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How Auditory Brainstem Neurons Develop Biophysical Specializations for Temporal Processing, presented in partnership with American Auditory Society

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DEVELOPMENT OF BIOPHYSICAL SPECIALIZATIONS FOR TEMPORAL PROCESSING

As a result of this continuing education activity, participants will be able to:

• Identify anatomical and physiological components of the lower auditory brainstem important for temporal processing.

• Define biophysical problems that result in the inability to accurately encode temporal aspects of sound based upon animal research.

• Describe physiological components related to temporal processing deficits in the auditory brainstem.

LEARNER OUTCOMES
OUTLINE

• Auditory system and temporal processing
• Biophysical specialization of the auditory system
• Development of synaptic properties
• Development of intrinsic properties
• Research summary
• Relationship with clinical populations
• Questions
NEURAL SYNCHRONY & TEMPORAL PROCESSING

CLINICAL EXAMPLE OF NEURAL SYNCHRONY

Auditory Brainstem Response
Neural Synchrony

Click 85 dB nHL

Neural (Dys)Synchrony

CLINICAL EXAMPLE OF NEURAL SYNCHRONY
BIOLOGICAL BASIS OF NEURAL (DYS)SYNCHRONY

Auditory Neuropathy Spectrum Disorders
& Central Auditory Processing Disorders

BRAINSTEM
Midbrain
Thalamus
Cortex
Nerve
Ribbon

NEURAL SYNCHRONY

Amplitude (μV)
Time (ms)
Phase-Locked Action Potential Firing... Synchronized

Neuron 2

Neuron 1
NEURAL (DYS)SYNCHRONY

Reduced Phase-Locking... No Neural Synchrony

Amplitude (μV)

Time (ms)

Neuron2

Neuron1

10 mV
1 ms

AVCN Neuron

Adendritic neurons

Phasic release of neurotransmitter from presynaptic terminals

Activation of fast and reliable postsynaptic AMPA-type glutamate receptors

Amount and type of ion channels clustered at the site of action potential initiation

End-bulb of Held contact from auditory nerve fibers

BIOPHYSICAL CONTRIBUTION TO NEURAL SYNCHRONY
A DEVELOPMENT PERSPECTIVE

WHY AVIANS?

- Precocious animal
- Analogous to mammals
- Low-frequency hearing
- Decades of research
- Model system for development
MODEL SYSTEM FOR AUDITORY DEVELOPMENT

Events

Age (Embryonic Days)

E9  E11  E13  E15  E17  E19  E21

HATCH

~E13

Before

Hearing Onset

Hearing Refinement

~E16

During

Maturation

E21

After

Developmental Period

Relative to Hearing Onset

E9  E11  E13  E15  E17  E19  E21

MODEL SYSTEM FOR AUDITORY DEVELOPMENT
DEVELOPMENT OF SYNAPTIC RESPONSES

PATCH-CLAMP ELECTROPHYSIOLOGY

Electrical Stimulation

Record Excitatory Currents

1 nA

1 ms
SYNAPTIC TRANSMISSION

Excitatory Current

AMPA-Receptor

Postsynaptic Neuron

Action Potential

mV

ms

1 nA

1 ms

Glu

Ca\(^{2+}\) Channel

Presynaptic Axon

DEVELOPMENTAL CHANGE IN AMPA RECEPTORS

Before

After

GluA1 + GluA2

GluA3 + GluA4

Subunit Switch

Response Kinetics (ms)

V\(_{\text{CLAMP}}\)

-60 mV

Sanchez et al., 2010

Relative to Hearing Onset

Before

During

After

0

1

2

3

11

24

12

Norm
DEVELOPMENT OF INTRINSIC PROPERTIES

PATCH-CLAMP ELECTROPHYSIOLOGY

Inject Current

Record Action Potentials

10 mV
1 ms

Continued
Action Potential Recorded from a Cochlear Nucleus Neuron

**FAST & RELIABLE ACTION POTENTIALS**

**Action Potential Kinetics**

**Jitter**

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**Action Potential Recorded from a Cochlear Nucleus Neuron**

**ACTION POTENTIAL GENERATION**
ACTION POTENTIAL DEVELOPMENT

DEVELOPMENT OF TIME-CODING PROPERTIES
POTASSIUM CHANNELS REGULATE LATENCY & SPEED

After Hearing Onset

Development of Time-Coding Precision

Before Hearing Onset

During Hearing Onset

After Hearing Onset

Jitter = 6100 μs

Jitter = 450 μs

Jitter = 150 μs
POTASSIUM CHANNELS REGULATE PRECISION

UPREGULATION OF POTASSIUM CONDUCTANCES
• Auditory system is ideal for temporal coding
  Anteroventral cochlear nucleus neurons

• Biophysical specializations of the auditory system
  Neural synchrony and temporal processing

• Development of synaptic properties
  Change in AMPA-type glutamate receptors subunit content

• Development of intrinsic properties
  Upregulation of potassium channels that control action potential properties
RELATIONSHIP WITH CLINICAL POPULATIONS

Auditory Neuropathy Spectrum Disorders & Central Auditory Processing Disorders

NEURAL (DYS)SYNCHRONY

Reduced Phase-Locking… No Neural Synchrony
The pathophysiology underlying neural (dys)synchrony in the cochlear nucleus is partly due to:

- Alteration in AMPA-R subunit arrangement
- Changes in potassium channel expression and function
Autifony’s Approach to Hearing Disorders

Autifony’s approach to hearing loss is to target particular ion channels, known as Kv3 voltage-gated potassium channels, which play a key role at many levels of the central auditory pathway. Studies suggest that Autifony’s Kv3 modulators may help to restore the timing of firing of neurons in the auditory brainstem important for central auditory processing.

- **For Age Related Hearing Loss**
In age-related hearing loss, there is evidence for an age-related decline in expression of Kv3 channels. The reduction of these channels and the corresponding loss of function of certain auditory neurons may contribute to the reduction in hearing acuity and difficulty that patients experience in understanding speech. Autifony’s drug is designed to modulate Kv3 channels, improve hearing acuity, and thus reduce some of the symptoms of age-related hearing loss, in particular difficulty with speech understanding. Studies in preclinical models show that Autifony’s drugs can improve key aspects of hearing acuity in aged animals.

- **For Tinnitus**
Tinnitus is characterized by a range of empirical observations, several hypotheses exist to explain how altered central auditory processing leads to the emergence of phantom sounds. Studies to date confirm the importance of Kv3 channels at all levels of the auditory pathway. Profiling of our lead compound shows it can modulate function in both brainstem and cortex in ways that could be beneficial in the treatment of tinnitus. Our research shows that Autifony’s drugs can reduce both the behavioral and electrophysiological correlates of tinnitus in preclinical models.

- **For Noise Induced Hearing Loss**
Acute or chronic noise can damage the cochlea, initiating a series of adaptive as well as maladaptive changes within central auditory pathways that contribute to hearing loss and sometimes the emergence of tinnitus. In collaborative studies we have shown that one of the changes in the central nervous system following noise is the reduced function of Kv3 channels in the auditory brainstem (Pilati et al, 2012, Hearing Research 283:98-106). Further studies in preclinical models suggest that Autifony’s drugs can protect against hearing loss induced by noise.

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THANK YOU