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Review Article

Is central hyperacusis a symptom of 5-hydroxytryptamine (5-HT) dysfunction?

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Abstract

The subjective symptom of hyperacusis is described. The terms 'hyperacusis' and 'phonophobia' are considered to be synonymous as there is no recognized distinction between these two descriptions. Peripheral auditory pathologies with associated hearing sensitivity are reviewed and the likely mechanisms underlying the hyperacusis are listed. The neurological conditions, which have been reported to occur with hyperacusis, are reviewed. A separate aetiology of central hyperacusis is therefore proposed, with a symptom profile distinct from the peripheral hyperacusis.

A common factor to neurological conditions with hyperacusis, is disturbance of 5-HT (5-hydroxytryptamine) or serotonin function. The research literature on the role of 5-HT in sensory modulation (specifically auditory startle) in animals is presented. It is proposed that 5-HT dysfunction is a probable cause of increased auditory sensitivity manifested as central hyperacusis or phonophobia.

Key words: Serotonin; Hyperacusis

Introduction

'Hyperacusis' or 'phonophobia' is used to describe an unusual hypersensitivity or discomfort induced by exposure to sound. Mathisen (1969) defines phonophobia as 'an abnormal discomfort for suprathreshold sound that does not annoy healthy individuals'. It is a subjective phenomenon and cannot be verified or quantified by objective measurement just as tinnitus cannot usually be objectively verified. It can only be described through patient report. Although the symptom of auditory hypersensitivity is ill-defined and elusive, sufferers bear vehement testament to the impact it can have on the quality of life (Reich and Griest, 1992).

The term 'hyperacusis' is, strictly speaking, a misnomer for the symptom, as it describes hyperacute hearing thresholds, rather than suprathreshold hearing hypersensitivity (*Dorland's Illustrated Medical Dictionary*, 1988). The alternative term for central hyperacusis is 'phonophobia' which may be a more accurate term in that it suggests a central aetiology whereas 'hyperacusis' infers a peripheral site of a lesion. Some authors consider that 'phonophobia' and 'hyperacusis' describe separate conditions (Axelsson and Anari, 1993), however, as there is no recognized distinction, these terms will be treated as synonymous here. This paper follows historical precedent and usually refers to the symptom as 'hyperacusis'.

The prevalence of hyperacusis in the general population is unknown and is probably underreported when occurring with other medically-recognized symptoms like tinnitus, headache or depression. It is important to acknowledge that patients with hyperacusis will not necessarily be confined to the ENT caseload but may be under the care of other hospital specialities.

Recruitment

Hyperacusis is a separate phenomenon to 'recruitment' which describes abnormal loudness growth. Although the mechanism for recruitment is not clearly understood, it has a well-defined association with sensory hearing-impairment, specifically cochlear outer hair cell damage (Moore *et al.*, 1985). Recruitment may be demonstrated in the abnormal loudness growth of sensory hearing impairment. A method of objectively estimating loudness discomfort level in sensorineural hearing loss has been developed by Thornton *et al.* (1989) using auditory

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brain stem responses. The fact that recruitment occurs with hearing impairment, indicates that it is a separate entity to central hyperacusis, which typically occurs in patients with normal audiograms.

The alternate binaural loudness balance test (ABLB) allows quantification of recruitment in asymmetric hearing loss. Priede and Coles (1971) described the value of loudness discomfort level (LDL) testing to give an index of recruitment in bilateral sensorineural hearing loss.

The relationship between over-recruitment and hyperacusis is not clear.

Peripheral hyperacusis

There are several documented auditory impairments, causing changes in the peripheral hearing mechanism, which give rise to sensitivity for loud sounds.

The best documented of these relates to loss of the acoustic or stapedial reflex (AR). The AR is the bilateral contraction of the stapedius muscle, in the middle ear, in response to loud sound (usually at or above 85 dBHL for pure tones). The effect of this is to reduce energy transmission through the middle ear, primarily in the low frequency range. This affords some protection to the cochlea, from high levels of noise exposure. Although it is a simple reflex arc there is evidence that the AR is under tonic facilitatory influences from higher centres in the brain (Mangham, 1984).

Hyperacusis has been described following abolition of the stapedial reflex as seen in idiopathic (Bell's) facial nerve palsy (Adour, 1982), Ramsey Hunt syndrome (Wayman *et al.*, 1990) and myasthenia gravis (Laurian *et al.*, 1983). Although hyperacusis in myasthenia gravis is historically ascribed to loss of the stapedial reflex, the described hearing sensitivity is not entirely consistent with this aetiology and may warrant further examination.

Hyperacusis can also occur with Ménière's disease (Cawthorne, 1948) and perilymph fistula (Fukaya and Nomura, 1988). Changes in perilymph pressure may cause acoustic reflex reversal and 'audiosensitivity' as proposed by Gordon (1983). Alternatively, endolymphatic fluid pressure variation may modify the microdynamics of the cochlea and the basilar papillae causing changes in the excitation pattern of the outer hair cells.

The diagnosis of hyperacusis, arising from peripheral auditory impairment, can be made by applying standard audiology test techniques as shown in Table I. Peripheral hyperacusis is distinct, both in symptom history and causation, from the proposed central hyperacusis which is the focus of this paper.

Mathisen (1969) reports that stapedectomy patients typically complain of auditory over-sensitivity which subsides over the post-operative months. There are changes in the auditory protection mechanism of the ear (McCandless and Goering, 1974) as the stapedius muscle is cut. However, as the auditory sensitivity improves over time, Mathisen (1969) proposed a central component to this hypersensitivity, arising from a 'lack of central nervous inhibition due to inactivity'.

Evidence for a central hyperacusis

After excluding all the patients with absent acoustic reflexes, positive history of vestibular disorders or a diagnosis of Ménière's disease, there are still a number of people who complain of the inability to tolerate specific, but not necessarily loud, sounds.

There is a range of 'normal' sensitivity to sound in the general population. Some people will tolerate the squeak of chalk on the blackboard or fireworks, while others will not. It is therefore helpful to establish some criteria to distinguish normal sensitivity from the pathological state of hyperacusis. In order to apply a working definition for this symptom, 'auditory sensitivity' is recognized if a patient reports discomfort for sounds that would be acceptable to most normally-hearing people. 'Hyperacusis' will be used if the condition is having an impact on the quality of life by restricting what the patient chooses to do in day-to-day life.

Hazell and Sheldrake (1991) noted that sound intolerance may be part of a global sensitivity, including bright lights and tactile stimulation. The fact that auditory and visual over-sensitivity occur together (SSISG, 1991; Solomon *et al.*, 1992) would argue for a common central causation rather than peripheral sites of lesion.

Phillips and Hunter (1982) objectively measured reduced endurance time for intense auditory and light stimuli in headache-prone and non-headache prone patients. They reported significant group differentiation on the basis of auditory stimulus sensitivity, irrespective of current pain state.

There is no study which specifically assesses the relationship between peripheral auditory sensitivity

TABLE I
OBJECTIVE TESTS FOR PERIPHERAL MECHANISMS OF AUDITORY SENSITIVITY

		Test technique	
Diagnosis	Site of pathology	Acoustic reflex	BSER slope of lat/int function
Bell's palsy	VII cranial nerve	Absent	
Ramsay Hunt	VII/VIII Cranial nerves	Absent	
Myasthenia gravis	Stapedius muscle	Absent	
Ménière's disease with HL	Cochlea and vestibular system	Present/abnormal	? < 0.1 ms/10 dB
Sensory HL with recruitment	Cochlea	Present	< 0.1 ms/10 dB

BSER = Brain stem evoked responses.

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as quantified by the audiogram and self-rated hypersensitivity. Many hyperacusics are reported to have 'normal' audiograms, presumably excluding hyperacute thresholds as well as hearing impairment (Hazell and Sheldrake, 1991; Axelsson and Anari, 1993). The range of sensitivities may therefore reflect differences in processing of suprathreshold sound in the auditory centres in the brain. Priede and Coles (1971) observed that loudness discomfort level testing to assess recruitment, was of little value in patients habitually exposed to intense noise. This suggests that there is an additional central factor in tolerance ability, not relating directly to peripheral hearing ability as reflected by the audiogram.

There are apparent cognitive influences in sensitivity as demonstrated by the increased sensitivity of a mother to her newborn baby, or the ability to hear the phone ring when in a state of anxiety. The correlation of loudness tolerance with anxiety was reported by Stephens (1970) and may account for the variability in loudness discomfort measures over other audiometric indices.

Present management for hyperacusis

At present the commonest ENT management for hyperacusis involves reassurance that it is not an indication of a serious underlying pathology and probable discharge.

The use of tinnitus maskers to change the sensitivity of the sufferer has proved helpful (Hazell and Sheldrake, 1991). The technique was originally found to be helpful with hyperacusis occurring with tinnitus, but can be used with equal success in hyperacusis alone. This technique requires long-term exposure to white noise, starting at very low levels of stimulation, with a gradual increase in intensity over time. A programme of hyperacusis desensitization necessitates more frequent and ongoing intervention than provision of masking for tinnitus alone. The fact that hearing sensitivity can be modified, by controlled exposure of the ear to noise, does not necessarily argue against a central aetiology. The auditory efferent system may well be implicated in the interaction between peripheral and central hearing function.

The types of sounds causing discomfort, to patients with central hyperacusis, are very variable in intensity and frequency, typically including electrical noises such as a washing machine or vacuum cleaner noise. Intolerable sounds may be as quiet as a distant dog bark, a tissue being taken out of a box or newspaper being folded. Patients report that anxiety or tiredness makes their sound tolerance worse, and that specific (though not necessarily loud) sounds cause physical pain and 'nerve grating'. Exposure to such sounds also causes an increase in pulse rate and sweating. These metabolic reactions imply an interaction between pathological hypersensitivity and higher central functions. The description by Jastreboff and Hazell (1993) of hyperacusis as 'a manifestation of increased central gain' is compatible with the profile of central hyperacusis. Coles and Sood (1988) also propose a central aetiology for this symptom. Subjects complaining of auditory over-sensitivity, who have no other peripheral auditory or vestibular symptoms, should be considered to be 'central hyperacusics'.

Neurological conditions and hyperacusis

After excluding known middle ear and cochlear conditions associated with auditory over-sensitivity, the following clinical conditions have been reported to co-occur with hyperacusis. These do not imply a peripheral auditory site of a lesion:

(a) Migraine (Solomon *et al.*, 1992).
(b) Depression (Carmen, 1973).
(c) Pyridoxine deficiency (Oppe, 1992).
(d) Benzodiazepine dependence (Lader, 1984).
(e) Musicogenic epilepsy (case study by Fujinawa *et al.*, 1977).
(f) Tay-Sach's disease or gangliosidosis type 2 (Gordon *et al.*, 1988; Gascon *et al.*, 1992).
(g) Post-traumatic stress disorder.
(h) Chronic/post-viral fatigue syndrome (CFS/PVFS) or myalgic encephalomyelitis (ME) (Behan and Bakheit, 1991; Merry, 1991).

Two other symptoms are reported to occur with hyperacusis: (i) tinnitus (Vernon, 1987; Coles and Sood, 1988); (ii) photophobia (Phillips and Hunter, 1982).

To gain further insight into the possible causation of central hyperacusis, a search was made to identify any feature which is **common** to these neurological conditions. Although there are a number of different neurotransmitter abnormalities in these clinical conditions it is notable that there is a disturbance in serotonin or 5-HT function in each of these diagnoses.

Neurotransmitter systems

Neurotransmitters are the chemicals utilized within the functional neuronal systems in the brain. The behavioural effect produced by a specific neurotransmitter when released at a synapse, depends on the system in which it is operating. Different receptors for the same transmitter may mediate different (inhibitory or excitatory) actions. The interconnections between the noradrenergic, dopaminergic and serotonergic systems cause considerable overlap in the functions of each. This is borne out by the fact that other neurotransmitters are involved in these neurological conditions and none can be exclusively ascribed to 5-HT. However despite the difficulties associated with isolating a specific chemical, the evidence for examining serotonin function is multifacetted.

5-Hydroxytryptamine or serotonin

5-HT is a biogenic amine produced in the brain and the gut in man. There are four main groups of receptors with at least 14 distinct subtypes having been cloned, each with specific actions (Kalkman

and Fozard, 1991; Hoyer *et al.*, 1994). The enormous amount of current work on 5-HT definition and classification coupled with rapid progress in molecular biology techniques inevitably means that new classifications will continue to be made.

There are many documented roles for serotonin based on animal studies and analysis of their behavioural actions in man.

Known roles of 5-HT

5-HT is involved in stimulus reactivity and sensory reception (Davis *et al.*, 1986) in the central nervous system. This includes inhibition of nociception and response to painful stimulation (Langer, 1989). 5-HT is also implicated in the organization of sleep (Langer, 1989). Further studies show that it is altered in depression (Blier and DeMontigny, 1994) along with other neurotransmission systems such as alpha-adrenoceptors. 5-HT has a role in anxiety control (Iversen, 1984; Marsden, 1989). It is the major controlling factor in lower bowel peristalsis (Craig and Clarke, 1991) and has an influence on vasoconstriction/vasodilation (Fozard *et al.*, 1989). Headache and migraine are associated with receptor subtypes 5-HT_{1D} and 5-HT_{2C} (was 5-HT_{1C}) (Lance, 1991). It also has a role in controlling food intake (Langer, 1989).

Table II presents the main known effects of the different subtypes of 5-HT reception in man. The effects of serotonin in the receptor subtypes 5-HT_1 are usually inhibitory and, in subtypes 5-HT_2 5-HT_3 and 5-HT_4, are broadly excitatory. More recent receptor subtype classifications have yet to be fully characterized operationally in intact tissue and are therefore omitted. The precise classification has been updated by Hoyer *et al.* (1994) but the functional significance is unchanged.

The role of 5-HT in sensory modulation

The specific association between sensory oversensitivity and 5-HT has been studied by Davis *et al.* (1980 and 1986) using the behavioural acoustic startle response in rats. Davis *et al.* (1980) demonstrated that the normal startle response to a 90 ms burst of white noise at 115 dB is modified by changes in serotonin levels. The startle response is depressed when serotonin levels in the forebrain are raised and increased by low levels of 5-HT in the forebrain (Davis *et al.*, 1980). The magnitude of the effect is directly related to the dose of the 5-HT agonist. The opposite effect is found when the 5-HT is infused into the spinal cord thus underlining the importance of the different types of receptors and their locations. Activation of 5-HT_{1B} receptors in the forebrain appears to depress the startle reflex (Davis *et al.*, 1986).

In the rat, the latency of the acoustic startle is 6 ms in the foreleg and 8 ms in the hindleg (Ison *et al.*, 1973). This indicates that only a few synapses could be involved in mediating the acoustic startle. The reflex pathway has been delineated by Casella and Davis (1986). It is confirmed that the action of 5-HT is not by mediating the excitation of the reflex pathway, as depletion of 5-HT does not eliminate the reflex. The action of forebrain 5-HT is through inhibitory modulation of the sensory input, though not in a simple, unidirectional fashion.

TABLE II

REPORTED EFFECTS OF 5-HT SUBTYPES (DERIVED FROM KALKMAN AND FOZARD, 1991 AND HOYER *ET AL.*, 1994)

Receptor subtype	Operational characteristics
5-HT_{1A}	Hypotension, anxiety, depression
5-HT_{1B}	Inhibition of neurotransmitter release, startle and sensory modulation (Davies *et al.*, 1986)
5-HT_{1D}	Inhibition of neurotransmitter release, migraine
5-HT_{2A}	Vasoconstriction, platelet aggregation, depression
5-HT_{2B}	Rat stomach fundic muscle contraction
5-HT_{2C}	Migraine, anxiety and eating disorders
5-HT_3	Emesis, anxiety and psychosis
5-HT_4	Gastric stasis, tachycardia

The role of 5-HT in central hyperacusis

Many conditions occurring with hyperacusis as a symptom (migraine, depression, pyridoxine deficiency, benzodiazepine dependence and postviral fatigue syndrome) involve a disturbance in 5-HT activity:

(A) 5-HT agonists are reported to induce migraine headaches (Brewerton *et al.*, 1988). Fozard and Kalkman (1992 and 1994) related 5-HT_{1D} receptor activation to migraine onset. The new generation of anti-migraine drugs are based on 5-HT pharmacology (Muskowitz and Cutner, 1993). Phonophobia is a frequent symptom of migraine alongside the more commonly recognized photophobia (light-sensitivity).

(B) Benzodiazepines are reported to reduce 5-HT concentrations in the hippocampus and thus diminish stimulation of 5-HT receptors (Kennett *et al.*, 1989). Benzodiazepine-dependent patients undergoing withdrawal are referred to audiology departments complaining of tinnitus and hyperacusis and typically these symptoms subside when they complete benzodiazepine withdrawal (Beeley, 1991; Rocco *et al.*, 1992).

(C) 5-HT receptors are implicated in the treatment of chronic depression (Meltzer, 1990; Owens and Nemeroff, 1994).

(D) Vitamin B6 is a co-factor in the synthesis of 5-HT as well as other neurochemicals like GABA and dopamine. With pyridoxine (vitamin B6) deficiency 5-HT availability is changed (Sharma and Dakshinamurti, 1994) and is associated with hyperacusis (Berman *et al.*, 1969).

(E) Work reported by Andorn *et al.* (1989) suggested that serotonergic (5-HT) activity is involved in the generation of auditory halucinations and may therefore underlie the occurrence of hyperacusis with musicogenic epilepsy.

(F) 5-HT has a role in the genesis of fatigue in man (Wilson and Maughan, 1992). Evidence for serotonergic abnormalities in chronic fatigue states is

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provided by Bakheit *et al.* (1992) demonstrating up regulation of 5-HT receptors in the hypothalamus in CFS subjects when compared to primary depressive subjects while Jakeman *et al.* (1994) report down regulation of 5-HT in endurance-trained athletes.

Symptoms associated with hyperacusis

Photophobia and tinnitus, two further symptoms which co-occur with hyperacusis, have a strong association with other symptoms of disturbance in 5-HT function.

Photophobia and phonophobia (hyperacusis)

There are common features apparent in the profile of patients complaining of photophobia (sensitivity to light) and phonophobia. Light flicker can be epileptogenic for patients susceptible to epilepsy (Wilkins *et al.*, 1980).

A series of studies by Wilkins *et al.* (1984) found that specifically tinted glasses reduced flicker from fluorescent lights and visual display units and could reduce migraine in children suffering from periodic syndrome (regular occurrence of headache). People who report many pattern illusions tend to suffer frequent headaches. These perceptual problems give rise to specific reading and writing disorders. Wilkins *et al.* (1984) proposed that these symptoms result from a failure of a cortical inhibition mechanism. The strong association between photophobia and migraine reported by Marcus and Soso (1989) provides indirect evidence that 5-HT may be the specific neurotransmitter responsible for photophobic experiences.

Hyperacusis and tinnitus

There are many published hypotheses on the mechanisms of tinnitus generation. Tinnitus presents as a symptom in a wide range of disorders in both the peripheral and central parts of the auditory system (Jastreboff and Hazell, 1993). There is increasing recognition that tinnitus frequently co-occurs with hyperacusis and that there is a shared association between the mechanisms of some types of tinnitus and hyperacusis (Hazell and Sheldrake, 1991). Axelsson and Anari (1993) considered that the frequent co-occurrence of hyperacusis with tinnitus, hearing loss and sometimes distortion suggested a cochlear rather than retrocochlear pathology. This is dependent on the presumed mechanisms underlying tinnitus and distortion and to some extent on the clinical population from which the patients are derived.

In contrast, Coles and Sood (1988) proposed that the generator site of phonophobia must be above the brain stem nuclei involved in the stapedial reflex arc, and was more likely to be at a cortical level rather than within the brain stem. Jastreboff and Hazell (1993) described hyperacusis as a 'manifestation of increased central gain' which may cause enhanced perception of peripheral signals. In some cases this may be the sole cause of tinnitus as seen in normal hearing subjects who are deprived of sound in an anechoic chamber (Heller and Bergmann, 1953). It may be that the presumed cause and effect of tinnitus with sleeplessness and depression (Tyler and Baker, 1983; Harrop-Griffiths *et al.*, 1987) has a common causation in 5-HT imbalance.

There is little evidence of serotonin receptors in and around the mammalian cochlea (Eybalin, 1993) but a recent study by Thompson *et al.* (1994) reports the occurrence of serotonin receptors in the auditory nuclei. These authors speculate that the serotonergic system may have a role in modulating central auditory processing.

Primary and secondary causes of central hyperacusis

On the basis of this clinical and research evidence the primary cause of central hyperacusis is related to 5-HT function. The precise mechanism by which the 5-HT may exert the effect is not yet clear. Hyperacusis may occur with deficiency of 5-HT or with increased levels as demonstrated by Coleman (1973) who gave high levels of tryptophan to children with Down's syndrome to increase 5-HT concentration. The direction of the effect is dependent on the receptor site affected by the drug intake and the balance between 5-HT and other neurotransmitters.

There is a secondary mechanism for hyperacusis which develops from the learned association of discomfort with exposure to sound. This evolves into a fear-potentiated enhanced startle. The pharmacology of fear-potentiated startle and the neural pathways involved are described by Davis (1989). This is a secondary mechanism for sustaining chronic, debilitating hyperacusis and underlies the importance of behaviour modification in parallel to the specific desensitization techniques for management of hyperacusis.

Possible methods of objective assessment of hyperacusis

Initial investigations on the audiological manifestations of hyperacusis have shown no consistent changes. However, Butler (1993) found that the post-auricular myogenic (PAM) response is significantly increased in amplitude in chronic fatigue syndrome patients compared with matched controls. Additionally, when attention was diverted from the auditory stimulus there was almost complete abolition of the PAM in controls but little change in the CFS patients.

Collet *et al.* (1993) described a reduced contralateral suppressive effect in the evoked oto-acoustic emissions of hyperacusic autistic patients. Interestingly, 40 per cent of autistics are known to have high levels of 5-HT (Schain and Freedman, 1961) and 40 per cent have hyperacusis (ARRI, 1990). Unfortunately, to date no-one has investigated whether these are the same subject groups.

These two audiological techniques (PAM and

contralaterally masked oto-acoustic emissions) demonstrate that it is likely to be the central processing systems of auditory function that will give insight into the mechanism of central hyperacusis.

Conclusions

ENT specialists and audiologists need to be alert to hyperacusis as a clinical entity that can result in considerable patient discomfort. Peripheral types can be differentially diagnosed with relative ease from central aetiology cases using standard audiological test techniques. Although the case is made for a central type of hyperacusis, no assumptions are made about the interaction between central and peripheral parts of the hearing system. It may be that there are peripheral auditory influences on the central processing mechanisms as seen in the beneficial use of maskers in reducing the impact of hyperacusis on the quality of life.

In an attempt to further localize the pathology giving rise to this phenomenon, serotonin (or 5-HT) is considered as it has an inhibitory role in sensory modulation at a central level. A reduction in forebrain 5-HT activity is the most likely underlying pathology causing central hyperacusis. There are no assumptions made about the specific causes of 5-HT changes in any of these conditions. The association of two other symptoms (tinnitus and photophobia) with hyperacusis strengthens this argument. This proposed mechanism for hyperacusis needs verification by other specialist fields of science research. A randomized and controlled trial of 5-HT agonists in hyperacusis may clarify this. By gaining a better understanding of the causes of hyperacusis it will be possible to design appropriate desensitization, behaviour modification and pharmacological strategies for therapy.

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