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The NO/ONOO⁻ Cycle as the Etiological Mechanism of Tinnitus

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Abstract: Peripheral tinnitus is a good candidate for inclusion under the NO/ONOO⁻ cycle etiological mechanism, fitting each of the five principles of this mechanism. Cases of tinnitus are initiated by at least 11 short-term stressors increasing nitric oxide or other cycle mechanisms. Such cycle elements as *N*-methyl-D-aspartate activity; oxidative stress; nitric oxide; peroxynitrite; vanilloid activity; NF-κB activity; and intracellular calcium levels are all reported to be elevated in tinnitus. Tinnitus is comorbid with some putative NO/ONOO⁻ cycle diseases. Most important, multiple agents that down-regulate NO/ONOO⁻ cycle biochemistry are reported to be helpful in the treatment of tinnitus and related diseases. Previous studies suggested that NO/ONOO⁻ cycle diseases may be best treated with complex combinations of agents predicted to lower NO/ONOO⁻ cycle biochemistry, and such combinations may be helpful in tinnitus treatment. Other inner-ear-related defects, such as acute or progressive hearing loss, vertigo, and dizziness, may also be NO/ONOO⁻ cycle diseases.

Key Words: chronic inflammatory disease; cochlea; excitotoxicity; reactive nitrogen species; vicious-cycle mechanism

Tinnitus is a disease characterized by several important properties. Cases of tinnitus are initiated by a variety of short-term stressors, among them hyperacusis, physical trauma in the region of the ear, infection, and aminoglycoside antibiotic exposure. These then lead to the chronic disease called *peripheral tinnitus*, which is characterized by local oxidative stress, excitotoxicity (including excessive *N*-methyl-D-aspartate [NMDA] activity), excessive nitric oxide, and other aspects of inflammatory biochemistry.

All these basic properties are shared by a group of multisystem illnesses, including chronic fatigue syndrome (CFS), multiple chemical sensitivity (MCS), fibromyalgia (FM), and posttraumatic stress disorder (PTSD), which are now thought to be caused by a vicious-cycle mechanism known as the NO/ONOO⁻ ("no, oh no!") cycle mechanism [1–7]. Tinnitus is also comorbid with these illnesses [8–11], and these are comorbid with one another, suggesting a possible common etiology. The thrust of this study is to outline the basis of the NO/ONOO⁻ cycle as it has been developed for the multisystem illnesses and then to review much of the available data to determine whether tinnitus is a good candidate for inclusion under the NO/ONOO⁻ cycle explanatory model of disease.

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NO/ONOO⁻ CYCLE MECHANISM IN MULTISYSTEM ILLNESSES

Cases of each of the multisystem illnesses—CFS, MCS, FM, and PTSD—are initiated by at least a dozen diverse short-term stressors, including bacterial, viral, and even protozoan infections; exposure to organic solvents or any of three classes of pesticides; exposure to other neurotoxicants, including carbon monoxide and ciguatoxin; physical trauma; and severe psychological stress [1,2,6]. Each of these diverse stressors can initiate a biochemical response leading to increased levels of nitric oxide. A question raised by these observations is how can an increase in nitric oxide lead to the initiation of chronic illness? The proposed answer is that nitric oxide acting primarily through its oxidant product, peroxynitrite, can trigger a biochemical vicious cycle, the NO/ONOO⁻ cycle (Fig. 1).

In the NO/ONOO⁻ cycle, as depicted in the figure, each arrow represents one or more mechanisms by which

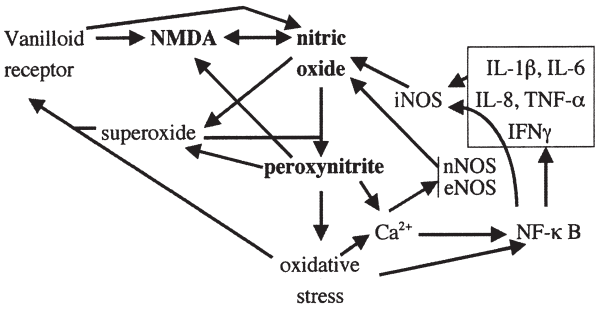

Figure 1. NO/ONOO⁻ cycle mechanism. The vicious-cycle nature of the overall NO/ONOO⁻ cycle mechanism is indicated by the many cyclical patterns shown by these combinations of arrows. This figure is used with permission from the author's Web site (http://molecular.biosciences.wsu.edu/faculty/pall/pall_cfs.htm). (*eNOS* = endothelial nitric oxide synthase; *IFN* = interferon; *IL* = interleukin; *iNOS* = inducible nitric oxide synthase; *NF* = nuclear factor; *NMDA* = *N*-methyl-D-aspartate; *nNOS* = neural nitric oxide synthase; *TNF* = tumor necrosis factor.)

one element of the cycle acts to increase the levels of a second element of the cycle [1–5]. The multiple cycles diagrammed suggest that once the cycle is initiated, it will continue in a self-sustaining cycle. Accordingly, diseases caused by the cycle are initiated by stressors that act to start the cycle going, but the chronic phase of illness is independent of the originating stressor. We have, therefore, both initial causes and ongoing causes of chronic illness. Two components of the cycle are not apparent from Figure 1.

Mitochondrial Dysfunction

Mitochondrial dysfunction is produced primarily but not exclusively through the action of peroxynitrite on mitochondrial proteins and in stimulating poly-adenosine-phosphate ribosylation (poly-ADP-ribosylation) [1–3,5]. Such mitochondrial-energy metabolism dysfunction is an important element of the NO/ONOO⁻ cycle, leading to increased NMDA activity and, possibly, increased levels of intracellular calcium [1,3].

Partial Uncoupling of the Nitric Oxide Synthases

Partial uncoupling of the nitric oxide synthases (NOSs) may be produced through the oxidation of the cofactor tetrahydrobiopterin by peroxynitrite [1,12]. Uncoupled NOS enzymes produce superoxide in place of nitric oxide, with such superoxide reacting with nitric oxide from coupled NOS proteins to produce peroxynitrite. Peroxynitrite oxidizes tetrahydrobiopterin, which leads to further partial uncoupling [1,12]. Partial NOS uncoupling may be of substantial importance in initiating and maintaining the NO/ONOO⁻ cycle, not only because it generates peroxynitrite but because peroxynitrite stimulates NF-κB activity, an important cycle element, whereas nitric oxide lowers NF-κB activity, suggesting that a shift in the ratio of these two may have a key role [1,12].

There are 22 distinct mechanisms diagrammed in the cycle. Of these, 19 are well-accepted, well-documented biochemistry [1]. The other three appear to be correct but are certainly more susceptible to question [1]. It follows that there is a massive amount of data that support one or more aspects of the cycle here, and the only original aspect in proposing the NO/ONOO⁻ cycle is to assume that they may fit together in a reasonable way on the basis of individual interactions. Three generic types of evidence support the existence of the NO/ONOO⁻ cycle, in addition to substantial evidence for its central role in each of the multisystem illnesses [1].

Five principles underlie the NO/ONOO⁻ cycle as an explanatory model [1–3]:

1. Initiating stressors act to stimulate the synthesis of nitric oxide or possibly other elements of the cycle, such as superoxide.
2. The chronic nature of illness is explained by the action of the NO/ONOO⁻ cycle. Each of the elements of the cycle (see Fig. 1) should be elevated in the chronic phase, including nitric oxide, peroxynitrite, oxidative stress, intracellular calcium, NF-κB activity, inflammatory cytokines (upper right corner, Fig. 1), nitric oxide synthase activity, superoxide levels, and activity of two receptor systems, the vanilloid receptor and the NMDA receptors.
3. The symptoms and signs of illness must be explained as being consequences of elevation of one or more elements of the cycle.
4. The basic mechanism of the cycle is local. This is because the half-lives of the compounds of the cycle—NO, ONOO⁻, and superoxide—are relatively short in biological tissues, such that they diffuse only short distances from where they are initially synthesized, and the mechanisms of the cycle act at the cellular level. Because of this local nature, one can have one tissue impacted by NO/ONOO⁻ cycle biochemistry, but an adjacent tissue may be largely unaffected. Variation of tissue distribution in different individuals may lead, in turn, to much variation of symptoms and signs from one individual sufferer to another.
5. These illnesses are best treated by using agents that down-regulate NO/ONOO⁻ cycle biochemistry.

POSSIBLE RELEVANCE TO TINNITUS

Is tinnitus a candidate for inclusion under the NO/ONOO⁻ cycle paradigm? We can ask this question by asking to what extent tinnitus fits these five principles. One of us (MLP) has already made a superficial case for tinnitus [1], drawing on the previous master-of-science studies of the other of us (SAB). Furthermore, a number of important arguments relevant to this question have already been developed by Takumida et al. [13] and by Sahley and Nodar [14]. Here, we will further explore each of the five principles listed above in relation to tinnitus, to determine whether tinnitus and the principles are a good fit.

Short-Term Stressors

Twelve stressors, eleven of which are short-term and the twelfth (genetic) chronic, are reported to initiate tinnitus in humans or animal models (or both) [13,15–45], and all twelve are able to increase nitric oxide levels or other cycle elements (Table 1). It follows that tinnitus has an excellent fit for the first principle of the NO/ONOO⁻cycle model: that stressors initiating the disease should be able to produce elevation of nitric oxide or other cycle elements.

Elevation of Cycle Elements in the Chronic Phase of Illness

Most of the NO/ONOO⁻ cycle elements have been studied in humans or animal models of tinnitus (or both), and each that has been studied is reported to be elevated. Each of these is expected to affect the cochlea in the inner ear. These include nitric oxide [13,28,44]; peroxynitrite [13,44]; oxidative stress [13,44]; intracellular calcium levels [46–48]; mitochondrial dysfunction [45,49,50]; excitotoxicity, including NMDA activity [13,14,45,51–55], inducible NOS (iNOS) induction [13,43]; NF-κB activity [46,56]; and vanilloid activity [57]. It follows that there is substantial evidence that a variety of NO/ONOO⁻ cycle elements are elevated in tinnitus, supporting the second principle underlying this mechanism.

Symptoms and Signs of Disease

Tinnitus is defined as the perception of ringing, buzzing, whistling, or other sounds in one or both ears, in the absence of such sounds. The third principle predicts that one or more cycle elements can stimulate such perception. The role of excessive glutamatergic activity, including activity of NMDA receptors in the hearing transduction process [54,58,59], shows that these NO/ONOO⁻ cycle elements should be able to produce such symptoms. Both nitric oxide [60,61] and intracellular calcium [61] may have a role in hearing transduction as well. Peroxynitrite is known to be able to produce apoptotic cell death [1,3] and may be responsible in part for cellular death in the cochlea in peripheral tinnitus [50,62]. Thus, the third NO/ONOO⁻ cycle principle may also be supported in tinnitus.

Local Nature

The finding that injection of bacterial lipopolysaccharides in the inner ear of animal models produces tinnitus [13,16] argues for the local nature of peripheral tinnitus. Similarly, tinnitus initiation by local physical trauma to

Table 1. Stressors Initiating Tinnitus

Stressor	Nitric Oxide and/or Other Cycle Element Response
Acoustic overstimulation [13,30,36]	Excitotoxicity, including NMDA stimulation, leading to increased nitric oxide levels [4,13,30]; iNOS induction [15]; NF-κB elevation [41]
Bacterial LPS [13,16]	iNOS induction [3]
Gentamicin and other aminoglycoside antibiotics [17,40,44]	Nitric oxide and oxidative stress elevation [44]; NMDA stimulation [17]; iNOS and peroxynitrite induction [44]
Carbon monoxide [21–23]	Known nitric oxide increase [6] and oxidative stress [31], due in part to increased NMDA activity [22,23]
Ischemia [19]	Known increase in superoxide production [1,3]; increased glutamate neurotoxicity (NMDA and non-NMDA activity) [19]
Salicylate [24–26]	Increased NMDA activity [25,26]
Cisplatin [26–29]	iNOS induction due to NF-κB activation [27–29,43]; other?
L-Glutamate [13,19,20]	NMDA stimulation [4,13,14]
L-Arginine [13]	Increase in iNOS activity; increased nitric oxide [13]
Physical trauma [31–34,36]	Increased NMDA activity; other? [1,2]
Infection, especially in the inner ear [35–39]	iNOS induction producing increased nitric oxide levels [1,3]
SDHD, other mitochondrial mutations [40–42]	Lowered energy metabolism leading to increased NMDA activity [4,41,42,45]; possible increase in superoxide generation [3]

iNOS = inducible nitric oxide synthase; NMDA = *N*-methyl-D-aspartate; LPS = lipopolysaccharide; SDHD = succinic dehydrogenase subunit D.

the ear [32–34], acoustic overstimulation [13,30], or local infections [35–39] also supports such an inference.

Though this study is focused on the possible etiology of tinnitus, other inner-ear-related defects, including some cases of acute or progressive hearing loss, vertigo, and dizziness, may also be candidates for a local NO/ONOO⁻ cycle etiology, albeit with differences both quantitative and qualitative in the inner-ear distribution of the biochemistry.

Therapy Via Agents that Lower NO/ONOO⁻ Cycle Biochemistry

The fifth principle of the NO/ONOO⁻ cycle explanatory model is that NO/ONOO⁻ cycle disease should be treated with agents predicted to down-regulate NO/ONOO⁻ cycle biochemistry. Some 30 classes of such agents that are currently available are predicted to act to lower one or more aspects of NO/ONOO⁻ cycle biochemistry [1]. Ten years ago, Shulman [63] suggested using several of these for tinnitus treatment, including calcium channel blockers to lower intracellular calcium levels; free radical scavengers to lower oxidative stress; NMDA and non-NMDA antagonists and GABAergic agents to lower excitotoxicity (including NMDA activity); corticosteroids that lower iNOS induction; calpain to lower the effects of excessive intracellular calcium; and several others. These recommendations were made primarily because of the general neuroprotective activities of these agents, but they may well be prescient. Takumida et al. [13] provided experimental support for a similar group of agents in the treatment of their animal model of tinnitus, including agents that lower excitotoxicity (e.g., NMDA activity, nitric oxide synthase activity, superoxide levels, and peroxynitrite levels) and antioxidants to lower oxidative stress.

Other studies provide support for the use in tinnitus treatment of a number of agents that are predicted to lower NO/ONOO⁻ cycle biochemistry. These are as follows:

- Agents that lower nitric oxide levels [43,44]. High-dose vitamin B_{12} injections, which may act via the hydroxocobalamin form of B_{12} to scavenge nitric oxide [64], are also reported to be helpful [65].
- Agents that lower glutamatergic activity, including NMDA activity [13,14,44,51–55,58].
- Agents that stimulate GABAergic activity and consequent lower NMDA activity [66–68].
- Antioxidants that lower oxidative stress [13,69–75]. In addition to these studies on tinnitus and closely related diseases, antioxidants have been widely reported to protect against damage created by several of the stressors that initiate tinnitus.
- Agents that improve mitochondrial function [49].
- Agents that lower intracellular calcium or the consequences of elevated intracellular calcium [47,48].
- Agents that lower NF-κB activity [46,56].

It can be seen from the foregoing that not only are NO/ONOO⁻ cycle elements elevated in tinnitus but that lowering them is reported to produce improvements, suggesting a significant causal role. Explaining this pattern of evidence is difficult unless the NO/ONOO⁻ cycle or something similar to it is the central causal mechanism in tinnitus.

In the treatment of the multisystem illnesses, agents lowering NO/ONOO⁻ cycle biochemistry individually generally produce modest improvements, but complex treatment protocols, including 14 or more such agents, are reported to be substantially more effective [1,2]. Most agents used in these complex treatment protocols are classified as nutritional supplements and are, thus, widely available. Possibly tinnitus and other good candidates for inclusion under the NO/ONOO⁻ cycle disease paradigm will also respond well to such complex treatment protocols.

SUMMARY

Where it is available, evidence provides support for all five of the principles of the NO/ONOO⁻ cycle explanatory model in tinnitus. These principles are the tests of whether any disease is a good candidate for inclusion as an NO/ONOO⁻ cycle disease, and they suggest that tinnitus should be considered an attractive candidate. In cases in which it affects the cochlea, the cycle is expected to produce tinnitus, but where such cochlear impact does not occur, an affected individual will not have the symptoms of peripheral tinnitus. Most important from the standpoint of tinnitus sufferers, the NO/ONOO⁻ cycle suggests approaches to therapy, and substantial evidence corroborates that such suggestions are consistent with a variety of observations about tinnitus therapy. Complex combinations of agents that lower NO/ONOO⁻ cycle biochemistry may provide improved clinical responses, as they appear to do for such diseases as CFS and FM [1].

Many of the concepts explored here are similar to those discussed by Takumida et al. [13], except that those authors did not have a mechanism for the conversion of short-term stressors initiating tinnitus to the chronic disease. The NO/ONOO⁻ cycle as described in Figure 1 provides such a mechanism and should be viewed, therefore, as a putative keystone to the entire issue of the etiology of peripheral tinnitus. The NO/ONOO⁻ cycle may also cause such other inner-ear-related defects as some cases of acute or progressive hearing loss, vertigo, and dizziness, with symptom variation depending on the tissue distribution and severity of the NO/ONOO⁻ cycle biochemistry in the inner ear.

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