-incyl.usal.es](http://www-incyl.usal.es/)

Entrance hall INCYL
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<tr>
<td>11:00</td>
<td>Resumed session VI&lt;br&gt;21- MASS1 regulates MAG expression via Gas/Gaq-mediated PKA/PKC pathways&lt;br&gt;Louis Ptáček (Department of Neurology, University of Utah, Salt Lake City, UT, USA)</td>
<td>Auditorium INCYL (Second floor)</td>
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<td>12:00</td>
<td>Concluding remarks and closing ceremony</td>
<td>Auditorium INCYL (Second floor)</td>
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<td>12:45</td>
<td>Group photo</td>
<td>Auditorium INCYL (Second floor)</td>
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<tr>
<td>13:00</td>
<td>Lunch</td>
<td>Colegio Mayor Tomas Luis de Victoria.</td>
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<tr>
<td>18:30</td>
<td>Reception in the Mayor City Council of Salamanca&lt;br&gt;Starting from: Under the archway clock of the Plaza Mayor de Salamanca. (Address: Plaza Mayor, 1, Salamanca)</td>
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<tr>
<td>20:30</td>
<td>Gala dinner&lt;br&gt;Palacio de Figueroa – Casino de Salamanca. (Address: Calle Zamora, 11, Salamanca)</td>
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1- Reflex epilepsies in humans

Antonio Gil-Nagel Rein (Neurology, Hospital Ruber International Hospital, Madrid, Spain)

No abstract available

2- Reflex epileptic mechanisms in humans: lessons about natural ictogenesis.

Peter Wolf (Danish Epilepsy Centre Filadelfia, Dianalund, Denmark)

Abstract: The definition of reflex epileptic seizures is that specific seizure types can be triggered by well-defined sensory or cognitive stimuli. Simple triggers are usually sensory (most often visual, more rarely tactile or proprioceptive; simple audiogenic triggers in humans are practically non-existent) and act within seconds whereas complex triggers like praxis, reading and talking, music etc are mostly cognitive and work within minutes. The constant relation between a qualitatively and often even quantitatively well-defined stimulus and a specific epileptic response provides unique possibilities to investigate seizure generation in natural human epilepsies. For several reflex epileptic mechanisms this has been done.

A fundamental distinction is that reflex epileptic mechanisms are much less common in focal lesional epilepsies than in so-called idiopathic “generalized” epilepsies (IGEs) which are primarily genetically determined. The key syndrome of IGE is Juvenile Myoclonic Epilepsy (JME) where more than half of the patients present reflex epileptic traits (photosensitivity, eye closure sensitivity, praxis induction and language-induced orofacial reflex myocloni).

Findings with multimodal investigations of cerebral function concur to indicate that ictogenic mechanisms in IGEs largely (ab)use pre-existing functional anatomic networks (CNS subsystems) normally serving highly complex physiological functions like deliberate complex actions or linguistic
communication. Whereas reflex mechanisms in IGEs, thus, are primarily function-related, in focal epilepsies they are primarily localization-related.

3- **Human genetic epilepsies**

Jose M. Serratosa (Neurology, Fundación Jiménez Diaz, Madrid, Spain)

No abstract available

4- **AGS-induced rat model including viral transfact application and the work with seizure-sensitive mice**

James R. Coleman (Department of Psychology, University of South Carolina, Columbia, South Carolina, USA)

**Abstract:** This conference can be the focus of research strategies that can help formulate the direction and future of research in epilepsy and in particular the great testable models of audiogenic seizures which are influenced by genetic and/or environmental factors. This conference offers the prospect of nourishing and growing understanding of audiogenic seizures. The research on the developmentally induced Long-Evans rat model which includes strategies of repair using genetically modified cells such as those enhancing GAD activity or using direct neural transplants. A most innovative strategy is use of gene transfer to alter audiogenic seizure activity. This conference offers a unique venue for us to present and publish research on genetic alteration at the GABA synapse in inferior colliculus using viral transfects (herpes; lentivirus) by modifying AGS susceptibility through GAD and GABA-A (e.g. α1 receptor) expression. In addition, we have data on other mouse and rat models. We believe that the Audiogenic Seizure Conference offers a special opportunity for sharing this body of work to point to novel directions in epilepsy research.

5- **The Wistar Audiogenic Rat (WAR) Strain: Contributions to Neuroscience and Epilepsy Studies**

Norberto Garcia-Cairasco (Neurophysiology and Experimental Neuroethology Laboratory, Physiology Department, Ribeirão Preto School of Medicine, University of São Paulo, Ribeirão Preto, São Paulo, Brazil)

**Abstract:** Wistar Audiogenic Rats (WAR), are a genetically selected strain susceptible to audiogenic seizures and represent a very strong research
substrate to increase our knowledge on ictogenesis and epileptogenesis and for the development of new antiepileptic drugs. Our laboratory has produced over almost three decades neuroethological, EEG, cellular and molecular data on this model. With the integration of those methodologies we have shown, for example, that acute audiogenic seizures, a model of tonic-clonic seizures, depends on activation of brainstem networks, and that chronic audiogenic seizures or audiogenic kindling (AK), a model of temporal lobe epilepsy, are expressed as behavioral and EEG limbic seizures.

Together with the data on epileptology, WAR studies have more recently demonstrated that known epilepsy-neuropsychiatric comorbidities such as anxiety, stress, depression, compulsion, cardio-respiratory alterations and neuroendocrine dysfunction, among others, can also be modeled with this strain. Anatomical and functional alterations in sensorimotor (audiomotor) and sensorilimbic systems are included in this context.

Putting all these data together we demonstrated how the complexity associated to the expression of those alterations are the consequence of the genetically-dependent background of WARs, in addition with seizure experience (induced by kindling or convulsant drugs). In order to track and characterize this complexity, we are currently facing the challenge of adding the power of an integrated (but still traditional) behavioral/EEG/molecular biology approach, to the contribution of network modeling and computational neuroscience methods.

Acknowledgements: FAPESP, Cinapce-FAPESP, PROEX-CAPE, CNPq, FAEPA, USP-USAL.

6- The rats of Krushinsky-Molodkina strain. Study of audiogenic epilepsy during 65 years

Inga I. Poletaeva (Laboratory of Behavioral Physiology and Genetics, Department of Higher Nervous Activity, Biological Faculty, M.V. Lomonosov Moscow State University, Moscow, Russia)

Abstract: Audiogenic prone rat strain, founded in 1948 by Leonid V. Krushinsky, Liudmila N. Molodkina and Dmitry A. Fless, who selected “audiogenic” rats from commercial Wistar population. At mid 1950 the strain as outbred selected strain already existed. Later it was named as KM strain (for Krushinsky-Molodkina). The basic traits of these animals were
described in papers (mostly, but not exclusively in Russian) published during 1950-1960. They were: the conserved succession of fit phases, the EEG pattern of the fit (i.e. no spike and wave activity in neocortex), the modulation of fit intensity by anticonvulsants, the phenomenon of audiogenic kindling and the general genetics of these traits. Later the complicated role of membrane processes (oxidative stress etc) were shown to determine the fit intensity and further anticonvulsants effects were performed, and neurochemical peculiarities in brain amines of KM strain being indicated as well. During the end of 1980-begin of 1990 the strain was transformed into inbred strain, their genetic homogeneity being firmly established. Starting from 1998 the selection program started for creating two new strains started using as basic the hybrid population between RV rats and Wistar "sound-resistant" rats. The genetic peculiarities of the trait were described on the basis of these selection data. The correlation of evoked potentials in the midbrain in the during audiogenic seizure fit development was described in details, as well as the new data on the behavioral-seizure proneness correlations in KM rats.

Acknowledgements: RFBR grant N 12-04-00360

7- The GASH:Sal. Where do we stand and where we're going?

Melissa Carballosa-Gautan (University of Salamanca, Neuroscience Institute of Castilla y León, Salamanca, Spain)

Abstract: The GASH:Sal hamster constitutes an experimental model of reflex epilepsy of audiogenic origin derived from an autosomal recessive disorder producing generalized seizures. These paroxysmal events are triggered by a high intensity white noise and manifest with greater severity in young animals, progressively declining with age.

Cortical electroencephalogram (EEG) patterns were acquired with a wireless implanted radiotelemetry system synchronized with video recordings of seizure events. GASH:Sal seizure EEG profiles paralleled recordings of human epilepsies propagated within the brainstem. Histologic analyses demonstrated apparent abnormalities within afferent auditory pathways manifesting as neuronal loss within the Organ of Corti as well as other auditory nuclei. Further imbalance was noted among the concentration of diverse neurotransmitters. Although the signal conduction along the auditory pathway can be considered functional, GASH:Sal
Further development of this experimental model through multiple approaches is required. Firstly, we intend to isolate and characterize the genetic determinant of this seizure susceptibility. Further histologic analyses of the auditory circuitry can clarify the possible role of abnormal neurotransmitter physiology and impaired metabolites implicated. Along with ethological analyses, convulsive symptoms may be correlated with the affected cerebral circuitry. These observations will serve as a basis to determine the feasibility and effectiveness of using GASH:Sal as a model to investigate current antiepileptic pharmaceutical treatments as well as novel therapeutic drugs.

8- Audiogenic Seizures and Sudden Unexpected Death in Epilepsy

Huajun Feng¹ and Carl L. Faingold² (¹Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA. ²Department of Pharmacology, Southern Illinois University School of Medicine, Springfield, IL, USA)

Abstract: DBA mice are susceptible to audiogenic seizures (AGS), which are characterized by wild running, generalized clonic and/or tonic seizures, ending in tonic hind-limb extension. Sudden unexpected death in epilepsy (SUDEP) is a devastating epileptic event, and both DBA/1 and DBA/2 mice have been shown to be useful animal models for SUDEP. DBA mice exhibit respiratory arrest (RA) leading to sudden death after generalized seizures, which is also the most common sequence of events in witnessed cases of human SUDEP. Several pathophysiological mechanisms, including respiratory/cardiac dysfunction, have been proposed to contribute to human SUDEP. However studies of this issue indicate that cardiac dysfunction occur secondarily to RA in DBA mice, suggesting that RA may play a causative role in these SUDEP models. Several (but not all) selective serotonin (5-HT) reuptake inhibitors (SSRIs), including fluoxetine, can reversibly block RA, and several subtypes of 5-HT receptors are abnormal in the brainstem of DBA mice. DBA mice, which did not initially show AGS-induced RA, will exhibit RA after treatment with a non-selective 5-HT antagonist. These studies suggest that abnormalities of 5-HT neurotransmission are involved in the pathogenesis of RA in DBA mice. 5-HT transmission plays an important role in normal respiration, and the DBA
mice exhibiting RA can be resuscitated by supporting respiration with a rodent ventilator. Thus, we hypothesized that fluoxetine blocks RA in DBA/1 mice by enhancing respiratory function. To test our hypothesis, we compared the effects of respiratory stimulants, doxapram and PK-THPP (TASK potassium channel antagonists) to fluoxetine on AGS-induced RA in DBA/1 mice. Consistent with previous studies, fluoxetine (30 mg/kg, i.p.) significantly reduced the incidence of AGS-induced RA in DBA/1 mice. However, fluoxetine at the same dose failed to enhance baseline respiratory ventilation in these mice in the absence of AGS. Doxapram and PK-THPP significantly augmented the baseline respiratory ventilation in DBA/1 mice. However, these respiratory stimulants were ineffective in preventing RA in DBA/1 mice. These data suggest that fluoxetine blocks RA in DBA/1 mice only after AGS via mechanisms that are only active following the seizures rather than enhancing baseline respiratory ventilation. These findings also suggest that the respiratory stimulants are unable to block AGS-induced RA, probably because these agents do not affect the mechanisms that modulate seizure-induced RA that involve 5-HT neurotransmission.

9- Neurochemical correlates of the C57Bl10 SPS/sps (audiogenic seizure) mouse

José G. Ortiz (Department of Pharmacology, University of Puerto Rico School of Medicine, San Juan, Puerto Rico).

The C57Bl10 SPS/sps mouse mutant was identified by Dr. Steve Maxson. We identified altered GABA (GAD and GABA-T) and Excitatory Amino Acid (EAA, Asp-T and GDH) metabolism. Further characterization of these alterations revealed marked increases in GABA transmission. Further analysis of GABAergic transmission revealed regional decreases in GABA uptake and increases in GABAa binding. As these changes in GABA were consistent with compensatory mechanisms, we examined EAA uptake (EAAT activity) as an alternative target. The kinetic parameters corresponding to neuronal uptake (EAAT3) were reduced. In contrast, glial uptake (EAAT1 and 2) are increased. These patterns are also observed during development and are also consistent with compensatory mechanisms. In contrast, EAAT activity is reduced in audiogenic kindling (priming).
10- **Audiogenic kindling as a valuable model for studying cortical hyperexcitability and epileptogenesis**

Liudmila Vinogradova (Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, Moscow, Russia)

**Abstract:** Audiogenic kindling produced by repeated sound stimulation of rodents with reflex audiogenic epilepsy can provide unique insight into corticosubcortical interplay and development of cortical hyperexcitability during epileptogenesis. The cortex is not involved in expression of acutely induced audiogenic seizures but becomes recruited secondarily with seizure repetition (audiogenic kindling) through activation of ascending brainstem-to-forebrain pathways. Audiogenic kindling may be induced by repetition of maximal full-blown audiogenic seizures (generalized brainstem seizures) or minimal running audiogenic seizures (focal brainstem seizures). The lecture will focus on behavioral and electrographic features of kindling produced by repeated focal brainstem seizures (sound-induced episodes of running) in Wistar rats with reflex audiogenic epilepsy. Issues relating to asymmetric behavioral phenotype of audiogenic seizure onset, asynchronous development of seizure activity in the cortex of the two hemispheres during kindling and regular triggering cortical spreading depression by repeated audiogenic seizures will be addressed.

11- **Untwining the concepts of excitability and synchronicity using animal models of epilepsy.**

Marcio F.D. Moraes (Universidade Federal de Minas Gerais, Instituto de Ciências Biológicas, Departamento de Fisiologia e Biofísica, Belo Horizonte, MG, Brazil)

**Abstract:** One of the prime questions in epileptology is how neural networks shift from normally processing sensory information towards abnormal epileptiform activity. A possible contributing factor for ictogenesis would be that specific neural attractors force, under abnormal network coupling, the synchronization of several micro-seizure domains. In fact, previously published data suggests that synchronicity is not always a direct consequence of hyper-excitability and that desynchronizing epileptogenic networks, even at the cost of increasing excitability, may favor seizure suppression. Devising methods to evaluate such abnormal coupling between endogenous oscillators, especially when driven by exogenous
Audiogenic Epilepsy: From Models to the Clinic

stimuli, has obvious implications as surrogate markers for seizure prediction and strategies for seizure suppression. Our research has focused on using exogenous stimuli (e.g. electrical or sensory stimulation) coupled to high temporal resolution markers of neuronal activity and network behavior in order to unveil such transition in neurodynamics. This lecture addresses our experiments using auditory steady-state responses (ASSR) in Wistar Audiogenic Rats (WARs), a genetic model of sound induced seizures, to evaluate the ictogenesis process. Results are coherent with previously published data using electrical stimulation in the PTZ animal model of chemically induced seizures. The ASSR approach allows dynamic assessment of sensory processing before, during and after epileptogenic networks take over control of neuronal activity.

12- Molecular and neurochemical substrates of the audiogenic strains

Carlos de Cabo (Complejo Hospitalario Universitario de Albacete, Unidad de Neuropsicofarmacología, Albacete, Spain).

Abstract: Animal models of audiogenic epilepsy are useful tools to understand the mechanisms underlying human reflex epilepsies. There is accumulating evidence regarding behavioral, anatomical, electrophysiological and genetic substrates of audiogenic seizures strains, but there are still aspects concerning their neurochemical basis that remain to be elucidated. Previous studies have shown the involvement of the γ-aminobutyric acid (GABA) in audiogenic seizures. The aim of our research was to clarify the role of the GABAergic system in the generation of epileptic seizures in the genetic audiogenic seizure prone hamster (GASH:Sal) strain. We studied KCC2, β2 and β3 GABA A-type receptor (GABAAR) subunit expression in GASH:Sal both at rest and after repeated sound-induced seizures in different brain regions using the Western blot technique. In the GASH:Sal epileptic animals, the β2 subunit predominates over the β3 subunit in most brainstem areas. This difference is exacerbated in the inferior colliculus after repeated seizures. The β2 subunit has been shown to confer upon the receptor a higher sensitivity to GABA. Interestingly, we found that the potassium-chloride cotransporter KCC2, responsible for GABAAR inhibitory actions, was lower in these areas. These data indicate that the GABAergic system is impaired in the GASH:Sal strain and suggest that this dysfunction may be related to the etiology of their syndrome. These
results are of potential clinical interest. GASH:Sal appears to be a good model to study the neurochemistry of genetic reflex epilepsy.

13- Increased numbers of GABAergic collicular neurons provide a basis for audiogenic seizures in Genetically Epilepsy-Prone Rats

Charles E. Ribak (Department of Anatomy and Neurobiology, University of California, Irvine, CA, USA)

Abstract: Audiogenic seizures in adult genetically epilepsy-prone rats (GEPRs) occur in response to loud alarm bells or even the jingling of a set of keys. Morphological studies of several auditory brainstem nuclei displayed many neurocytological changes that may underlie these seizures. Initially, we observed an increase in the number of neurons within the inferior colliculus (IC) of GEPRs as compared to Sprague-Dawley (SD) rats. This increase was present in the young GEPRs (4 and 10 PND) prior to the time at which seizure activity begins, and this finding suggests that the increase observed in adult GEPRs is not in response to the seizures, but is genetically programmed. Using GAD immunocytochemistry, we found a substantial increase in the number of GAD-positive (GABAergic) neurons in the GEPRs as compared to the SD rats. This increase was most evident in the middle of the rostrocaudal extent of the IC and was most pronounced in the central nucleus. It was due to a selective increase in the small (200%) and medium (90%) cell body size populations (10-15 micron and 15-25 micron in diameter, respectively). Consistent with these findings were results from in situ hybridization and emulsion autoradiographic studies showing elevated numbers of IC cells that contained the 67-kD form of mRNA for the GABA synthesizing enzyme. To determine whether an increase in neuron number in the IC was genetically associated with seizure behavior, the offspring of GEPR-9 and SD progenitor strains were studied as well as offspring from backcrosses made with F1 and either GEPR-9 or SD rats. The results from these studies indicated that the inheritance of audiogenic seizures is closely linked to the increase in cell number in the IC. Therefore, the increase in cell number in the IC may be an important determinant of seizure behavior for GEPR-9s. Additional studies were made to explore the role that the IC plays in audiogenic seizures and how seizure activity in the IC is propagated to other brainstem structures. Using selective lesions of the midbrain, we showed that the projection from the IC
central nucleus to the IC external nucleus is important for the propagation of seizure activity in GEPR-9s. Other data from these lesion studies showed that projections from the IC to the superior colliculus play a role in seizure propagation, and consistent with this observation was increased c-fos mRNA labeling in the superior colliculus following seizures in GEPRs. Together, these data show that an inherent GABAergic defect occurs in the IC of GEPRs and that the seizure activity initiated in this structure spreads to the superior colliculus for activation of descending motor pathways directed at the spinal cord.

14- Audiogenic Epilepsy and Auditory pathways: from Animals Models to the Otorhinolaryngology Clinical Practice

Miguel Hyppolito (Otorrinolaringology. Hospital das Clínicas de Ribeirão Preto, Universidade de São Paulo, Brazil)

Abstract: Despite recent advances, tinnitus pathophysiology has not been completely elucidated. There are estimated 12 million people with tinnitus. Ototoxicic drugs as the salicylate can increase and decrease the spontaneous neural activity in the inferior colliculus (IC) as well as decrease activity in the auditory cortex. Audiogenic limbic seizures (AS) may be related to pathophysiological mechanisms involved in the generation of tinnitus and the hyperactivity of IC which occurs after the acoustic trauma. In this lecture will be covered studies performed with ABR before and after audiogenic kindling (AK) on rodent models susceptible to audiogenic epileptic seizures. Changes in electrophysiological threshold on the right ear, a better definition of the waves and higher amplitude occurred after the AK, with largest amplitude variation to wave IV and disarrangement in the IHC cilia may be related to changes in the synapses between the IHC, spiral ganglion neurons and the auditory nerve, similar to auditory neuropathy. Changes in peripheral auditory system and IC as well as its central projections to the limbic system after AK can help understand the behavior, pathophysiology and neuroplasticity of audiogenic seizures, acoustic startle and tinnitus and the future use of drugs that increase CNS inhibition or reduce excitation on auditory pathways to tinnitus treatment.
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15- Molecular and neurochemical substrates of the audiogenic strains

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Abstract: Introduction: Audiogenic seizures in the hamster strain GASH:Sal, which is reflex epilepsy to audiogenic stimulus, can be considered as a valid animal model of generalized epilepsy. Based on interaction between classical neurotransmitters and neuropeptides between each other, a neural network in the hippocampus, the thalamus and the cortex is developed, while results from the audiogenic animal model are taken into consideration. In generalized epilepsy alterations of ion channels and neurotransmitter and neuropeptide concentrations can be induced genetically or exogenously.

An enlarged neuronal network is described in order to point out the epileptogenesis as a consequence of the interaction between the corresponding neurotransmitters and neuropeptides and of stimulus enhancing the neurotransmitter imbalance. The neural network reads as follows: Dopaminergic neurons in the hippocampus transmit a strong postsynaptic excitatory impulse via D2 receptors to glutaminergic neurons which strongly inhibit serotonergic neurons via NMDA receptors. The glutaminergic neurons can enhance epileptogenesis via an excitotoxic, postsynaptic excitatory effect via NMDA, AMPA and kainate receptors. The serotonergic neurons with a low activity transmit a weak activating impulse via 5-HT2C receptors to GABAergic neurons which weakly inhibit dopaminergic neurons via GABAA receptors. A withdrawal of GABAergic presynaptic inhibition of dopaminergic neurons can cause an epileptic seizure. GABAergic neurons weakly inhibit glutaminergic neurons in the thalamus, which transmit a strong activating impulse via NMDA receptors to dopaminergic neurons in the cortex. The cortical glutaminergic can enhance the activity of the dopaminergic neurons in the hippocampus via D2 receptors. Other serotonergic neurons transmit a weak activating impulse to serotonergic neurons via 5-HT7 receptors. Neuropeptide Y containing neurons in the dentate gyrus weakly inhibit glutaminergic neurons via NPY2 receptors and transmit a weak activating impulse to GABAergic neurons via NPY1 receptors. The serotonergic neurons transmit a weak postsynaptic excitatory impulse via 5-HT2C receptors to GABAergic
neurons which weakly inhibit adenosine neurons via GABAA receptors. The adenosine neurons with a high activity transmit a strong activating impulse via A2A receptors to glutaminergic neurons which strongly inhibit serotonergic neurons via the subtype 5 of the glutaminergic metabotropic receptors.

The mechanism of action of conventional and newer antiepileptic drugs, such as lamotrigine, levetiracetam and topiramate is pointed out according to the neural network. Results from experiments in the audiogenic seizures animal model are included in the discussion.

According to the neural networks described the following possible pharmacological options could exert an antiepileptic effect:

- Combined GABAA agonists and NMDA antagonists.
- KA or AMPA receptor antagonists, which would inhibit epileptic glutamate emptying.
- NPY2 receptor agonists, which would inhibit glutamate emptying.
- A2A receptor antagonists, which would enhance serotonin levels.
- m5GluR receptor antagonists, which would enhance serotonin levels.
- 5-HT7 receptor antagonists, which would increase serotonin levels.
- nAch alpha7 agonists.

Conclusion: It is important to examine neuronal networks in generalized epilepsy in order to optimize a multimodal pharmacotherapy of the disease.

16- **GEPRs and DBA/2 mice, two audiogenic models of seizures, able to evaluate anticonvulsant and proconvulsant drugs.**

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**Abstract:** NoSeveral strain of rodents display seizures after appropriate sound stimulation. Both audiogenic susceptible DBA/2 mice and GEPR rats have been widely used in preclinical research with different aims. DBA/2 mice, which represent a well validated animal model of generalized epilepsy, have been widely used for a quick and reliable analysis of possible anticonvulsant action of new potential anticonvulsant drugs and possible interactions between different drugs. Nearly 100% of the DBA/2 mice undergo an age-dependent, often fatal, sequence of convulsions (a wild running phase followed by clonic convulsions and a tonic extension, ending
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in respiratory arrest or full recovery) when initially exposed to a loud mixed-frequency sound (12-16 kHz; 90-120 dB) such as a doorbell. Pharmacological manipulations able to increase catecholamines, serotonin, GABA and adenosine neurotransmissions or to decrease the brain tone of aspartate and glutamate neurotransmissions are able to reduce seizure susceptibility in DBA/2 mice. All commonly used anticonvulsant drugs, acting with different mechanisms, are effective in suppressing the sound-induced seizures in this strain of mice; the validity of this model for predicting the anticonvulsant properties of new molecules has been widely demonstrated and accepted (Ferreri et al., 2004; De Sarro et al., 2003, 1988; Löscher & Meldrum, 1984; Chapman et al., 1984). Furthermore, different mixed-frequency sounds (~83 dB) have been able to identify the proconvulsant activity of benzodiazepines’ inverse agonist (Chapman et al., 1987).

The GEPR strains exhibit a broad range of seizure traits and are applicable to studies of the two major sets of convulsive seizure circuitry. Both the GEPR-3 and the GEPR-9 are characterized by a prominent level of seizure predisposition in the forebrain seizure circuitry and in the brainstem seizure circuitry. As would be anticipated under such conditions, either a focal or a generalized forebrain seizure in the GEPR-9 will trigger brainstem seizures (Coffey et al., 1996). This trait is of potential clinical relevance in that it appears to mimic a partial seizure secondarily generalized to tonic-clonic seizures. Two underlying components of seizure predisposition (noradrenergic and serotonergic deficits) also appear to give rise to a marked predisposition to the expression of comorbid affective disorder (Jobe, 2003, 2004). Partially because of the underlying noradrenergic and serotonergic deficits characteristic of the GEPR-3, these animals are prone to express not only limbic seizures but also GTCSs of the brainstem circuitry. Most of the commonly used anticonvulsant drugs are effective in suppressing the sound-induced seizures in this strain of rats. Subsequent studies demonstrated an important role mediated by excitatory neurotransmitters (Meldrum et al., 1988; De Sarro et al., 1992, 1993, 1999) as well as by calcium conductance (De Sarro et al., 1990, 2002). Three types of seizures are exhibited by GEPRs: (1) seizures that are triggered by endogenous and exogenous stimuli that do not initiate seizures in normal mammals, (2) exaggerated seizure responsiveness to stimuli that also cause seizures in nonepileptic mammals, and (3) abnormally low thresholds
to many convulsant agents. Finally, some examples of predisposition in GEPRs, characterized by abnormally low thresholds (or exaggerated seizure responsiveness), have been discovered. Seizures are induced in GEPRs by low-level exposures to aminophylline and other xantines alone or in combination with quinolones (De Sarro and De Sarro, 1991; De Sarro et al., 1993, 1997), electroshock (Browning et al., 1990), flurothyl (Franck et al., 1989), hyperbaric conditions (Millan et al., 1991), pentylenetetrazol (Browning et al., 1990), barbiturate withdrawal (Bourn and Garrett, 1983), ethanol withdrawal (Russo et al., 2008) and more recently chronic exposure to some antipsychotics (Citraro et al., 2014 in press).

In conclusion, both models have a high relevance to preclinical research both for the discovery of new possible anticonvulsant drugs and the study of epilepsy physiopathology.

17- **Pharmacological validation of the genetic audiogenic seizure hamster (GASH:Sal) using several antiepileptics**

Consuelo Sancho (Departamento de Fisiología y Farmacología, University of Salamanca, Salamanca, Spain)

**Abstract:** To find an ideal animal model for research on antiepileptic drugs is an old and still unresolved proposal. Considering the definition of epilepsy, animals with spontaneous seizures, chronically recurrent would be ideal models for human epilepsy. The Genetic Audiogenic Seizure Hamster (GASH:Sal) is a line of Syrian golden hamsters that is being validated as a model of epilepsy. Our model is a hamster genetically susceptible, in which generalized tonic-clonic seizures are induced by sound stimulation. As a part of the validation process of the GASH-Sal strain, we performed the current study using well-known and widely prescribed AEDs, including Phenobarbital (PB), Valproic Acid (VPA), Levetiracetam (LEV), Lamotrigine (LTG) and Retigabine (RGB). The goal of this study is to characterize the pharmacological and neuroethological response of GASH: Sal to these AEDs. AEDs dose that produces 50% seizure blockade (ED50) following acute administration was: 0.5 mg/kg for RGB, 5 mg/kg for LTG, 10 mg/kg in PB, 30 - 50 mg/kg for LEV, and 225 mg/kg for VPA. Anticonvulsant effects and possible neurotoxic effects of drugs are characterized determining the severity index of the seizures and by neuroethological analysis. The
behaviors present during the crisis are recorded and analyzed according to a dictionary of behavioral items and the ETHOMATIC program.

18- **A Genetic Context for the Study of Audiogenic Seizures**

Stephen C. Maxson (Department of Biobehavioral Sciences, University of Connecticut, Storrs, CT, USA)

**Abstract:** I will review four aspects of my past work on the genetics of audiogenic seizures. These include 1) Characterizing the behavioral and neural phenotypes. 2) Single gene mutations with effects on audiogenic seizures and on two neural phenotypes. 3) Effects of hippocampal lesions on audiogenic seizures. 4) Effects of diet on audiogenic seizures. I will also relate these to more recent findings on the genetic and neural bases for audiogenic seizures.

19- **The role of Egr2 and Egr3 in audiogenic seizures**

Dolores E. López (Neuroscience Institute of Castilla y León, University of Salamanca, Salamanca, Spain)

**Abstract:** Genetic animal models of epilepsy are important tools to understand better the basic cellular mechanism of epileptogenesis and disclose new targets for antiepileptic drugs. We conducted a comparative study of gene expression in the inferior colliculus, a nucleus that triggers audiogenic seizures, in two animal models, the Wistar audiogenic rat strain (WAR) and the genetic audiogenic seizure hamster (GASH:Sal). To do this, both models were exposed to auditory stimulation, and 90 min after the seizure, we collected the inferior colliculi for gene expression analysis. As controls, normal Wistar rats and Syrians hamster were exposed to the same stimulation and followed the same procedure. After the RNA isolation, microarray and data analysis were performed using Affimextrix arrays for rat (Gene 1.0 ST Array) and mouse (GeneChip® Mouse Gene ST Arrays), respectively.

Microarray comparison between stimulated Wistar and WAR rats showed that the genomic profile in these animals was affected with a significant (Fold Change, FC ≥ 2.0 and p < 0.05) up-regulation in 38 genes and down-regulation in 47 genes. Comparison between the gene expression profile of
stimulated control hamster and stimulated GASH:Sal resulted in up-regulation of 10 genes and down-regulation of 5 genes.

Among the common genes that were altered in both species, we found the zinc finger immediate early growth response, egr-2 and egr-3. The proteins encoded by these genes are transcription factors that are induced by distinct stress-elicited factors. By immunohistochemistry, we found these proteins distributed through the brain at basal and high levels after the audiogenic seizure in several regions, including the hippocampus. It has been reported that Egr3 mediates adaptation to stress and novelty, and might be required for induction of hippocampal LTD, which would explain their presence in regions where the cells are in stress and in the hippocampus.

Interestingly, we also found immunoreactivity to the Egr3 protein in the non-Hodgkin Burkitt-type neoplastic lymphoma that has been previously observed in the GASH:Sal.

20- **MASS1 regulates MAG expression via G\(\alpha\)s/G\(\alpha\)q-mediated PKA/PKC pathways**

**Louis Ptáček** (Department of Neurology, University of Utah, Salt Lake City, UT, USA)

**Abstract:** MASS1 (monogenic audiogenic seizure susceptible 1), also known as VLGR1 (very large G protein-coupled receptor 1), is an orphan G protein-coupled receptor that contains a large extracellular N terminus with 35 calcium-binding domains. A truncating mutation in the Mass1 gene causes autosomal recessive, sound-induced seizures in the Frings mouse. However, the function of MASS1 and the mechanism underlying Frings mouse epilepsy are not known. Here, we found that MASS1 protein is enriched in the myelinated regions of the superior and inferior colliculi, critical areas for the initiation and propagation of audiogenic seizures. Using a panel of myelin antibodies, we discovered that myelin-associated glycoprotein (MAG) expression is dramatically decreased in Frings mice. MASS1 inhibits the ubiquitylation of MAG, thus enhancing the stability of this protein, and the calcium-binding domains of MASS1 are essential for this regulation. Furthermore, MASS1 interacts with G\(\alpha\)s/G\(\alpha\)q and activates PKA and PKC in response to extracellular calcium. Suppression of signaling by MASS1 RNAi or a specific inhibitor abrogates MAG up-regulation. We
postulate that MASS1 senses extracellular calcium and activates cytosolic PKA/PKC pathways to regulate myelination by means of MAG protein stability in myelin-forming cells of the auditory pathway. Further work is required to determine whether MAG dysregulation is a cause or consequence of audiogenic epilepsy and whether there are other pathways regulated by MASS1.

21- Exploiting new technologies to better and understand and model genetic epilepsies in mice

Wayne N. Frankel (The Jackson Laboratory, Bar Harbor, ME, USA)

Abstract: Epilepsy is a common disease with significant heritability. For the past two decades a steady stream of gene discovery revealed some human variants. Additional seizure-causing genes have been identified in animal models. But together these account for only a fraction of all human disease. In the past few years, rapid improvements in genome sequencing, along with a sophisticated understanding of how to use sequencing to mine variants in human populations, have begun to transform many fields. Very recent individual and community-based genomic efforts, including the NIH-funded Epi4k consortium, provide a first glimpse into what a discovery boom for epilepsy looks like. These efforts mostly focused on a subset of disease - childhood epileptic encephalopathy (EE) - defined by intractable, seizures accompanied by cognitive decline, usually very severe. EE is not as common as idiopathic epilepsy, but because of the severity and effect on children, it is a very motivating. Dominant EE variants are not usually heritable in the classical manner, but are detected as de novo or somatic mutations.

The first wave of Epi4K results was very encouraging. We conservatively estimate that > 80 EE genes are now on the map from just these first efforts. Some genes were previously known in epilepsy, including ion channels and neurotransmitter receptors, but many are new. Standing between this unqualified success and new therapies are several key questions, including: How do we know for sure which variants are causal and which are bystanders? Does this group of 80 (or more) genes imply that there are 80 (or more) ways to get disease, or do they instead converge onto a smaller number of pathological mechanisms? What is the relationship between seizures and cognitive decline – is co-dependence the
rule or the exception? What neuron types/circuits are rate limiting for disease? Do milder alleles of EE genes also cause the genetically elusive, but more common, IGE?

Mutant mice provide powerful models for human disease. The field of mouse genetics evolved linearly over the years, slowly acquiring sophisticated tools such as conditional gene targeting and strain diversity panels. It has now exploded due to both genomic technologies and much more efficient and rapid genome editing using techniques such as TALEN and CRISPR. Until now our mouse genetics lab has focused on ‘forward genetics’ and the search for genetic modifiers of susceptibility with some success. We think the time has come to aggressively model precise human epilepsy mutations in mice and use them to address the questions posed above. In the presentation I will discuss the transition of our research from forward to reverse genetics, and also the convergence between the two towards better understanding the etiology of seizures and behaviors in these mice, and identification of convergent pathological mechanisms.
POSTER THEME I. ANIMAL MODELS FOR AUDIOGENIC EPILEPSY AND EXPERIMENTAL SEIZURES

1. Genetically epilepsy prone rats of Krushinsky–Molodkina strain as a model for study of cerebral circulation disturbances: protective effect of ischemic precondition

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Abstract: We used rats of Krushinsky–Molodkina strain (KMR) for investigation of some pathogenetic mechanisms of hemorrhagic disturbances in the brain circulation induced with prolonged acoustic stimulation. In rats of this strain the audiogenic stress induces epileptiform seizures. During long-term standard acoustic stimulation (1.5 min of the 120 dB sound, then 15 min with alternation of 10 sec of 120 dB and 10 sec of 80 dB with 10 sec intervals, and 1 min of 120 dB after 3 min interval), acute hemorrhagic disorders of cerebral circulation develop. A hour after sound stimulation in the middle cerebral artery (MCA) the histochemically stained NADPH-positive perivascular nerve fibers was not observed, while in control KMRs a net of nitrergic nerves occurred. Isolated MCA segments prepared 2 days after audiogenic stress had significantly attenuated vasoconstriction to serotonin in the range of concentrations 2x10^-7 to 10^-6 M. The erythrocyte deformability was significantly decreased 90 min after sound stimulation. These findings suggest that cerebral circulation disorders alter cerebrovascular function possibly leading to secondary disturbances in brain circulation. Ischemic precondition 24 hours before acoustic stress produced with alternation of occlusion of right or left common carotid artery for 5 min with 5 min intervals during 50 min increased the latency period before seizures, decreased motor disfunction during sound stimulation and mortality. The rats of this strain can be used as a model of audiogenic epilepsy and hemorrhagic stroke for study of therapeutic effects of drug-free approaches and drugs including nanoparticles.

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2. **Sex differences in behavioral reaction of Krushinsky-Molodkina rat strain**

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**Abstract:** Modern psychiatry recognizes the specific character traits in people with epilepsy. However, it is still not clear which features of an epileptic nature are associated with sex, and which are not.

In addressing this issue, studies performed in rats Krushinsky-Molodkina (KM) predisposed to audiogenic epilepsy, could be promising. The main aim of the study was to reveal sexual characteristics of behavioral reactions in KM rats. Presented investigations were carried out in epileptic (40 males and 40 females) and mongrel albinio laboratory rats (20 males and 20 females). Both stocks range in age from 4 to 6 months, and weight from 250 to 300g. Behavioral reactions were studied in open-field test (arena diameter - 1m), using video recording. Routine testing included four sets of 3 minutes. Interval between replicates was 30 minutes. Totally 11 indicators describing three main areas of open field activity (locomotor, exploratory and emotional) were estimated.

These findings suggest that there are significant changes in all spheres of behavioral reactions of KM rats. The greatest changes are observed for evolutionary higher levels of organization of behavioral reactions, such as orienting-exploratory behavior and emotions.

Epilepsy significantly affects sexual dimorphism of behavioral reactions, which is normally observed in healthy animals. The sexual differences are saved in locomotor activity (females crossing significantly greater number of arena square and moved at a faster speed than males), disappear in orienting reactions by increasing the vertical activity of the males (rearing), and occur in the emotional sphere of behavioral reactions due to lengthening of females grooming acts.

3. **Sex differences in character of audiogenic seizures in Krushinsky-Molodkina rat strain**

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¹Institute of immunology and physiology UB RAS, Ekaterinburg (Russia)

**Abstract:** It is known that the generalized seizures occurrence in epilepsy is often associated with primary or secondary changes in the level of sex hormones secretion. At the same time, a connection between the gender and the character of epileptiform seizures is practically unexplored. The study of epilepsy in animal models such as Krushinsky-Molodkina (KM)
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albino rats selectively bred for audiogenic seizure susceptibility can bring some clarity to this question. The aim of the study was to identify sexual characteristics of epileptiform seizure in male and female KM rats. Presented investigations were carried out in 4-6 month KM rats weighing 250-300g (30 males and 30 females). Provocation of convulsive activity was carried out in a special box equipped with a sound source (80±2 dB) and video camera. Audible stimulus stopped with the start of seizures, which was understood as the development of motor irritation. On the basis of external signs eight phases of epileptiform seizure and following postictal period were identified. The findings suggest that the sequence of pathological conditions which follow each other in the development of attack is the same in males and females. However, in males the total duration of the convulsive seizure period is significantly higher than in females. That fact is reflected in all of its components – phases of the locomotor excitation, tonic-clonic and clonic convulsions. Females are distinguished by a prolonged phase of postictal breathing resumption. At the same time latency period and postictal phases of dyspnea and catalepsy do not depend on sex of the animals.


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Abstract: The Wistar Audiogenic Rats strain (WAR), a result of endogamic selection for over fifty generations, has been reliably used to reproduce key features of epilepsy. The goal of the current study is to propose the use of the WAR strain, as a suitable model for the study of memory alterations associated to neuropsychiatry comorbidities in epilepsy. Young adult, naive (seizure-free) male WARs were submitted to either Morris Water Maze (MWM), Y-maze or Novel Object Recognition (NOR) cognitive tests. In addition, Y-maze and NOR analysis were performed in middle aged animals. Ethics Committee (protocol number 002/2011). MWM revealed an impairment of reference memory in WARs assessed by the probe trial, while no learning deficits during training sessions in spatial navigation were detected. No difference between Wistar and WAR young adult animals in short-term memory and spatial working memory (in the NOR and Y-Maze tests, respectively) were detected. However, when middle-age animals were submitted to NOR, we found a significant deficit in the WAR group. Data
from different memory-related tests indicate that WAR rats present, along with the epilepsy phenotype, some cognitive comorbidities that could be based on the bidirectional relationship between midbrain and limbic structures.

**Financial Support:** FAPESP, FAPESP-Cinapce, CNPq and CAPES-PROEX. USAL-USP, Program for the Promotion of the Bilateral Cooperation in the Field of Research

5. **The Wistar Audiogenic Rat (WAR) strain: A genetic model to study neuropsychiatry comorbidities in the epilepsies (II). Response to stress and compulsive behavior induced by amygdala application of oxytocin.**


**Neurophysiology and Experimental Neuroethology Laboratory, Ribeirão Preto Medical School,**

**Abstract:** The Wistar Audiogenic Rats strain (WAR), a result of endogamic selection (fifty generations) is proposed in the current study as a suitable model to study neuropsychiatry comorbidities such as anxiety and compulsive disorder in epilepsy. Naive male WARs (n= 7-8/ group; PND70), were treated with corticosterone receptors antagonists or vehicle and submitted to restraint stress before repeated auditory stimulation (audiogenic kindling). Seizure severity index (SSI) and latencies for wild running and tonic-clonic seizures were recorded. Additional naive male WAR and Wistar (270-300 g, n=5/group) were bilaterally cannulated into the amygdala central nucleus (CeA) and microinjected with saline (SAL) or oxytocin (OT). Ethics Committee (054/2007; 012/2011). Restraint-stress enhanced SSI after audiogenic kindling, and blocking gluco- and mineralocorticoid receptors reversed stress effects on SSI and latencies for wild running and tonic-clonic seizures. When the groups Wistar-SAL, WAR-SAL, Wistar-OT and WAR-OT were compared with the group WAR-Basal, we observed that the grooming behavior reached the greatest expression in the WAR-Basal. The grooming score in the group WAR-OT was higher than in the group Wistar-OT. Wistars and WARs microinjected with OT had Fos+ labeling in orbitofrontal cortex, paraventricular hypothalamic nucleus, striatum, globus pallidus and substantia nigra. Data from the current and other experiments indicate that WARs present functional hormonal and behavioral alterations associated with increased anxiety. Endogenous grooming behavior was exacerbated in WAR and even greater than the one induced by OT microinjection in CeA in Wistar animals. Our data are
important for understanding the neurobiology of neuropsychiatric comorbidities associated to epilepsy.

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6. **Postictal catalepsy in audiogenic seizure prone KM (Krushinsky-Molodkina) rat strain and newly bred “0” rat strain**

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**Abstract:** Rats of Krushinsky-Molodkina (KM) audiogenic prone strain and rats of other genotypes which differed in audiogenic fit (AF) intensity were investigated. The reliable group of control animals was created by breeding KM and Wistar rats and selecting animals which lacked AF to sound (strain “0”) together with contrast strain “4” (sharing the same genetic background). In intact rats (KM, strains “0” and “4”) the penetrance and expressivity of audiogenic postictal catalepsy (PC) correlated with AF intensity, with no correlation in Long-Evans and WagRij rats. The intensity of AF and PC was maximal in KM rat strain. The modulation of AF severity by levetiracetam and caffeine confirmed this conclusion. Phenazepam, afobazol, discocilpine and D-serine caused dissociation between AF parameters and the duration of the PC. Low doses of haloperidol induced rather intense catalepsy in rats of KM strain and in strains “4” and “0”, while it was not so prominent in other rats, whose haloperidol catalepsy did not differ. The most marked «pinch» catalepsy (caused by multiple nape pinches) was observed in KM strain rats and in 17% of strain «0» rats and strain «4» rats, but did not develop in Wistar rats, WagRij and black-hooded rats. «Pinch» catalepsy after sound exposure was revealed in all rats, demonstrating AF, except black-hooded rats. «Pinch» catalepsy was significantly increased in rats of strain «0», in which sound exposure did not lead to AF. It means that this pathological trait in AE prone rats could provide the important knowledge for the study of epileptogenesis. **Financial Support:** RFBR grant N 12-04-00360

7. **Monitoring of the auditory brainstem responses during audiogenic seizures in genetically susceptible rats**

Alexey Pospelov, Inga Poletaeva

*Biology Department, Lomonossov Moscow State, University Moscow, Russia.*
Abstract: Audiogenic epilepsy in rodents was shown to be strongly related to the auditory brainstem. In many researches, tectum was shown to be possible primary generator of the epileptical activity. In different genetic and developmental models, various abnormalities of the superior and inferior colliculi were detected. However, a number of those works dedicated to detection of abnormalities in long-term perspective. Estimating that fast dynamics of tectum physiology during the seizure fit is essential for understanding of its pathogenesis, we create a protocol for simultaneous provoking of audiogenic seizures and auditory brainstem responses (ABRs) recording. Research was performed on rats of Krushinskij-Molodkina strain, genetically susceptible for audiogenic seizures. Rats were implanted with nickel-chrome wire electrodes into tectum. After recovery, they were stimulated binaurally by loud dashed noise (short pulses of white noise separated by periods of silence, 27-28 pulses per second). Each pulse provokes ABR, and average power of stimulation is enough to provoke audiogenic seizures with latency 10-20 sec, which also allows to collect baseline ABRs. Rats were tested under various conditions: intact, one hour after seizure fit (when they are mostly unsusceptible for audiogenic seizures) as well as after moderate dose barbiturate or chloral hydrate injection, which prevent seizures. Obtained results allow to suggest strong involvement of collicular system into audiogenic seizures generation. Late components of the ABRs were strongly affected during the fit: from reduction in amplitude to complete loss of detectable waves. No such effect was observed in rats during stimulation under seizure-suppressive conditions.

Financial Support: Russian Foundation for Fundamental research, grants № 09-04-00481 and 12-04-00360

8. Exploration of the Peromyscus Epilepsy Genetic Model

James R. Coleman and Gabor Szalai
University of South Carolina, USA

Abstract: Mice of the genus *Peromyscus* are among the most abundant mammals in North America. Though superficially resembling laboratory mice (*Mus musculus*) and rats (*Rattus norvegicus*), deer mice are not closely related to either of these species. In 1935 a spontaneous recessive mutation appeared among laboratory stocks of *Peromyscus maniculatus artemisiae*, which is controlled by a single gene locus "epl".

Aims: Behavioral characterization of the "epl" stock and identification of the chromosomal location of the "epl" site.

Methods: Behavioral testing has been carried out in a standardized testing chamber subjecting the animals to 105 dB white noise. Homozygosity
mapping has been carried out on 250 F2 and 100 N2 animals using 108 microsatellite markers.

**Results:** The experiments revealed that the severity of the seizure increases as the *Peromyscus* has had more seizures. Interestingly, after five inductions no further animal loss is observed. Through genetic mapping four candidate “epl” loci have been identified.

**Conclusions:** A comparative cytogenetic analysis reveals that the *M. musculus* homologs of the candidate markers on P.m. chromosome 1 and chromosome 23 would be on M.m. chromosomes 7 and 5, respectively. Taken together, our preliminary data suggests that the genetic mutation underlying seizure sensitivity in deer mice resides in a novel gene and is not a homolog of a previously identified susceptibility locus.

**Financial Support:** Supported by National Science Foundation, USA: DBI-0742680 to the National Peromyscus Genetic Stock Center at the University of South Carolina.

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**POSTER THEME II. AUDIOGENIC SEIZURE MODELS: KINDLING AND BEHAVIOUR**

9. **Functional, electrophysiological and microanatomic characterization of the inner ear of the Wistar Audiogenic Rat (WAR) strain.**

AA. Batista Murashima¹, T. Talbot¹, JA. Cortes de Oliveira³, DE. López ², N. García-Cairasco ³, MA. Hyppolito¹

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**Abstract:** The Wistar Audiogenic Rat (WAR) strain is an experimental model of reflex and genetic epilepsies. Acoustic stimulation associated with complex partial epilepsy with involvement of limbic structures and a genetic model of great importance to the study of epilepsy because it portrays the audiogenic crisis in rats. The main goal of this study was to investigate the morphological and functional changes in the inner and outer hair cells (IHC and OHC, respectively) of the WAR strain, before and after acoustic chronic stimulation (audiogenic kindling, AK). 40 animals, aged from 80 to 120 days were studied. All protocols were approved by the Institutional Commission on Ethics in Animals Experimentation. Animals were selected with normal cochlear function, evaluated through the Preyer Reflex, otoacoustic emissions by distortion product (DPOAE) and auditory evoked potentials (ABR). The functional assessment was performed before the acoustic
Audiogenic Epilepsy: From Models to the Clinic

stimulus and immediately after the last acoustic stimulus of the AK protocol. Cochleae were processed for scanning electron microscopy (SEM). DPOAE, signal-to-noise ratio, WAR-kindling group showed a significant difference, with pre-kindling responses significantly higher than those of the post-kindling. In relation to ABR there was a significant difference, ABR threshold in WAR-kindling group was higher than those in the Wistar kindling group. SEM in WAR had evidence of irregular structural bundles in stereocilia of the OHC and IHC. Auditory Function measured by both DPOAE and ABR associated with the SEM allowed to characterize the morphological and functional changes in IHC and OHC of the inner ear in animals with kindled acoustic stimulation in WARs. The present data confirm the hypothesis that audiogenic kindling causes functional and morphological alterations to the inner ear of WARs, with potential impact for tinnitus studies and those on audiogenic seizures.

Financial Support: FAPESP, FAPESP-Cinapce, CNPq and CAPES-PROEX. USAL-USP, Program for the Promotion of the Bilateral Cooperation in the Field of Research

10. Changes in ABR after Audiogenic Kindling in Hamsters of the GASH-Sal strain
AA. Batista Murashima¹, D. Sánchez-Benito², S. Hernández-Noriega², R. Gómez-Nieto², JA Cortes de Oliveira³, DE. López², N. García-Cairasco¹, MA. Hyppolito³

¹Laboratory of Neurobiology of hearing, Ribeirão Preto Medical School, University of São Paulo, ²Institute of Neurosciences of Castilla y León/IBSAL, University of Salamanca, ³Neurophysiology and Experimental Neuroethology Laboratory, Ribeirão Preto Medical School, University of São Paulo

Abstract: Genetic Audiogenic Seizure Hamster (GASH:Sal) is a rodent model susceptible to audiogenic epileptic seizures. Endogenous hyperactivity of the Inferior Colliculus (IC) as well as activity of recruited forebrain areas such as amygdala and hippocampus, after audiogenic kindling (AK), may be related to mechanisms involved in tinnitus generation and its behavioral consequences, respectively. We studied the changes in GASH:Sal ABR and the organ of Corti anatomy after AK. Eight GASH:Sal hamsters were evaluated by for ABR before and after 10 AK stimuli. After the electrophysiological recordings the animals were anesthetized and euthanized for morphological analysis of their cochlea using Scanning Electronic Microscopy (SEM). All protocols were approved by the Institutional Commission on Ethics in Animals Experimentation. There was a change in electrophysiological threshold in GASH:Sal in the right ear greater than 30 dB after AK, ranging from 60 dB to 99 dB. There was no
difference between the ABR latencies of waves I, II, III, IV and V, at 99 dB, before and after the AK. A better definition of the waves and higher amplitude occurred after the AK, with largest amplitude variation to wave IV (p< 0.001). Wave IV represents the activity of the IC and its increase in amplitude represents a high activity of this nucleus in the auditory pathway, without difference between the right and the left sides. SEM analysis showed outer hair cells (OHC) cilia maintenance and disarrangement and irregularity on inner hair cells (IHC) cilia. Trace organization of all waves post-AK is similar to the one in patients with auditory neuropathy and tinnitus after auditory stimulus. Irregularity and disarrangement in the IHC cilia may be related to changes in the synapses between the IHC, spiral ganglion neurons and the auditory nerve, similar to auditory neuropathy. Changes in peripheral auditory system and IC as well as its central projections to the limbic system in GASHs suffering the effects of AK can help understand the behavior, pathophysiology and neuroplasticity of audiogenic seizures, acoustic startle and tinnitus.

**Financial Support:** FAPESP, FAPESP-Cinapce, CNPq and CAPES-PROEX. USAL-USP, Program for the Promotion of the Bilateral Cooperation in the Field of Research

11. **Morphofunctional alterations in The GASH:Sal induced by Audiogenic Kindling**

S. Hernández-Noriega¹, D. Sánchez-Benito¹, JA. Côrtes de Oliveira², N. García-Cairasco², DE. López¹, C. Sánchez¹ and O. Castellano¹

¹Institute of Neurosciences of Castilla y León/IBSAL, University of Salamanca, ²Neurophysiology and Experimental Neuroethology Laboratory (LNNE) of the Ribeirão Preto School of Medicine - University of São Paulo.

**Abstract:** Animal models are important for the study of neural substrates involved in epileptic seizures phenomena. The GASH:Sal exhibits generalized tonic–clonic seizures of genetic origin in response to sound stimulation and is currently being validated as a reliable model of epilepsy. The main focus is to understand the nuclei are activated during a single audiogenic seizure (AS) and which of them are activated after repetitive acoustic stimulation (audiogenic seizure kindling; ASK).

We evaluated behavioral sequences with neuroethological tools, before, during, and after acute and kindled AS. We analyzed each behavioral item, measuring its frequency, duration, and their interactions with others through a validated neuroethological program called Ethomatic. The protocol of 20 stimulation sessions, during 10 consecutive days (twice a day) is known as “audiogenic kindling”. We correlated the behavioral data with histological
quantitative study of the c-fos expression, as a known marker of neuron activation.

We observed behavioral and morphological changes during ASK. Acute AS activated nuclei of the auditory pathway, such as cochlear nuclei and inferior colliculus. ASK is correlated with involvement of limbic areas, such as amygdala, hippocampus, as well as the median eminence and the periaqueductal gray. The behavioral alterations after ASK was demonstrated and was coincident with the increased expression of c-fos in the recruited nuclei.

The current study confirms data from rats about the ASK phenomenon and demonstrates that the exposure of GASH:Sal to acute AS induces c-fos expression and that the ASK activates mainly prosencephalic regions, a quite reliable correlate of the expansion of the original brainstem circuit to forebrain regions. We provide useful information to go forward on the comprehensive characterization of a model of audiogenic epilepsy and the recruitment of brain areas during the kindling.

Financial Support: USAL-USP, Program for the Promotion of the Bilateral Cooperation in the Field of Research

POSTER THEME III. AUDIOGENIC SEIZURE MODELS: BIOLOGICAL SUBSTRATES


C. De Cabo¹, Al. Prieto-Martín¹, S. Llorens², JM. Pardal-Fernández³, L. Muñoz⁴, DE. López⁴, J. Escribano, E. Nava⁵

¹Neuropsychopharmacology Unit, Albacete General Hospital, ²Department of Medical Sciences, Faculty of Medicine, University of Castilla-La Mancha, ³Department of Clinical Neurophysiology, University General Hospital of Albacete, ⁴INCYL-University of Salamanca/IBSAL, ⁵Department of Genetics, Faculty of Medicine, University of Castilla-La Mancha,

Abstract: Nitric oxide (NO) is a gaseous free radical synthesized from the oxidation of L-arginine by three different isoforms of NO synthase (NOS). NO has been connected with the pathophysiology of several neurological disorders including epilepsy. In this work, we investigated the changes in NOS activity and levels in different brain regions after repeated seizures in the novel genetic audiogenic seizure prone hamster (GASH:Sal). Constitutive NOS (cNOS; i.e.: nNOS and (or) eNOS) activity was assessed by a conversion of radiolabeled arginine to citrulline technique in
unstimulated control hamsters and GASH:Sal as well as in controls and GASH:Sal after exposure to 10 epileptogenic sound stimulations. Western blot experiments for nNOS and endothelial NOS (eNOS) were also performed. In the GASH:Sal, cNOS activity increased in the mesencephalic areas studied while cNOS activity decreased in both striatum and cerebral cortex after repeated seizures. nNOS (but not eNOS) expression paralleled the variations in cNOS activity. Our data show a different NOS adaptive response in the regions close to the original epileptic focus (more caudal, in our auditory model) versus the more distant rostral areas possibly recruited at a later stage or after repeated crises. These results provide basis for the discrepancies regarding the role of NO in epilepsy found in previous studies. These opposite caudal versus rostral responses should be taken into account when considering NOS as a possible target for the treatment of epilepsy.

Financial Support: FIS-FEDER: 01/3018 and JCCM: 04048-00, GC 05011 and JI 03001.

13. Physical and chemical composition of urine of rats and hamsters

M. Gómez Juárez Sango1, A. Gómez Juárez Sango2, MG. Picazo1, MJ. Herreros1, JA. Jiménez3, DC. García Olmo3

1Experimental Research Unit, 2Preventive Medicine Department, 3Clinical Analysis Department, Albacete General Hospital, Spain

Abstract: The urinalysis is one of the most informative tests in laboratory animals, and it is useful for knowing the health and physiological status of animals. There is scattered information in the literature about the physical and chemical composition of the urine from rodents, and it would be useful to have reference values. The objective of this study was to define physical and chemical urine values for two rat strains and two hamster strains. We analyzed urine samples from Sprague-Dawley rats (n=26), BD-IX rats (n=13), Golden Syrian hamsters (n=15), and GASH:Sal hamsters (n=15). Commercial metabolism cages were used for urine collection. For chemical urinalyses, the commercial test was ten-patch test strip (Combur 10 Test®, cobas, Roche), and the urinary sediment was analyzed by optical microscopy. The appearance of the hamster urine was a white creamy paste, which contained amorphous calcium phosphate (ACP), while the rats showed pale yellow urine. In all strains except for BD-IX, the urine from male animals showed higher pH than female (8.2±0.2 vs 7.4±0.3; means±sd). In addition, the urine from male hamsters had higher specific gravity and proteins than the male rats. In the urine sediment, hamsters exhibited an increased incidence of ACP, phosphate acid calcium crystals, oxalate calcium monohydrated crystals and total crystals. Thus, GSH and GASH hamsters might be useful for the study of alterations in which
metabolism of calcium/phosphate is involved. All reference ranges of values of urine analyses will be detailed in the poster.

14. **Sequencing of the complete transcriptome of two strains of Mesocricetus auratus, bioinformatic analysis and SRA and TSA online submission.**

D. López-López¹, LJ. Herrero-Turrión¹, LJ. Muñoz², C. Sancho¹, S. Hernández-Noriega¹, D. Sánchez Benito¹, R. Gómez-Nieto¹, T. López-Alburquerque¹, O. Castellano¹, L. Millian Morell¹, DE. López¹

¹INCYL-University of Salamanca/IBSAL, Salamanca, Spain
²Animal Research Center. University of Salamanca, Salamanca, Spain

**Abstract:** Researching gene expression changes after acoustic stimulation on the *Mesocricetus auratus* strain GASH:Sal (a genetic audiogenic seizure hamster, inbred at the University of Salamanca), it was decided to study the *Mesocricetus auratus* Inferior Colliculus Transcriptome after controlled stimulation. Genome sequencing of *Mesocricetus auratus* (also known as the Syrian hamster) has not been completed yet, so it was decided that the readings were going to be mapped opposite to last version of *Cricetulus griseus*’ (the Chinese hamster) genome (with the code NW_003613580 in NCBI’s database). The study was done through two experiments, resulting in the complete transcriptome of the Inferior Colliculus of the GASH:Sal strain and also of the *Mesocricetus auratus* HdsHan®:AURA strain, which was used as control.

After mapping, there were more analysis with results and data that are still being processed, including the gene annotation through various databases of biological process, associated phenotype, molecular function, metabolic pathways and so more. In a first analysis of the annotation, there were found several genes related to the current research on audiogenic epilepsy, as Pgf, Ntrk2, Abcb1b, Npy1r, Slc6a1, Glud1, Grik5 and Aqp4 among others, with associated phenotypes related to epilepsy, temporal lobe epilepsy or seizures. It was also observed the manifestation of two genes that had previously pop up during the research of audiogenic epilepsy on the Wistar audiogenic rat strain (WAR), Npy, related to seizures, and Abcb1a, related to human epilepsy and Status Epilepticus (both involved in the current research focussed on *Mesocricetus auratus*).

In addition, the sequences obtained from the process were uploaded to the NCBI’s databases to be used in other research when released to the public after different adjustments to the data, error correction and various files creation.
15. *Morphological changes of auditory nuclei in the hamster GASH:Sal*

D. Sánchez Benito¹, S. Hernández Noriega¹, L.J. Muñoz², D.E. López¹, L. Millian Morell¹, R. Gómez-Nieto¹

¹INCYL-University of Salamanca/IBSAL, Salamanca, Spain. ²Animal Research Center. University of Salamanca, Salamanca, Spain

Abstract: A hamster strain from the University of Salamanca, the genetic audiogenic seizure hamster (GASH:Sal), is being validated as a new model of epilepsy. As a part of this process, we are studying its auditory nuclei to determine the anatomical substrate involved in the mechanism for inducing audiogenic seizures.

Four control hamsters and six adult GASH:Sal were used in this study. The perfused brains were double stained; by immunochemistry for visualization of calbindine to highlight the superior olivary complex (SOC) nuclei, and by histochemistry with Nissl stainings to stand out the morphology of the nuclei observed with calbindine.

During this first stage, we have specifically analyzed the medial nucleus of the trapezoid body (MNTB), and the lateral superior olive (LSO) by means of the software Neurolucida (v. 10.0, MicroBrightField Inc., Williston, VT, USA) for tridimensional reconstruction, and Neuroexplorer (MicroBrightField) for the morphometric analysis. Statistical differences were analyzed with SPSS.

Results showed that the SOC nuclei MNTB and LSO in the GASH:Sal hamsters exhibited a significant reduction of the volume and area when compared to control hamsters. The number of calbindine-immunolabeled neurons in the MNTB of the GASH:Sal was fewer than controls. Plus, these neurons presented an area and perimeter significantly smaller than neurons of the MNTB in controls. Moreover, the GASH:Sal hamster showed morphological changes in the studied nuclei, being more pronounced in the LSO with a 30% of volume reduction compared to controls. In any case, the changes are smaller than those observed in the original strain.

POSTER THEME IV. ANTI-EPILEPTIC DRUGS IN EXPERIMENTAL ANIMAL MODELS OF EPILEPSY AND CLINICAL ASSAYS.

16. *Treatment of the status epilepticus according to a neural network*

FM. Werner¹,², R. Coveñas²

¹Euro-Schulen Pößneck, Pößneck, Germany. ²Institute of Neurosciences of Castilla and León, University of Salamanca, Spain
Abstract: Status epilepticus is a complication of mostly generalized epilepsies which requires a quick therapy. A neuronal network is developed, and different pharmacological options are derived from it. In audiogenic seizure animal models efficacy of antiepileptic drugs can be examined. In generalized epilepsies exists a neurotransmitter imbalance in the hippocampus with a hyperactivity of dopamine, noradrenaline and glutamate and a hypoactivity of GABA and serotonin. The neuronal network can be described as follows: Dopaminergic neurons in the hippocampus with a high activity transmit a strong postsynaptically excitatory impulse via D2 receptors to glutaminergic neurons, which strongly inhibit serotonergic neurons via NMDA receptors. The glutaminergic neurons have an excitotoxic function as well and exert it towards dopaminergic neurons via NMDA receptors and also via kainate and AMPA receptors. The serotonergic neurons with a low activity transmit a weak activating impulse via 5-HT2C receptors to GABAergic neurons, which weakly inhibit dopaminergic neurons via GABAA receptors. Further neurons and subreceptors play also a role, while NPY2 receptor agonists have an antiepileptic effect by inhibiting the glutamate release. GAL1 receptor agonists which have their effect in the thalamus increase the serotonin concentration. Antagonists of the subtype 5 of the metabotropic glutaminergic receptors have an antiepileptic effect by increasing the serotonin concentration through a reduced glutaminergic inhibition. At the beginning of a status epilepticus, benzodiazepines, i.e. GABAA agonists should be administered in order to increase the GABAergic inhibition of dopaminergic neurons.

In a refractory status epilepticus the administration of the following drugs is possible: Valproic acid which enhances the GABAergic inhibition, Phenytoin which blocks ion channels, Levetiracetam, which increases the GABAergic inhibition and reduces glutamate hyperactivity, Topiramate, which inhibits kainate and AMPA receptors and partly NMDA receptors. In a still refractory status epilepticus ketamine, a NMDA antagonists can be administered, since the number of synaptic GABAA receptors decreases and the number of NMDA receptors increases. An additional mGlu5 receptor antagonist could furthermore stabilize the neuronal network. In audiogenic seizure animal models, valproic acid exerts a good antiepileptic effect, whereas levetiracetam only has a weak effect. It is important to examine neuronal networks in generalized epilepsies in order to optimize the pharmacological options in a status epilepticus.
POSTER THEME V. HUMAN EPILEPSIES

17. Outcome of Intensive Care management of neurosurgical patients before and after the commencement of neurosurgical service in a resource poor Centre: A Nigerian perspective.

OV. Olutayo

1Epilepsy Neurology department, Medical school, University of Ibadan, Nigeria

Abstract: Outcome of intensive care management of neurosurgical patients depends not only on the standard and effectiveness of the treatment obtained but also on the available technical and human resource. We aimed at evaluating the impact of a new neurosurgeon-led team on the outcome of neurosurgical patients managed in our multipurpose resource scarce ICU. Demographics, neurological data, length of stay (LOS) and mortality rates (MR) of patients admitted 5 years before (n=22) and five years after (n=159) the commencement of the neurosurgical service were collated and analyzed. Outcome was retrospectively compared between the two periods. Neurosurgical patients (n=181) constituted 24.6% of 735 admissions into the ICU during the ten-year period. The commonest indications for admission were head injury (157, 86.6%), spinal cord injury (9, 5%) and post brain tumor excision (13, 8.2%). From the first to the second period, the overall MR declined from 77.3% to 47.2%, while MR in head and spinal cord injured patients dropped from 83.3% to 49.6% and 50% to 40% respectively. Among the head injured, outcome was significantly influenced by post-resuscitation GCS (p <0.001) at admission. Contrary to expectation, the mean LOS from admission to discharge and death increased from 5.5 ±4.3SD and 2.1±2.0SD days in the before to 11.1±20.7SD and 3.1±4.6SD in the after-period respectively. The service of a neurosurgeon-led team was associated with improved outcome among neurosurgical patients requiring intensive care management in our resource poor Centre.
General information

Conference Venue

The Congress will be held in the Neuroscience Institute of Calilla y León (INCYL) of the “University of Salamanca”, located within 20 minutes walking distance from the city centre and from most accommodation.

Neuroscience Institute of Castilla y León

Calle Pintor Fernando Gallego, 1, 37007 Salamanca

Telephone +34 923 294 500
Ext. 5300
Fax +34 923 294 750
http://www-incyl.usal.es
Conference venue floor plans

First Floor
- Terrace and coffee room

Second Floor
- Computer Room
- Auditorium (Conference room)
Registration

The registration desk is located in the entrance hall of the Neuroscience Institute of Castilla y León.

It will be open during the following hours:

• Tuesday, September 9th: from 17:00 to 19:00.
• Wednesday, September 10th: from 8:00 to 8:45.
• Thursday, September 11th: from 8:00 to 8:45.
• Friday, September 12th: from 8:00 to 8:45.

Presentations

Oral communications, gathered by themes, will be presented in a total of six subsequent sessions. Presentation and discussion time at disposal for each Guest Speaker will be 20 to 25 minutes for presentation followed by 5 to 10 minutes for questions/discussion (time limit: 30 min).

Please, provide the PowerPoint and other necessary files in a USB memory stick to the moderator before the beginning of the oral presentation session. You may check and edit, if necessary, your presentation during the congress.

All poster communications should remain posted in the designated area (Entrance Hall INCYL - Ground floor) from Wednesday morning to Thursday evening. Presenting authors should be at their posters during the indicated presentation times (see congress program above).

All presentation will be in English
Lunches and coffee breaks

Lunches and Coffees will be provided from Wednesday to Friday free of charge to registered participants.

Coffee breaks will be held in the Neuroscience Institute of Castilla y León (first floor and roof terrace), from Wednesday to Friday, according to the Congress program.

Lunches will be held at the Colegio Mayor Tomas Luis de Victoria (Address: Avenida de los Maristas, 122, Salamanca), located within 7 minutes walking distance from the conference venue.

Gala Dinner

The Gala Dinner will be held in the Palacio de Figueroa – Casino de Salamanca (Address: Calle Zamora, 11, Salamanca) at 20:30 according to the congress program.

A limited number of tickets for the Gala Dinner will be available for purchase at the Registration Desk.
Internet Access

Internet access and PC computers will be available at the Computer Room in the Neuroscience Institute of Castilla y León (second floor) for the registered participants. There will be free WiFi.

SSID Name: audiogenic
Password: audiogenic2014

Guided Visits

A limited number of tickets for the guide visits will be available at the Registration Desk. The guided visits will be free of charge to registered participants. Contact the Program Organizers for more information.

1.-Tourist guided visit to the city’s historical center of Salamanca. Wednesday, 10th September at 18:00 hours.

2.-Tourist guided visit to the old library of the University of Salamanca. Thursday, 11th September at 12:00 hours.

3.-Tourist guided visit to the Casa Lis (Museum of Art Nouveau and Art Deco). Thursday, 11th September at 18:00 hours.

4.-Reception in the Mayor City Council of Salamanca. Friday, 12th September at 18:30 hours.

Programme Book Online

The Congress Programme Booklet is available for download on your personal device. Either scan this QR code or visit the link:
http://gredos.usal.es/jspui/

Congress Website

For more information, either scan this QR code or visit the website: http://eventum.usal.es/go/audiogenic
The Program Organizer Committee gratefully acknowledges the financial support, insight, and participation of the following collaborators: