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Potential Roles of Fibrinoid Microclot Complexes in Inhibiting the Cochlear Microcirculation During the Development of Tinnitus

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Review

Potential Roles of Fibrinaloid Microclot Complexes in Inhibiting the Cochlear Microcirculation During the Development of Tinnitus

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Abstract

Tinnitus is an extremely common condition that involves the perception of sound without an external auditory stimulus. However, its origins are not well understood and established treatment options are very limited. Based in part on well-established comorbidities, we here develop the idea, with considerable, mechanistic, and self-consistent evidence, that tinnitus is fundamentally caused by a disorder of the cochlear microcirculation leading to ischaemia and oxidative stress, that this disruption is effected via fibrinoid microclot complexes that inhibit the microcirculation, and that their avoidance or removal by pharmacological or other means might provide considerable benefits to tinnitus sufferers. Such means include anticoagulants, fibrinolytics and antioxidants, the latter commonly acting via the transcription factor Nrf2, and there is evidence for their efficacy, usually (to date) just when they are tested alone. The evidence, including imaging evidence, and extensive evidence regarding the thrombotic mechanisms of toxicity of ototoxic drugs, and in particular of cisplatin, seems sufficiently strong to warrant further development.

Keywords: tinnitus; fibrinoid microclot complexes; microcirculation; coagulopathy; inflammation; oxidative stress

Introduction

Tinnitus is a common and sometimes devastating condition that involves the perception of sound without an external auditory stimulus [1-9]. While truly objective measures are elusive [2, 10-12], it may be classified into subjective or objective, depending on whether, respectively, it is detected only by the patient or also by an external examiner [13]. However, its nature and severity can be quite heterogeneous [7, 14, 15]. In addition, tinnitus may be classified into pulsatile or non-pulsatile; the former is much rarer (ca 4% of patients) and is synchronous with the patient’s heartbeat [16]. Tinnitus can be quite debilitating [17], and pulsatile tinnitus can potentially have multiple origins, including structural, metabolic, and vascular [18]. By contrast, the origins of non-pulsatile tinnitus are much more obscure, and pharmacological and other therapeutic options are seen as limited [12, 19-24]. While standard inflammatory biomarkers have mostly not been found in plasma for simple tinnitus [25-27] (cf. [28])(they have for tinnitus with distress [29] or after noise-induced hearing loss [30]), oxidative stress is a feature of all of these kinds of chronic disease [31] (including tinnitus [32-35]), and there is fairly extensive evidence, developed further below, that antioxidants may be of value [23, 32, 36-41].

Our chief argument herein is that a pro-thrombotic state of the microcirculation, involving microclots leading to oxidative stress and cochlear cell death, is core to the development of (both hearing loss [42] and) tinnitus. Mean platelet volume (MPV) is considered to be associated with highly pro-thrombotic states [43-70]. Importantly for our analysis here, MPV is increased in tinnitus sufferers [28, 71-76], as are the platelet width distribution [73] and the neutrophil:lymphocyte ratio [75]. Similarly, microvascular compressions of the cochlear nerve can lead to tinnitus [77-83], and these can be caused by blockages in the microcirculation, again consistent with our thesis.

We note explicitly that the cochlea is mainly supplied by one terminal artery, the labyrinthine artery, which renders it very sensitive to circulatory alterations and ischemia [84-97]. Consequently, as with many related syndromes [98, 99], and while downstream effects are clearly neural in nature [100-103], we argue here that it is an impairment of the microcirculation (and, in particular, the cochlear microcirculation) that is chiefly involved [32, 39, 97, 104-111]. For instance, arterial stiffness can lead to impaired cochlear microcirculation [112], to ischaemia [112] and to tinnitus [113-116]. A vascular origin for at least pulsatile tinnitus (PT) is also implied by the considerable success of stenting [117-124], and we rehearse other evidence below.

Fibrinaloid Microclot Complexes

Some time ago we discovered that blood can clot into an anomalous, amyloid form [125, 126], to create what are referred to as fibrinaloid microclot complexes, and this was true in a variety of diseases (see Table 1). These insoluble microclots are typically observed to have equivalent diameters in the range 2-200 μm , and so are entirely capable of restricting blood flow to the capillaries and microcirculation. In the case of Long COVID, as an example, the microclots observed [127-137] provide a straightforward explanation for many of the observed symptoms, including fatigue [138], post-exertional symptom exacerbation [139], autoimmunity [140], postural orthostatic tachycardia syndrome (POTS) [141], atrial fibrillation [142], and fibromyalgia [143], as well as accounting for the success of fibrinolytic enzymes [144] and anticoagulation therapies [145] and the anomalous amyloidogenic proteome observed in the microclots that differs greatly from that of normal clots (that roughly reflects the plasma proteome) [146-148]. As with all amyloids, fibrinaloid microclot complexes may be stained using the fluorogenic stain thioflavin T that exhibits green fluorescence when bound to amyloid [149-153]. Figure 1 shows an example taken from an Open Access (CC-BY 4.0) paper [125] that we published in 2016. In this case the microclots can be induced by bacterial lipopolysaccharide, but other papers show that the addition of 17- β -oestradiol [154, 155] or the SARS-CoV-2 spike protein [156, 157] can also do this.

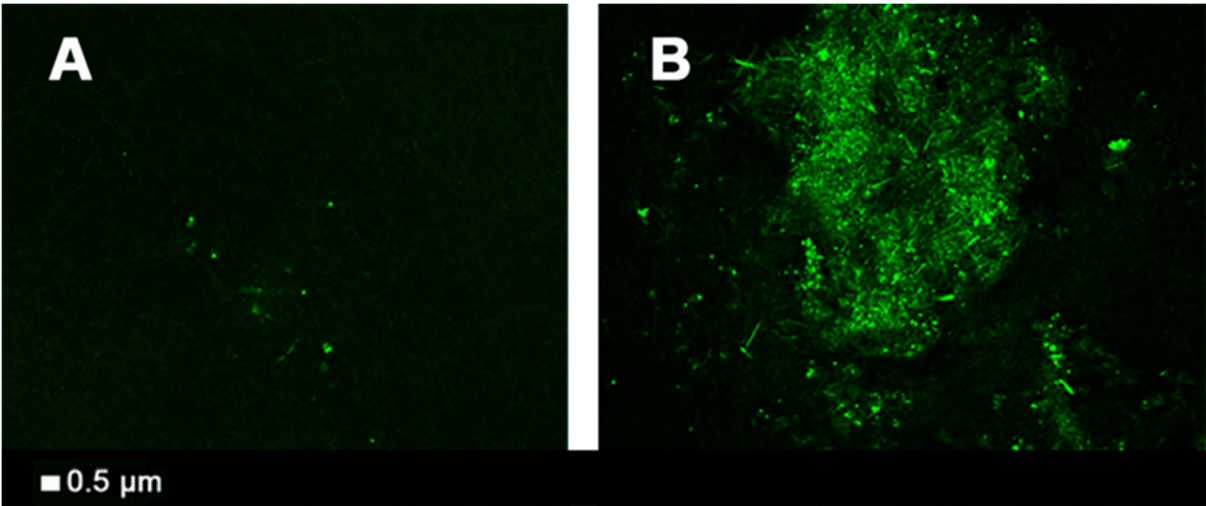


Figure 1. Staining of fibrinaloid microclot complexes in platelet-poor plasma (PPP) using the fluorogenic stain thioflavin T (ThT). A. Control PPP with ThT and thrombin. B as panel A but pre-incubated with 0.2 ng.L^{-1} bacterial lipopolysaccharide (LPS). Taken from the CC-BY 4.0 publication [125].

The purpose of the present article, therefore, summarised in the style of a Graphical Abstract in Figure 2, is to bring together the extensive and self-consistent evidence that supports the idea that fibrinaloid microclot complexes impacting the cochlear microcirculation can account for the symptoms of tinnitus; this leads to some immediate suggestions for effective treatments, for which scattered evidence also exists.

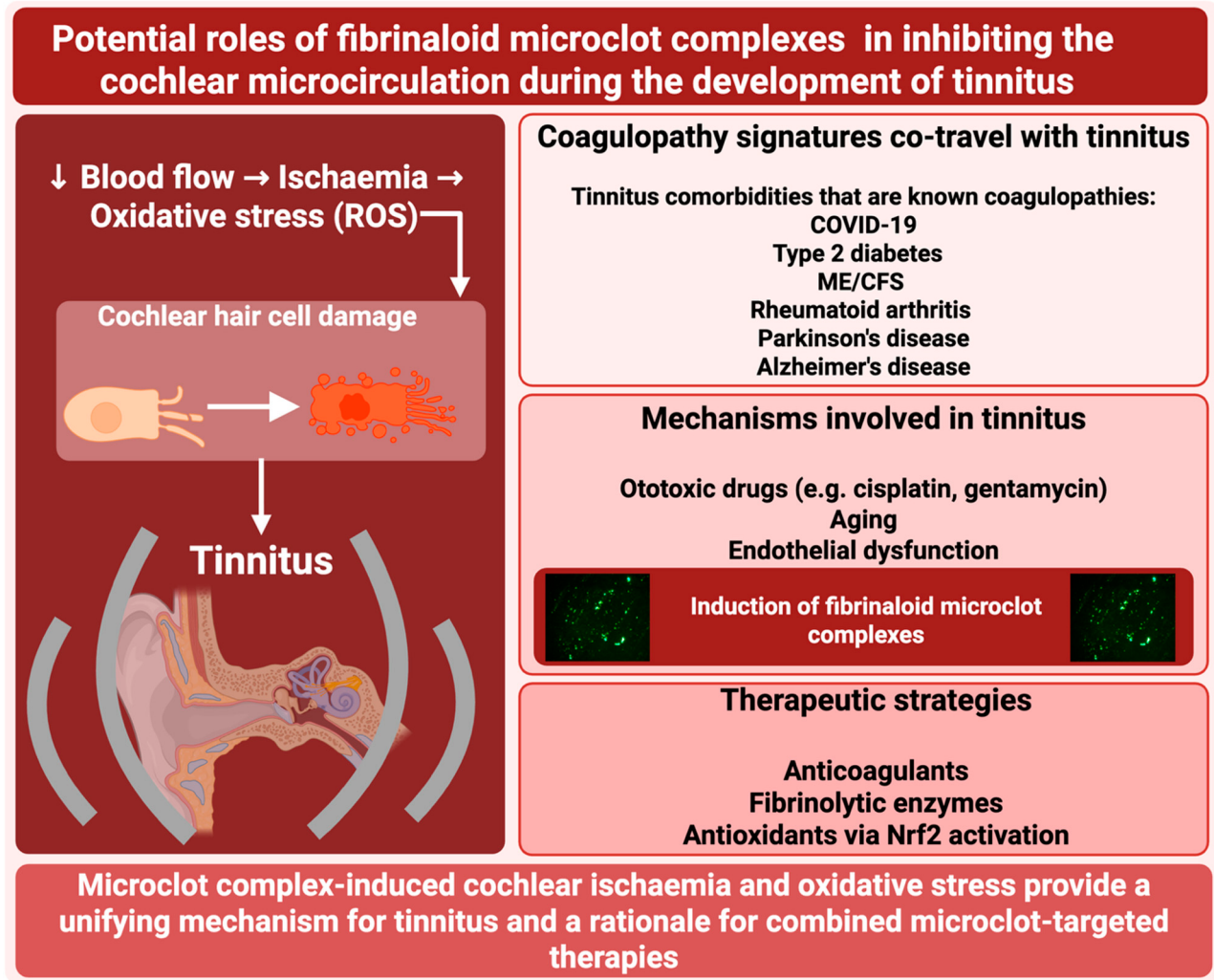


Figure 2. A summary of what follows, in the style of a ‘graphical abstract’.

Results and Analysis

Comorbidities of Tinnitus and Fibrinaloid Microclot Measurements

As with a previous set of strategies [98, 99, 146-148, 158], we begin by comparing those diseases in which microclots have been determined experimentally with those that are known comorbidities of tinnitus (Table 1). Many are cardiovascular in nature [9, 159-161], though note that some are also comorbidities of age [2, 162], and age-related hearing loss and tinnitus are related [10, 163-165].

Table 1. Diseases that are comorbidities of tinnitus and for which fibrinaloid microclot complexes have also been measured.

Disease or syndrome	References indicating tinnitus as a comorbidity	References showing the presence of fibrinaloid microclot complexes
Alzheimer’s dementia incl cognitive impairment. Clear amyloid involvement	[166-174] [175, 176]	[31, 177-180]
COVID19	[95, 111, 181-193]	[127, 128, 156, 157, 194]

Diabetes, type 2	[9, 195-199]	[194, 200-202]
Migraine	[203]	[204]
Myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS)	[95, 205]	[206-208]
Parkinson’s disease	[167]	[200, 209-211]
Post-COVID syndromes	[95, 212-220]	[127-129, 133, 134, 221-223]
Rheumatoid arthritis	[9, 224-226]	[139, 227-229]

The principle of this strategy is straightforward [142]: if diseases X and Y have comorbidities it is likely that they one may cause the other or – especially when there are so many comorbidities – that each is caused by something upstream of both, and here we suggest both that this is the case and that an important ‘upstream’ element on the aetiological is represented by fibrinaloid microclot complexes. The conclusion is equally obvious: every single disease in Table 1 in which fibrinaloid microclot complexes have been detected is also accompanied by tinnitus, and we consider this to be a causal relationship because of other contributing and mechanistic evidence that we shall adduce below.

Syndromes for which fibrinaloid microclot complexes are known but for which we have yet to find published evidence of tinnitus include hereditary haemochromatosis [230] and, in particular, sepsis (see [231, 232]). Hearing loss is a frequent severity-related accompaniment – and possible cause – of tinnitus [164, 233-240]) and is also an accompaniment of experimental sepsis in mice [241] and post-septicaemia in humans [242, 243]). By contrast, many articles show comorbidities of tinnitus but where microclots have not yet been assessed. Some are summarised in Table 2.

Table 2. Some diseases or syndromes that show comorbidities of tinnitus but where microclots have not yet been assessed.

Disease or syndrome	Selected references	Comments
Atherosclerosis	[244]	Atherosclerotic plaques frequently display amyloid
Atrial fibrillation (AF)	[245, 246]	Fibrinaloid microclot complexes provide a ready explanation as being a cause rather than an effect of AF [142]
Congestive heart failure	[109]	
Erectile dysfunction	[247]	This is well known to be overcome by vasodilators [248]
Fibromyalgia	[95, 249-251]	Microclots are also strongly implicated [143]
Myocardial infarction	[252]	
Postural orthostatic tachycardia syndrome (POTS)	[95, 253-255]	Fibrinaloid microclot complexes provide a ready explanation for POTS [141]
Psoriasis	[256-259]	
Raynaud’s phenomenon	[260, 261]	

Sickle cell disease	[262-265]	Clear example in which a primary cause that leads to a lowered microcirculation is associated with tinnitus
Sjögren’s syndrome	[167]	
Systemic sclerosis	[266-271]	

We note here that psoriasis [272-276], Raynaud’s phenomenon [277-284], Sjögren’s syndrome [284] and systemic sclerosis [285-289] are well established as disorders of the microcirculation [98], so it is close to certain that microclots will be found in these cases too. Psoriasis too is certainly a coagulopathy [290].

In addition, a variety of infectious or post-infection disorders that bear similarities to Long COVID (well established to be associated with fibrinoid microclot complexes) predispose to tinnitus [291]. These include Ebola [292, 293], Gulf War illness (tinnitus was the only symptom reported by more than 30% of veterans from this conflict [294]), HIV/AIDS [295, 296], Lyme disease [297, 298] and Varicella Zoster Virus [291, 299, 300].

Cancer is also prothrombotic [301-304], and cancer survivors too are far more prone to tinnitus [305, 306], though we recognise that disentangling these phenomena from the ototoxicities of various cancer chemotherapies is not easy [307-309]. Finally, periodontitis is associated with tinnitus [310], and microbes and their cell wall components are entirely causative of fibrinoid microclot complexes (e.g. [31, 125, 126, 178, 210, 211, 311]). *Porphyromonas gingivalis* and its protease gingipain are also heavily involved [180, 312, 313].

One particular feature of (especially pulsatile) tinnitus is that it may be a harbinger of haemorrhagic or ischaemic stroke [112, 314]. It is thus highly relevant that we recently demonstrated that the thrombi removed by mechanical thrombectomy following an ischaemic stroke are also amyloid in character [315, 316], and that this is entirely consistent with the amyloidogenic contents of the proteome of such thrombi [146, 148], giving a strong indication that the macroclots of ischaemic stroke are formed by accretion of the fibrinoid microclot complexes.

Tinnitus, Hearing Loss, Ageing and Endothelial Senescence/Dysfunction

Any independent variable that correlates with tinnitus may be seen as a candidate for a causal role with a mechanistic basis. Age-related hearing loss (ARHL or presbycusis) and tinnitus are themselves correlated, so tinnitus is associated with ageing [164, 317-321]. While many things vary with age we would here highlight endothelial senescence or dysfunction [322-326], since this is strongly correlated with fibrinoid microclot formation [99, 128, 135, 136, 206, 208, 227, 327-331]. These observations are at least consistent with the mechanisms set down here.

Ototoxic Drugs

Ototoxic drugs are those that can potentially cause damage to the inner ear, leading for instance to hearing loss and/or tinnitus. While there is no certainty that they cause hearing issues by the same mechanisms as those occurring in their absence, the fact that they are ototoxic can certainly help to provide important mechanistic clues. The commonest examples [332, 333] are probably aminoglycoside antibiotics such as gentamycin [334-336] and, in particular, cancer chemotherapeutic agents such as cisplatin [309, 336-357]. As expected [358-363], drug transporters are heavily involved, and are being identified [342, 354, 356, 364-369]. Gentamycin toxicity occurs via an activation process involving the formation of an iron-gentamycin complex with free radical production [370, 371], and antioxidants are protective [372]. In the case of the platinum drugs, Reactive Oxygen Species and oxidative stress [373, 374] leading to apoptosis are certainly also involved in ototoxicity, since various antioxidants [375-377] such as N-acetyl cysteine [378, 379], α -lipoic acid [380, 381], astaxanthin [382],

astragalosides [383], ergothioneine [384] honokiol [385], other polyphenols [353, 386], resveratrol [387, 388] and sodium thiosulphate [389-393] are protective.

Obviously, in the present context, and since many drugs are prothrombotic [394-398], the question arises as to whether ototoxic drugs may also act by slowing cochlear blood flow, for instance by inducing microclots or microthromboses, and gentamycin certainly does decrease carotid blood flow [335]. **Most strikingly**, cisplatin, probably the most ototoxic drug known, is a well-known inducer of clotting (e.g. [399-434]), though as yet it does not seem to have been assessed whether such clots are amyloid in nature. Cisplatin raised cochlear α -fibrinogen levels six-fold, while the protective antioxidant and mucolytic molecule erdosteine more than reversed this [435]. Overall there is a vast literature showing the thrombogenic potential of cisplatin, and since it is also the most ototoxic drug it would seem to be beyond coincidence that ototoxic drugs serve to induce clotting if fibrinaloid microclot complexes are not on the aetiological pathway to both ototoxicity and tinnitus.

Role of Anticoagulants in Treating Tinnitus

If fibrinaloid microclot complexes are involved, it is to be supposed that inhibiting their production might be of benefit. Importantly, this has been shown in a number of cases, including via the use of sulodexide, alone [436] or in combination with the antioxidant melatonin [437, 438], enoxaparin [439, 440], and apixaban [441]. Haemofiltration was also effective [440]. Note that both sulodexide [442, 443] and enoxaparin [444] have also shown themselves to be of value in the treatment of Long COVID, a syndrome closely associated with fibrinaloid microclot complexes (Table 1).

Role of Fibrinolytic Enzymes in Treating Tinnitus

As well as anticoagulants that lower the rate of production of fibrinaloid microclot complexes, a number of protease enzymes are known to have fibrinolytic properties, and consequently can remove microclots [144]. These include nattokinase [445-456], serrapeptase [457-460] and lumbrokinase [461-466] and it is therefore to be predicted that these too will have benefits in treating tinnitus. This has indeed been shown for nattokinase [467] and lumbrokinase [468], and a website also reports <https://www.ehealthme.com/ds/nattokinase/tinnitus/> that of "58,751 people who take Nattokinase (nattokinase) or have Tinnitus... no report of Tinnitus is found in people who take Nattokinase."

Role of Antioxidants in Treating Tinnitus

By blocking up the microcirculation, fibrinaloid microclot complexes necessarily induce oxidative stress [138, 139], and as mentioned, oxidative stress is a significant feature of the development of tinnitus [32-35]). Consequently there is evidence that antioxidants may be of value in contributing to treating it [23, 32, 36-41, 469-474]. Yang and colleagues [35] point out the likely involvement of the transcription factor Nrf2 in this. Nrf2 activation has widespread cardiovascular benefits [475-482], leads to the transcription of a large number of antioxidant response elements [483-488], and, importantly here, to cochlear protection [489-498]. Other antioxidant nutraceuticals such as ergothioneine [499-510] and kynurenic acid (KYNA) [511-514], whose mechanisms of action include Nrf2, may thus be useful components of therapies designed to alleviate tinnitus. While we are not aware of direct studies, hearing loss is a common accompaniment to tinnitus [233, 234, 515], and ergothioneine has been shown to ameliorate it [384, 516]. KYNA did serve to antagonise glutamate-induced cochlear neurotoxicity in neonatal rats [517]. Melatonin, that may also act via blocking iron-catalyses ROS production [518], is a well-established antioxidant [519] that acts via Nrf2 (e.g. [488, 520-524], and has also been stated to be of benefit in tinnitus [469, 525-533]. Sulforaphane, an isothiocyanate cytoprotective commonly found in brassicas, also activates Nrf2 [534-545], but does not seem to have been assessed for tinnitus [490]. Other natural product antioxidants known to activate Nrf2 include polyphenols such as curcumin [546, 547], epigallocatechin gallate [548, 549], quercetin [550] [551, 552] and resveratrol [553-556], and certain diterpenoids [557, 558] and triterpenoids [559-563] (see also [147]). Finally, here, and most pertinently, it is also worth

commenting that Nrf2 activation, which can also involve autophagy [542, 564-568], seems to assist in the amelioration of amyloid-induced issues by a variety of means [569-580].

Dosing

We note that the above says nothing about dosing, since this is intended to be a high-level analysis. This said, experience of many other chronic, inflammatory diseases suggests that what works for one individual may have no effect in others [581]. In an elementary combinatorial sense [582], if 10 out of the ~25,000 human genes can each have two alleles whose gene product varies in activity by a factor two, this variation alone, not even accounting for lifestyle, can explain a roughly 1000-fold (2^{10}) variation in any trait of interest. However, by narrowing treatment modalities to just three classes (antioxidants, anticoagulants, fibrinolytics, plus maybe vasodilators [24]) it is anticipated that discovering the best combined treatments and doses for an individual should be more straightforward.

Consonance of Therapeutics Against Microclots

Taken together, the fact that three different kinds of therapeutics can be of benefit in treating tinnitus, each of which would antagonise the amount or effects of fibrinoid microclot complexes (as would stenting), is very striking and entirely consistent with an aetiological role for the microclots in the development of tinnitus. Other preliminary data linking improvements in the cochlear microcirculation to tinnitus improvement include pycnogenol [583, 584] (a mixture of antioxidant procyanidins [585]) and a cocktail referred to as Acustop [586]. Since causing or adding fibrinoid microclot complexes to assess their effects would be unethical, the best we can do is to seek to relate their presence and number to the severity of the disease, just as has been done in Long COVID [130].

Discussion

We have brought together a number of strands of public data that lead to a coherent picture (in the sense used by Thagard [587-591]) in which fibrinoid microclot complexes have a causal or aetiological involvement in the development of tinnitus:

1. Every disease in which microclots have been measured experimentally demonstrates a comorbidity with tinnitus, making it hard not to suppose that the microclots are causative of each
2. There is extensive evidence that ototoxic drugs such as cisplatin can induce clotting
3. Activation of Nrf2 and its antioxidant response elements is protective against ototoxicity
4. Microclots provide a straightforward mechanistic explanation for tinnitus by decreasing the cochlear microcirculation
5. Microclots thereby produce reactive oxygen species, inflammation [592-595] and, in particular, oxidative stress, a hallmark of tinnitus
6. Stenting also improves tinnitus (by increasing blood flow)
7. Three other therapies designed to obviate microclots or their effects have shown promise when applied singly, namely the use of various anticoagulants, the use of fibrinolytic enzymes, and the use of antioxidants
8. The transcription factor Nrf2 seems to play an important role.

These points are illustrated in Figure 3.

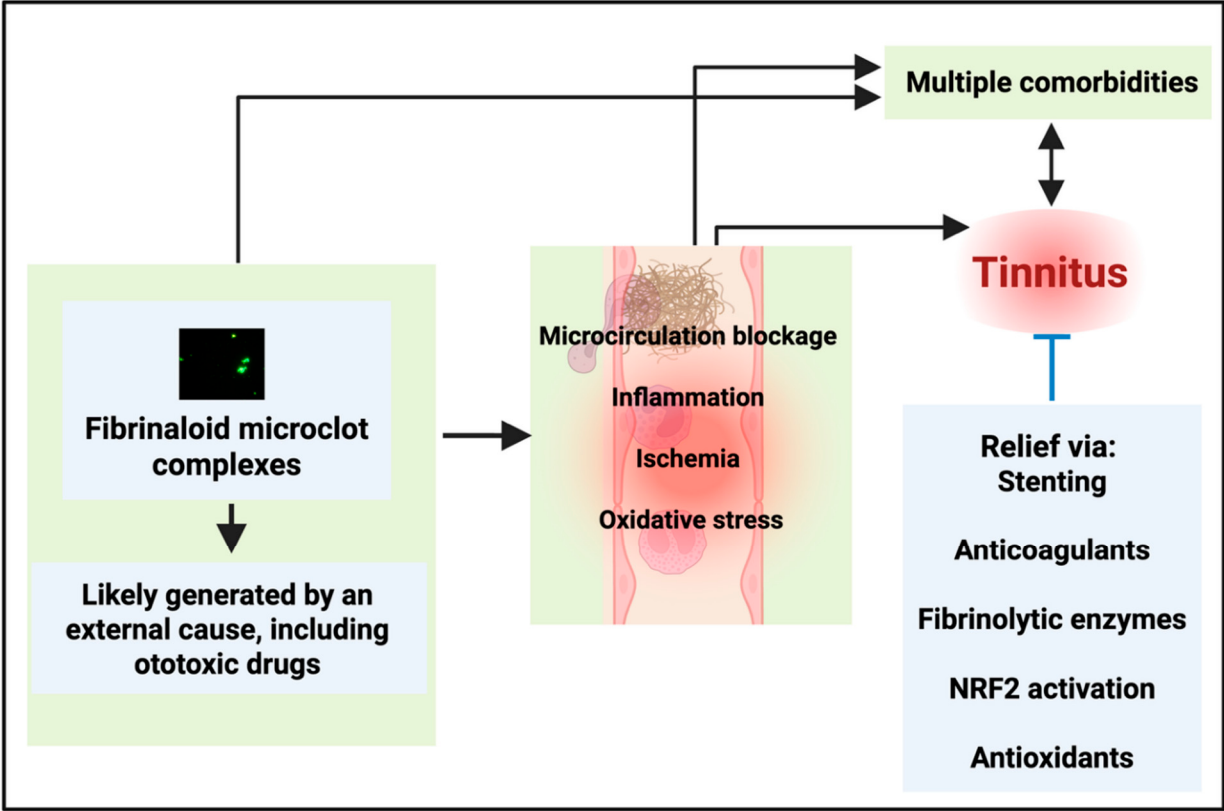


Figure 3. A summary of the main features of the self-consistent set of ideas developed herein (Created in <https://BioRender.com>).

Conclusions and Prospects

We consider that the disparate evidence we have brought together, in this purposely synthetic review [596], provides a robust set of interlinked and self-consistent arguments to the effect that microclot impairment of the cochlear microcirculation is likely to be a significant contributor to tinnitus, and that this recognition offers exciting and novel microclot-based treatment prospects by combining those nostrums that even alone seem to have shown efficacy in some individuals.

The evidence above, to the effect that tinnitus starts as a coagulopathy, includes measurements of mean platelet volume, the extensive comorbidities with known coagulopathies, the demonstrable deficiencies in the microcirculation, and the beneficial effects of interventions (stenting, anticoagulation, antioxidants, fibrinolytics) that would help ameliorate the effects of poor blood flow (‘blood stasis’) within the microcirculation. As such, the proposal is entirely self-consistent. Consequently there are some obvious and technically implementable strategies or measurements that will help to sustain or refute these arguments. These include:

- Fibrinaloid microclot complexes measurements, using fluorescence microscopy or flow clotometry, on platelet-poor plasma of individuals with tinnitus, and an assessment of their relationship to disease severity.
- Correlation of these with endothelial dysfunction [32] (measured e.g. by EndoPAT [597, 598]) and tinnitus severity measured with suitable scales [599] such as the Tinnitus Functional Index [600, 601] and/or the Tinnitus Handicap Inventory [602] and/or the Tinnitus and Hearing Survey [603]
- Assessment of whether known ototoxic drugs can induce fibrinaloid microclot complexes

- *In vivo* imaging of the cochlear and more general microcirculation of those with tinnitus and controls, using methods [604] such as endoscopy [605], fluorescence microscopy [30, 606-608], two-photon microscopy [609], and optical microangiography [84, 610, 611], and especially laser speckle contrast imaging and laser Doppler optical microangiography [99, 612-625]; many of these have already demonstrated a lowered blood flow accompanying hearing loss. There is also a role for the more widely (and financially) accessible methods of capillaroscopy [98].
- Controlled therapeutic trials of suitable mixtures of anticoagulants, fibrinolytic enzymes and antioxidants, as well-established systems biology considerations (e.g. [147, 626-629]) tell us that normally multiple targets must be hit simultaneously to have substantial biological effects.

Hopefully the arguments raised in this review will encourage domain experts to take up some of these ideas and approaches.

Author Contributions: Conceptualization, DBK & EP; Formal Analysis, DBK & EP; Resources, DBK & EP; Writing – Original Draft Preparation, DBK; Writing – Review & Editing, DBK & EP; Visualization, DBK & EP; Funding Acquisition, DBK & EP

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Conflicts of Interest: EP is a named inventor on a patent disclosing the use of fluorescence microscopy in Long COVID.

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