The Search for Tinnitus Cures in the Laboratory: Past, Present, and Future

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The search for tinnitus cures can be traced back to antiquity.

Ancient Egypt, Greece, and Rome used ear infusions: oils, frankincense, tree sap, herbs, soil, radish or cucumber juice, honey, vinegar.

Progress in tinnitus treatment since that time has been slow.

Turning point reached in 1980s and 1990s with the development of the first animal models.
Benefits of Animal Models

- Has resulted in a surge in number of scientific studies
- Has lead to a better understanding of the abnormality and its mechanisms
- Identification of potential drug targets
- Growth in the number of drug candidates that show promise in the laboratory
- Paved the way for clinical trials
What does the abnormal activity look like?

- Hyperactivity

normal spontaneous activity

activity after noise exposure
Where does the abnormal activity occur?

Map of auditory areas (yellow) where tinnitus-related activity has been observed.
Is it possible to turn down the activity in the auditory system pharmacologically?

Yes
How a hyperactive cell is thought to be created

Normally active

Hyperactive

Noise exposure
2 New Approaches of the 21st century

1. Work at the synaptic level:
   Test drugs that increase inhibition
   Test drugs that decrease excitation

2. Work at the ion channel level:
   Test drugs that decrease electrical excitability
Drugs that target synapses that have a tinnitusolytic effect in laboratory studies:

Drugs that activate inhibitory synapses
- Vigabatrin
- Gabapentin
- Taurine
- Carbachol
- Pilocarpine

Drugs that block excitatory synapses
- Memantine
- Ifenprodil
- MK-801
- Gacyclidine
- 7-Chlorokynurenate
- AM-101
Drugs that target ion channels that have a tinnitusolytic effect in laboratory studies:

- **Lidocaine**: Sodium channel blocker
- **Retigabine AUT3**: Potassium channel opener
Summary of drugs that have been found to be tinnitusolytic in laboratory studies

Drugs that reverse tinnitus in animals
- EGb-761
- Lidocaine
- Memantine
- Ifenprodil
- MK-801
- D-AP5
- AM-101 (Esketamine)
- 7-Chlorokynurenate
- Gacylcidine
- Vigabatrin
- Gabapetin
- Taurine
- Sildenafil
- AUT3
- Flufenamic acid

Drugs that reverse tinnitus-related neural activity in animals
- Carbachol
- Pilocarpine

Drugs that prevent development of tinnitus in animals after noise
- Retigabine
- EGB761
Do any of these agents work in humans subjects with tinnitus?

- Ifenprodil
- 7-Chlorokynurenate
- Taurine
- Retigabine
- AUT3
- Sildenafil

The answer is unknown because they are still awaiting clinical trials.
Some drugs that work in animals also work in humans but have limited clinical use:

- **Vigabatrin**
- **Carbachol**
- **MK-801**
- **Lidocaine**

These agents cause dangerous side effects when given systemically, but can reduce or eliminate tinnitus when administered intra-tympanically. Unfortunately, in most cases, the effects are short lasting (less than a few days).
Do any of these agents work in humans subjects with tinnitus?

Some drugs that work in animals have been tested in clinical trials

- **Ginkgo (Egb-761)**
  - Gabapentin
  - The clinical trials have yielded **mixed results** when administered systemically in humans:
    - Some studies show no benefit above placebo
    - Others show benefit superior to that of placebo

- **Memantine**
  - This agent failed to show evidence of a tinnitusolytic effect when taken orally.

- **Pilocarpine***
- **Gacyclidine***
- **AM-101**
  - Intratympanic injections of each of these agents produced improvements in tinnitus that were superior to those of placebo; duration of effects: *<72 hours; **90 days.
What is on the horizon?

We should see more clinical trials with agents that have shown efficacy in animal studies

In particular, look for studies of the following drugs:

NMDA receptor antagonists (Ifenprodil, 7-Chlorokynurenate, AM-101)
Agents with glycinergic activity: Taurine
Potassium channel promotors: AUT3, Retigabine, EGb-761,
What is on the horizon?

There will be increasing effort to define drug targets that do not cause major side effects when activated.

- Look for studies that target specific subtypes of cholinergic receptors
  - Look for clinical studies of AUT00063/AUT3
Summary and conclusions

We have more knowledge than ever before about the mechanisms and substrates of tinnitus.

Numerous drug candidates have been introduced for use in animals that are awaiting clinical trials.

New drugs with more specificity are likely to be introduced in the near future that offer hope of relief from tinnitus with reduced severity of side effects.

At some point in the more distant future, we can expect improvements in pharmacotherapy that will reduce tinnitus symptoms with minimal side effects.

Because tinnitus has multiple mechanisms and multiple causes and profiles, it is reasonable to expect advances in drug therapy to be made for subgroups of tinnitus sufferers, rather than for the patient population as a whole.