

Similarities Between Chronic Pain and Tinnitus

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Objective: The aim of this study is to review hypotheses about the mechanisms of chronic pain and to compare them with that of tinnitus. Hypotheses about the pathophysiology of severe tinnitus and chronic pain have been of mainly two kinds: one of which claims that pathology located in the periphery (the ear for tinnitus, and peripheral nerves for pain) can explain the symptoms, while the other claims that the symptoms are caused by changes in the function of nuclei of the central nervous system.

Data Sources: A search of the literature from the past 35 years was used.

Conclusions: There is considerable evidence that both chronic pain and some forms of tinnitus are caused by changes

in the central nervous system and that the anatomic location of the physiologic abnormality causing the symptoms of chronic pain and some forms of tinnitus is not the same location to which the symptoms are referred, i.e., the ear for tinnitus and the location of injury for pain. Such changes in the central nervous system may have been induced by peripheral processes such as tissue damage, but the changes can persist a long time after complete healing of a peripheral lesion. Different forms of tinnitus may respond to different treatments as is the case for chronic pain. If the different forms of tinnitus cannot be separated, then the results of studies of the efficacy of different kinds of drugs may be misleading. **Key Words:** Chronic pain—Neural plasticity—Tinnitus.
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Chronic pain and some forms of severe tinnitus are characterized by hypersensitivity to sensory stimulation and a change in the perception of certain stimuli. In patients with chronic pain, stimuli that normally evoke a sensation of touch or vibration may become painful, whereas other types of stimuli may actually alleviate the pain. In patients with severe tinnitus, sounds may be perceived as painful and some sounds may cause the patient's tinnitus to increase, whereas other sounds may cause the tinnitus to decrease.

Hypotheses about pain and about tinnitus have concerned a peripheral cause versus a central cause. Hypotheses that support a peripheral cause have claimed that receptors in the ear (for tinnitus) or receptors in the body (for pain) become hypersensitive and thus cause the pain. The "central" hypothesis claims that it is specific parts (nuclei) of the central nervous system that become sensitized as a result of a peripheral lesion, and the resulting hyperactivity causes the tinnitus or pain. This means that the etiology can be peripheral but the location of the pathophysiology is in the central nervous system.

Over the past two decades, the hypothesis that the central nervous system is involved in the generation of pain has gained support (1-3). The hypothesis about a central origin of pain is based on evidence that even the adult so-

matosensory nervous system has the capability of reorganizing itself and modifying synaptic efficacy (neural plasticity). There is, however, still considerable evidence of a peripheral involvement in both tinnitus (4) and pain (5).

Conceptually, it is difficult to accept the possibility that abnormal neural activity causing a certain sensation is not being generated at the anatomic location where the sensation exists, i.e., in the ear in individuals with tinnitus and in the specific part of the body that is hurting in individuals with pain. Thus, a person with tinnitus refers his or her tinnitus to the ear because it is perceived the same way as would a sound that reaches the ear, and a person with chronic pain will refer his or her pain to a specific part of the body because it is perceived in the same way as acute pain.

When investigating the cause of tinnitus, it is important to regard it as a multimodal disorder that may have different causes and different pathophysiologies (6-8). Consequently, a search for a single treatment for all forms of tinnitus would be futile. The heterogeneity of tinnitus is another similarity to chronic pain whose symptoms are greatly diverse (2,9).

Tonndorf (10) stated, as have others, that the anatomic location (the cochlea or various parts of the auditory nervous system) of the physiologic abnormality that causes tinnitus may be different in different individuals. Subsequent studies support that concept (7,8). The involvement of the central nervous system in the generation of certain forms of tinnitus through neural plasticity has become increasingly evident over recent years. Thus, it is described

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that in some patients with tinnitus, the auditory nerve may be severed near the brain stem without relief of tinnitus (11).

Although the gating hypothesis (12) claims that the central nervous system is involved in pain mainly by controlling the transmission of pain impulses to the brain by peripheral input, there is considerable evidence that chronic pain is a result of changes in the function of specific structures of the central nervous system and that these changes are induced by novel input from the periphery of the nervous system (neural plasticity) (1,2).

NEURAL HYPERACTIVITY AS A CAUSE OF TINNITUS AND PAIN

Most investigators agree that it is the activation of C-fibers that causes sensations of acute pain; it is also accepted that the chronic pain that some individuals experience is generated by a more complex mechanism than that involved in acute pain and that in chronic pain, neural plasticity most likely plays an important role. It is generally assumed that hypersensitivity can be caused either by a centrally mediated increase in the sensitivity of peripheral receptors or by sensitization of structures in the central nervous system (1,2). This also seems to be the case for tinnitus, as there is convincing evidence that there is a difference between acute tinnitus, i.e., that experienced after exposure to loud sounds, and chronic tinnitus. Chronic pain is often associated with hyperalgesia, which is an increased response to a stimulus that is normally painful and that some patients experience in response to noxious stimuli (2,13).

There is thus considerable evidence that both chronic tinnitus and chronic pain involve sensitization of structures of the central nervous system, and that the changes in the function of specific parts of the central nervous system cause a reduction in threshold or an increased excitability of specific nuclei of the central nervous system to result in hyperactivity and hypersensitivity. There is considerable evidence that such changes are brought about by a chain of events that is initiated at the peripheral level of the nervous system rather than by simple abnormal neural activity of specific neural circuitry.

DEVELOPMENT OF CHRONIC PAIN

The fact that the chronic pain that is often seen in connection with (or sequela to) injury of peripheral nerves is often associated with hyperalgesia has resulted in a hypothesis that postulates that chronic pain is caused by hyperactivity of certain neurons in the central nervous system, and the wide dynamic range (WDR) neurons are believed to develop hyperexcitability over a period of time because of events that occur more peripherally in the nervous system (2,9,14). Normally, the firing of WDR neurons does not result in pain sensations, but when they fire at a high rate, which occurs only when these neurons have been sensitized, it results in a sensation of pain in response to stimulation of mechanorecep-

tors that normally does not give rise to the sensation of pain. This is known as "allodynia."^a Somehow this abnormal activity of the WDR neurons spreads to ascending pain tracts of the spinal cord, probably by an increase in synaptic efficacy brought about by neural plasticity.

The contemporary hypothesis of chronic pain assumes that such novel neural activity may over time affect central structures in such a way that specific structures become hypersensitive and hyperactive. Devor (15) outlined different possibilities for neuropathic pain mechanisms and stated that several processes may be active and contribute to neuropathic pain: 1) nociceptive afferents may change their sensitivity in the periphery, and spontaneous activity may cause ongoing pain; and 2) high threshold receptors may become sensitized and nociceptor afferents may develop new pathologic impulse generating capabilities.

The evidence of an involvement of the central nervous system in chronic pain includes the results of studies that show that a peripheral nerve that innervates a painful region can be blocked without resulting in a change in the pain, and indeed it has been reported that in some cases a spinal cord block did not alleviate the pain (1).

Abnormal neural activity generated by an injured nerve can make centrally located structures become hyperactive or hypersensitive, and thereby prone to reverberant, self-sustained activity that causes the sensation of pain. It could be that some external stimulation of such hypersensitive nuclei may trigger "micro seizures" in the respective nuclei to trigger pain. It is interesting to note that not all individuals with peripheral nerve lesions develop chronic pain syndromes. It thus seems that there must be certain conditions present for the development of such hyperactivity.

It is generally accepted that sensory input normally modulates the transmission of neural activity that causes pain (gate hypothesis) (12), which may be one of the reasons why not all seemingly similar kinds of injuries lead to the development of chronic pain. It may also explain why certain forms of stimulation can reduce pain (such as electrical stimulation of the skin—transdermic electrical nerve stimulation [TENS]), whereas other forms of stimulation can exaggerate pain.

The prevailing hypothesis on the development of chronic pain claims that an increased peripheral input or an abnormal peripheral input such as that resulting from injury to peripheral nerves may over time sensitize WDR neurons, and the subsequent high rate of firing of these

^aThe term "allodynia" is usually defined to mean the pain that is elicited by stimuli that ordinarily are innocuous (77). "Allodynia" has, however, also been used to refer to distress caused by pain, and it has been claimed by some investigators (13) that it is not a response to a different modality but rather an increase in pain sensation. The word "hyperpathia" is used to describe an explosive increase in reaction to pain when a painful stimulus exceeds a certain threshold, with a continuing sensation of pain after that the stimulation has ceased (77). The terminology in this respect also used by different investigators differs somewhat (13).

neurons results in the sensation of pain (9,14). There are several ways how sensitization of WDR neurons might occur (9) (Fig. 1). It is possible that a loss of inhibition from low-threshold mechanoreceptors (LTM) causes such hyperactivity (9,16) (Fig. 1B). In such patients, TENS stimulation, or rubbing the skin, causes rather than reduces pain. Normally, activation of LTM neurons does not evoke pain. The pain evoked in such patients is characteristic of C-fiber pain, which indicates that there must be new connections being made between neurons that receive LTM input and those that receive nociceptive afferents. The second mechanism of chronic pain (Fig. 1C) involves an exaggerated response from nociceptive afferents (C-fibers), which would likely be caused by either sensitized mechanoreceptors or an abnormal central facilitating mechanism (9). Such sensitization can occur as a result of injury to peripheral nerves because of the abnormal neural activity generated in such nerves when they are injured (15).

It has been suggested that an injured nerve can generate nerve impulses (15) and that the time pattern of such abnormal neural activity differs from that of naturally occurring impulse traffic in the nerve in question.

DEVELOPMENT OF SEVERE TINNITUS: SIMILARITIES TO THE DEVELOPMENT OF PAIN

In some patients, a strong sound can aggravate tinnitus, a phenomenon similar to pain triggered by light touch of specific areas of the skin or to other forms of neuropathic pain. These attacks of chronic pain may be similar to the hyperacusis that many individuals with tinnitus experience—in these individuals, even weak sounds can be unpleasant. The worsening of tinnitus after exposure to a strong sound may be similar to hyperpathia or allodynia in cases of chronic pain. As is the case for chronic pain, the worsening of tinnitus after exposure to a strong sound can last for many hours. There are also similarities between tinnitus and the “wind-up” phenomenon in pain (17,18). Thus many patients with severe tin-

nitus report that strong sounds are painful and that repeated exposure to strong sounds lowers the threshold for pain from any sound.

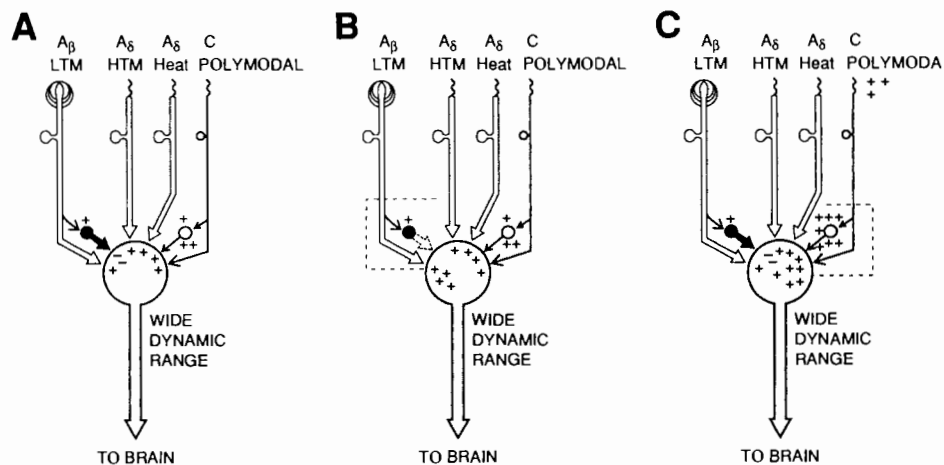
Some patients with tinnitus find relief after specific sound stimulation, and the relief can last for hours after the termination of the specific sound that caused the relief (19), a phenomenon known as residual inhibition. This phenomenon of residual inhibition may be similar to the phenomenon that some kinds of pain can be relieved by stimulation of nerve fibers of the skin, such as that accomplished by TENS, after which the relief from pain sometimes outlasts the stimulation by minutes, hours, and even days (20). Relief from tinnitus after electrical stimulation of the cochlea may be effective in reducing some forms of tinnitus (21) because such electrical stimulation activates neural circuitry in the auditory nervous system similar to that in the pain system.

Tonndorf (10) likened the suppression of some forms of tinnitus by electrical stimulation of the ear with what is known as the “gating hypothesis” for pain that was presented by Melzack and Wall (12). This gating hypothesis assumes that activation of afferent fibers of large diameter (A-fibers) can modulate the conduction of pain impulses in the spinal cord.

IS THE ROLE OF THE INFERIOR COLLICULUS FOR TINNITUS SIMILAR TO THAT OF THE WDR NEURONS FOR PAIN?

There are several observations that point toward the inferior colliculus (IC) as the anatomic location of abnormalities in some forms of tinnitus. Some neurons in the IC may play a similar role in tinnitus as the WDR neurons play in chronic pain. It is known that the neurons in the IC are normally under strong GABAergic inhibitory influence (22) and that they can fire at a high rate if the inhibitory influence is eliminated. Tinnitus may thus result from a decrease of the normal inhibitory input similar to what has been suggested for pain (Fig. 1B) or an increase in firing rate of certain neurons as a result of specific input (Fig. 1C). The abnormal input could be

FIG. 1. Mechanisms that may explain certain states of chronic pain. **A:** Normal nociceptive transmission mechanisms within the spinal dorsal horn. Large circles: Sensory transmission; small open circles with + signs: facilitatory interneurons; filled circles and - signs: inhibitory interneurons. **B:** Loss of inhibitory controls and access to facilitatory mechanisms by A[beta] afferents. **C:** Exaggeration of facilitatory mechanisms activated by C polymodal afferents. LTM, low-threshold mechanoreceptor afferent; HTM, high-threshold mechanoreceptive afferent (9).



loud sounds or neural activity generated by irritation of the auditory nerve or injury to hair cells in the cochlea. As a result, neurons of the IC may fire at an abnormally high rate, which may open connections to other neural circuits normally not activated by sounds; this result is similar to that assumed to occur in the WDR neurons in chronic pain. This would explain the hypersensitivity to sound that some patients with tinnitus experience and the feeling of pain when they are exposed to loud sounds. The observation that the extralemnisal system is involved in certain forms of tinnitus (23) support this hypothesis. The observation that GABAergic neurons die at a faster rate than excitatory neurons with age (24,25), which may result in a decrease of GABAergic inhibition in the inferior colliculus (26), may explain why tinnitus occurs more frequently with increasing age.

There is other evidence that novel stimulation can result in a development of hyperactivity in specific nuclei of the brain. The "Kindling" phenomenon is one such example that was first demonstrated using electrical stimulation of the amygdala (27), but similar stimulation has later been found to cause hyperactivity in other nuclei. Evidence has supported this in that vascular irritation of a cranial nerve such as the facial nerve can lead to hyperactivity in the respective nucleus through mechanisms similar to the Kindling principle (28,29).

INVOLVEMENT OF THE SYMPATHETIC NERVOUS SYSTEM IN CHRONIC PAIN

The sympathetic nervous system may also be involved in the mechanism of chronic pain. Reflex sympathetic dystrophy (RSD) and causalgia are the terms used for pain with sympathetic involvement. These forms of chronic pain are characterized by a high sensitivity to light touch (mediated by mechanoreceptors—not pain receptor) (30). Causalgia is associated with injuries to peripheral nerves, such as those of gunshot wounds. Patients with RSD have characteristic changes of the skin, which becomes red and loses its hair, but there is considerable individual variation in the symptoms (9,14). These conditions are also known as sympathetically maintained pain (SMP) and it is often, but not always, seen as a sequela to injury of peripheral nerves. Chronic pain with sympathetic involvement can often be alleviated by blocking the sympathetic nervous system (by blocking the appropriate sympathetic ganglion or extirpating the ganglion).

Because pain increases sympathetic activity, pain activation will increase, which again increases sympathetic activity (9,13,14). Figure 2 shows a schematic diagram of a physiologic model of how chronic pain may result from trauma to a skin area (14). As a result of the trauma, action potentials elicited by stimulation of C-nociceptors reach the spinal cord (via the dorsal root ganglion, DRG) where WDR neurons are activated and sensitized so that there is an increase in the activity that ascends to high centers of the central nervous system from these neurons. With the WDR neurons sensitized (Fig. 2B), these neu-

rons respond to activity in nerve fibers of large diameter (A-fibers) from mechanoreceptors, which are activated by light touch and produce pain and discomfort (allodynia). The model in Figure 2C shows how the sensitized WDR neurons that respond to activity in fibers of large diameter, but in Figure 2C the activity was not initiated by touch but by sympathetic efferent action on sensory receptors. The model in Figure 2C thus shows how sympathetic activity can cause pain in the absence of physical stimulation. Because pain increases sympathetic activation, the basis for creating a vicious circle is then in place. It has been shown that sympathetic activation can sensitize mechanoreceptors (31). If this vicious circle is interrupted for a period of time (e.g., by sympathetic blockade), the pain may be permanently cured (14,15).

The role of the sympathetic nervous system in chronic pain has been downplayed by Ochoa (5), who found evidence that the antidromic firing of C-fibers is often implicated in specific pain syndromes. Ochoa claimed that

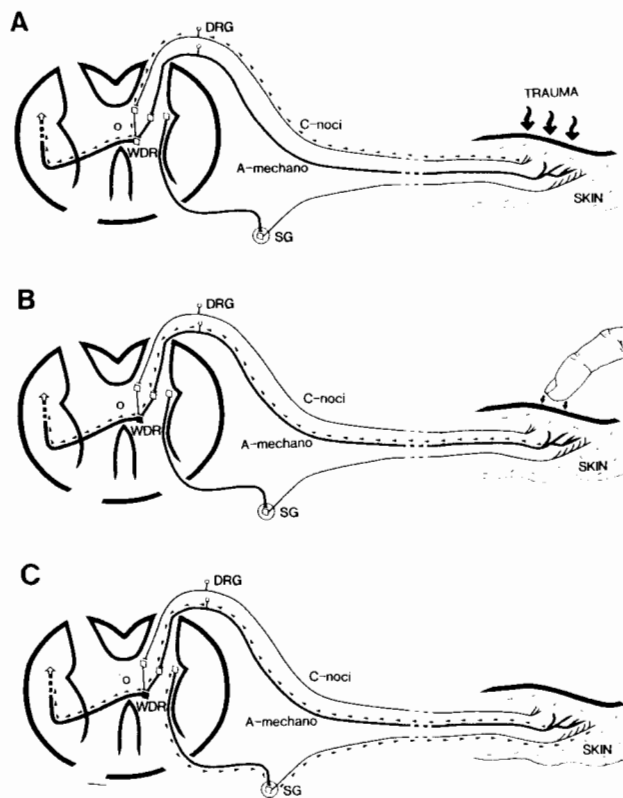


FIG. 2. A physiologic model of pain involving the sympathetic nervous system. **A:** Immediate response to cutaneous trauma. Action potentials in C-nociceptors propagate through the dorsal root ganglion (DRG) to the spinal cord where they activate and sensitize wide-dynamic-range (WDR) neurons whose axons ascend to higher centers. **B:** The WDR neurons remain sensitized and now respond to activity in large diameter A-mechano receptors which are activated by light touch. This state produces allodynia. **C:** The same sensitized WDR neurons respond again to A-mechano receptor activity, but this activity is initiated by sympathetic efferent actions on the sensory receptor, in the absence of cutaneous injury or chronic stimulation (13).

antidromic C-fiber activity (an axon reflex) may cause neuropathic pain that does not involve A-fibers and can be reduced by cooling the skin where signs of sensitized specific modalities of polymodal C-nociceptors indicate hyperalgesia (which can also explain why pain can be modulated by changing skin temperature). Ochoa claimed that many of the signs regarded to be typical for RSD can, in fact, be explained by local phenomena on multimodal C-fiber receptors where the sensitivity of different modalities are modulated in connection with antidromic vasodilation (angry backfiring C-nociceptors, or ABC syndrome) (5).

THE ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN CHRONIC PAIN AND TINNITUS

Cochlear hair cells have abundant sympathetic innervation, the function of which is not well known (32,33); however, it seems reasonable to assume that the liberation of norepinephrine at the terminals of the cochlear hair cells may have an effect on the function of hair cells similar to the one has on mechanoreceptors of the skin, and thus may explain the hypersensitivity to sound in some patients with tinnitus. It has been shown that norepinephrine is present in the cochlea and that most of it is not a result of sympathetic activation (34,35). A few animal experiments show ambiguous results regarding the effects of sympathetic stimulation (36,37), and only small effects were seen on click-evoked auditory nerve compound action potentials from the cochlea, thus not changes that could be associated with an increased sensitivity of hair cells. However, these studies were done in the normal animal, and there may be effects of sympathetic activation that occur only under pathologic conditions and thus may have escaped observation in these animal studies. Other studies indicate that the most apparent effect on the ear from sympathetic activation involves cochlear blood flow (38).

It has been shown that sympathectomy reduces the temporary threshold shift that follows an exposure to loud noise (39). The fact that the sympathetic nervous system has a complex role in tinnitus seems similar to its role in chronic pain. It has been difficult to determine its exact role for the latter (refer to the previous discussion of sympathetically maintained pain). It is not known if there are similar multimodal C-fiber receptors in the ear, the modulation of which could cause hyperactivity that could explain tinnitus. An interaction between the effects on blood flow and sympathetic stimulation may represent a multifunction similar to what is seen in pain mediation of C-fiber receptors that could differentially modulate neural firing in auditory nerve fibers. Such an abnormal firing of auditory nerve fibers could then in turn cause a change in the function of specific nuclei of the auditory system.

Blocking sympathetic input to the ear or a sympathectomy can alleviate tinnitus in some patients (40-44). These results, however, were obtained mostly in patients diagnosed with Meniere's disease. This would support

the hypothesis that the sympathetic nervous system has a function regarding the generation of neural activity that results in some forms of tinnitus similar to what it has in some forms of chronic pain.

THE IMPORTANCE OF TEMPORAL INTEGRATION OF NEURAL ACTIVITY

Pain

One of the phenomena associated with chronic pain consists of a gradual increase in excitability in response to stimuli presented in succession, which results in a progressive increase in the discharge rate of central neurons (known as "wind-up") (17,18). This phenomenon can be demonstrated in response to repetitive stimulation of afferent nerve fibers of small diameters (45), but it cannot be induced by stimulation of afferent fibers of low threshold (46). "Wind-up" may be regarded as a form of temporal integration that is a result of temporal summation of slow synaptic potentials. It is interesting to note that "wind-up" depends on the activation of N-methyl-D-aspartic acid receptors (NMDA) (18). This observation may be important to the treatment of chronic pain, and it may be an effective treatment when substances that block the NMDA receptor become available for treatment purposes (experimental drugs such as MK 801 and D-CPP are currently being tested for this purpose) (2,47). It is interesting to note that, although the sensation of pain from repeating stimuli is stronger when stimuli are delivered at longer intervals, the number of nerve impulses that such stimuli generate in C-fibers is larger when the interstimulus intervals are longer (48-50). This fact supports the hypothesis that the temporal integration in the "wind-up" phenomenon occurs at a central location (17,18). This paradox, how a smaller number of nerve impulses per stimuli causes a stronger pain sensation when stimuli are delivered closer together in time, indicates the importance of temporal summation in the central nervous system in the sensation of pain.

Tinnitus

Several investigators provided evidence that in some cases it is the time pattern of the neural activity in the ascending pathways in the central nervous system that determines whether an activation of a peripheral nerve results in a (normal) sensory perception or a pain sensation (51).

It has also been suggested that the auditory nervous system may detect the presence of a weak sound on the basis of the temporal pattern of nerve activity in many auditory nerve fibers by sensing the temporal coherence of neural impulses in a number of auditory nerve fibers (52). This hypothesis has been used to explain certain forms of tinnitus that might be related to an abnormal generation of neural activity in the auditory nerve (52-54). However, much less is known about the importance of the temporal pattern of sound in eliciting tinnitus than what is known about pain. It is, however, known that many patients with tinnitus experience an increase in

tinnitus after an exposure to sound and that this increase can persist for a long time after cessation of the exposure to the sound.

IS TINNITUS GENERATED IN THE EAR OR IN NEURAL STRUCTURES THAT USUALLY RESPOND TO SOUND?

Although there is indeed evidence that some forms of tinnitus are generated in the ear, evidence has been accumulating that implicates other parts of the auditory system being involved in certain forms of severe tinnitus (7,8,55,56).

There are also reasons to believe that chronic tinnitus is generated in a different way than is the acute tinnitus that is caused by events such as overexposure to sound, thus similar to what is the case for chronic pain in which the neural mechanisms are different from those for acute pain. It is also possible that severe tinnitus is not caused by neural activity in the anatomic structure that was injured or otherwise primarily affected (the cochlea or the auditory nerve), but instead is a result of changes in specific (and different) parts of the central nervous system in which changes were induced by the injury or by other affects on peripheral structures (the cochlea or the auditory nerve) as a result of mechanisms similar to neural plasticity. This assumption is supported by the observation that people who are deaf as a result of cochlear injury or severance of the auditory nerve can have tinnitus (55–58). This makes chronic tinnitus resemble a phantom perception, similar to that of patients with phantom limb pain (7,59–61). Melzack assumed that phantom limb somatosensory sensations were generated in the same brain areas that are activated by normal stimulation of the respective limb, and he argued that tinnitus is also a phantom sensation (61,62).

There is evidence that tinnitus that can be cured by microvascular decompression (MVD) of the auditory nerve where it enters the brain stem (63–67), but the tinnitus may not be generated in the auditory nerve but rather be caused by hyperactivity in nuclei of the ascending auditory pathway that have become hyperactive as a result of vascular irritation of the cochlear nerve (68). The fact that auditory evoked potentials recorded from the auditory nerve intracranially and the components of the brain stem auditory evoked potentials (BAEPs) generated by the auditory nerve and the cochlear nucleus in patients with tinnitus are not statistically different from those in individuals with hearing threshold but no tinnitus that indicates that the neural activity that gives rise to the tinnitus in such patients is not generated in the auditory nerve. Small (but not statistically significant) abnormalities (shorter latency) observed in the components of the BAEP assumed to originate in midbrain structures may be taken as an indication that central auditory structures are hyperactive in tinnitus patients. However, these differences in latency between patients with and without tinnitus were too small to be significantly different from those of individuals with hearing threshold but no tinnitus (68).

Stypulkowski (69) showed in animal experiments that the administration of salicylate, which in humans would likely cause tinnitus, did not cause an alteration in spontaneous neural firing in single auditory nerve fibers. However, and maybe more important, some investigators found an abnormal time pattern in the discharges of auditory nerve fibers (70,71) after an administration of salicylate, suggesting an effect on the coherence of neural activity.

DOES TINNITUS RESULT FROM ACTIVATION OF THE SAME NEURAL STRUCTURES THAT ARE ACTIVATED BY SOUND?

Thus, it seems that enough evidence has accumulated by which investigators can now agree that tinnitus is not always generated in the ear; however, are the structures in the central nervous system that generate the neural activity that gives rise to the sensation of tinnitus in (all) cases of tinnitus the same auditory nervous system that processes normal information from the ear when a sound reaches the ear? Jastreboff and Sasaki (72) found that the spontaneous activity of neurons in the inferior colliculus increased considerably in animals that had been administered salicylate, but there were no similar increases in the discharges of cortical neurons under these same conditions (53,73). Assuming that the treatment of these animals produced tinnitus, these results support the results of other studies that indicate that the sensation of tinnitus may be mediated via means other than the classical auditory pathways (74).

The possibility that tinnitus is the result of an activation of brain areas other than those normally activated by sound is supported by the finding that in some patients the sensation of tinnitus can be modulated by electrical stimulation of the median nerve, whereas the sensation of a (physical) sound in general cannot be modulated in a similar way (74). Møller and Møller noted one patient who reported that rubbing his back with a towel gave rise to a sensation of sound (unpublished observation, 1982). It is known that the extralemnisal (or adjunct) ascending auditory system receives input from other sensory systems, including the somatosensory system (75,76). These results therefore indicate that the extralemnisal system may be involved in some forms of tinnitus. Thus, neural activity that results in tinnitus may not always be transmitted via the same neural pathways that are ordinarily activated by sound.

The strong psychological component that often accompanies chronic tinnitus, just as it does chronic pain, may partly support the assumption that brain areas other than those that are normally concerned with sensory (auditory) stimuli are involved. The extralemnisal system that projects to association cortices may be responsible for evoking the emotional components of tinnitus. Little is known about this system, except that its neurons indeed respond to sound, although in a much less specific way than do neurons in the classical auditory pathway (75).

TREATMENT OF TINNITUS AND PAIN

If one should attempt to make use of the knowledge from research on pain for the treatment of tinnitus, it may be important to note that both chronic pain and tinnitus have many different forms and thus tinnitus should be treated as many different disorders. The treatments that are effective in relieving different kinds of tinnitus may therefore be different from the treatment that is effective for another kind of tinnitus. An important similarity between tinnitus and pain is the hypothesis that some forms of tinnitus are caused by a change in the function of specific parts of the central nervous system that are brought about by a novel input from the periphery. The development of most diseases depend on several factors; all of which usually are necessary but none of which are sufficient to cause a manifestation of symptoms and signs. This is also generally the case for chronic pain and tinnitus and it may explain why diseases such as trigeminal neuralgia can be treated successfully both by medicine and by microvascular decompression that presumably removes the irritation of the trigeminal nerve with the irritation being a necessary (but not sufficient) factor for the development of the disease. The medical treatment for TN makes use of drugs that have anti-epileptic effect which are assumed to suppress reverberant neural activity in the trigeminal nucleus. Because such vascular irritation is necessary but not sufficient, removal of one of the other (necessary) factors represents an effective treatment.

The observation that vascular compression of cranial nerves can exist without any symptoms or signs is also evident from many studies that show that vascular compression is rather common (29). This supports the assumption that vascular compression is not sufficient (but necessary) to cause symptoms but another factor (or factors) must also be present in order that symptoms become manifest (29).

If this is applicable to tinnitus then it implies that removal of the peripheral pathologies may reverse the changes in the central structures, but the tinnitus may also be alleviated by medical treatment that reverse the central changes. There may also be forms of tinnitus where the peripheral cause can be reversed without a reversal of the central cause. The observation that severance of the auditory nerve does not alleviate tinnitus may be an example of that.

Other attempts to reverse the changes in the central nervous system that cause chronic pain by using electrical stimulation (TENS) have been rather successful. Maskers for tinnitus would be equivalent to TENS for pain. Although the presently available tinnitus maskers have proven effective in some patients with tinnitus, a search for more suitable stimuli for tinnitus maskers could be of value. The use of drug therapy is another area in which knowledge that has been gained in studies of chronic pain may find use in the development of effective treatment for severe tinnitus. Medical treatments that amplify GABAergic inhibition have already been shown to be effective in treating some forms of tinnitus, but anti-

epileptic drugs that are sodium channel blockers may also be effective. The observation that a combination of different drugs is often more effective than a single drug for treatment of pain may also be applicable to certain forms of tinnitus. However, it could be that the observation that tinnitus has many different causes is the most important lesson that can be drawn from pain research. That would also explain why different drugs are effective in treating patients with tinnitus.

The fact that different kinds of drugs may be effective in treating specific forms of tinnitus makes it difficult to test the efficacy of drugs that are aimed at treating tinnitus. If it is not possible to separate different forms of tinnitus that are treatable with different drugs, then the results may be that no drug has a beneficial effect in a sufficient number of patients because the group of patients who may respond to a certain drug become diluted in the experimental cohort so that the efficacy does not reach a level that is statistically significant. The result may then be that none of the drug or therapies appears to be a valid treatment.

CONCLUSIONS

There is ample evidence that there are similarities between the pathologic conditions of both tinnitus and pain. It is therefore possible that the considerable amount of research on pain may add to our understanding of the pathology of tinnitus and may be helpful in finding new and better methods for treatment of tinnitus.

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COMMENTS

Although the analogy between chronic pain and tinnitus was proposed by Tonndorf in 1987 (1) and further expanded in the 1990s (2,3), this article offers an excellent review and update of the available data relating pain and tinnitus and further expands Møller's recent postulate on the involvement of the somatosensory system and multisensory neurons in tinnitus (4,5). Although our understanding of tinnitus is still limited, it is possible to gain better insight into the potential mechanisms by using our knowledge of neurophysiology. This article can be added to the group of publications that are moving the mechanisms of tinnitus away from the "cochleocentric" view. Moreover, the postulate of the involvement of neuronal plasticity in tinnitus emergence, including the "kindling" and "wind-up" phenomena, has profound theoretical and clinical implications.

It seems that the limbic and autonomic nervous systems, which are involved in chronic pain (6), are also involved in tinnitus (2). Recent studies on patients with tinnitus using the positron emission tomography technique (7) support the involvement of the limbic system in tinni-

tus, as previously proposed (2,3). Additionally, the coexistence of gaze-related tinnitus with cutaneously evoked tinnitus (tinnitus that can be invoked by stroking an area of the left wrist) (8,9), suggests that, at least under some conditions, the interaction of the somatosensory and auditory systems can result in the emergence of tinnitus, which can be directly controlled by the somatosensory signals. Finally, the recently described changes in the temporal pattern of neuronal spontaneous activity may also be related to tinnitus (10). Developments in the last decade point out the importance of investigating other systems, in addition to the auditory, for the mechanisms of tinnitus. This article offers another exciting perspective.

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