Use of the guinea pig in studies on the development and prevention of acquired sensorineural hearing loss, with an emphasis on noise

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(Received 10 April 2019; revised 30 July 2019; accepted 12 August 2019; published online 27 November 2019)

Guinea pigs have been used in diverse studies to better understand acquired hearing loss induced by noise and ototoxic drugs. The guinea pig has its best hearing at slightly higher frequencies relative to humans, but its hearing is more similar to humans than the rat or mouse. Like other rodents, it is more vulnerable to noise injury than the human or nonhuman primate models. There is a wealth of information on auditory function and vulnerability of the inner ear to diverse insults in the guinea pig. With respect to the assessment of potential otoprotective agents, guinea pigs are also docile animals that are relatively easy to dose via systemic injections or gavage. Of interest, the cochlea and the round window are easily accessible, notably for direct cochlear therapy, as in the chinchilla, making the guinea pig a most relevant and suitable model for hearing. This article reviews the use of the guinea pig in basic auditory research, provides detailed discussion of its use in studies on noise injury and other injuries leading to acquired sensorineural hearing loss, and lists some therapeutics assessed in these laboratory animal models to prevent acquired sensorineural hearing loss.
 https://doi.org/10.1121/1.5132711

[JFL] Pages: 3743–3769

I. INTRODUCTION

Stebbins *et al*. (1982) suggested the guinea pig to be one of the most useful species in which to assess the effects of noise on the inner ear based on overlap with the audible frequency range in the human as well as presumed overlapping vulnerabilities and the relative ease of training of guinea pigs for use in psychophysical testing. Since then, the guinea pig has been widely used in studies on hearing loss induced by noise and drug injury and prevention of this acquired sensorineural hearing loss (i.e., otoprotection). Other species are also of interest such as the cat, chinchilla, and monkey (Stebbins *et al*., 1982). This review paper focuses on the use of the guinea pig in studies on acquired sensorineural hearing loss and otoprotection and is broken into four main sections in which (1) basic information about the guinea pig as a laboratory animal subject is provided, (2) strategies for the assessment of auditory function are introduced, (3) necessary regulatory requirements for the maintenance of guinea pigs are provided, (4) the effects of noise and ototoxic drugs on the guinea pig inner ear are discussed, and (5) efforts to prevent noise injury and drug ototoxicity using pharmaceutical interventions are reviewed. For detailed reviews of other species widely used in hearing science, noise and drug injury, and otoprotection research, readers are referred to other papers in this special issue for reviews of the mouse (Ohlemiller, 2019), rat (Escabi *et al*., 2019; Holt *et al*., 2019), chinchilla (Trevino *et al*., 2019; Radziwon *et al*., 2019), and non-human primate (Burton *et al*., 2019). Briefer discussion comparing the relative strengths and weaknesses of multiple rodent species in studies on noise injury and its prevention is available in Lynch *et al*. (2016). The overarching goal of the current series of species-specific papers is to provide comprehensive insight into the various laboratory animal models that are commonly considered for use in drug development research focused on the prevention of NIHL, with commentary on issues that may impact study design and outcomes.

II. THE GUINEA PIG AS A LABORATORY ANIMAL

A. Basic health

Guinea pigs (*Cavia porcellus*) are relatively large (female: 100–900 g; male: 900–1200 g) rodents; they are very docile animals that rarely bite or scratch, making them easy to work with in laboratory settings. Guinea pigs live approximately 5–7 years (Quesenberry, 1994). The guinea pig and chinchilla (*Chinchilla lanigera*) are subgroups of the order Rodentia, belonging to the suborder Hystricognathi and infraorder (family) Caviomorpha. Two of the most commonly used strains are the Hartley and Dunkin-Hartley albino strains; however, pigmented strains are also available. Detailed discussions of guinea pig physiology, husbandry, and diseases are readily available (Quesenberry, 1994; Donnelly and Brown, 2004). Healthy guinea pigs should be active, with bright eyes, shiny coats, and no discharge from the eyes or noise (Yarto-Jaramillo, 2011).

B. Pigmentation

Both pigmented and albino guinea pig strains have been used in auditory research; they exhibit differences in

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peripheral and central auditory function (Bock and Steel, 1984). These differences may be a consequence of the absence of melanin in the cochlea of the albino guinea pig. Melanin, produced by melanocytes in stria vascularis within the cochlea of pigmented animals, has been shown to protect against damage (Xiong *et al.*, 2011), perhaps mediated by the involvement of melanin in the active transport of Ca^{2+} into endolymph (Gill and Salt, 1997) or antioxidant properties of melanin. The effect of pigmentation, including a protective role of melanin, has also been described in noise- and drug-induced hearing loss (DIHL) in other rodent species (Wu *et al.*, 2001; Murillo-Cuesta *et al.*, 2010). Interestingly, this protective role of pigmentation is not observed in aging animals, as pigmented guinea pigs develop more age-related hearing loss (ARHL) than albino animals (Dum *et al.*, 1980a; 1980b; Dum, 1984). When possible, a discrimination between albino and pigmented guinea pig models is made in the descriptions of hearing loss induced by age, drugs, and noise below.

C. Diet and nutrition

Across rodents, there are important differences in digestive anatomy, leading to differences in dietary recommendations (Grant, 2014). Diet and nutrition are important considerations in the overall design of otoprotection research studies [see Spankovich and Le Prell (2019)] and are directly relevant to the use of guinea pigs in studies on noise injury and its prevention for two key reasons. First, guinea pig diets must contain vitamin C as the guinea pig, like humans, cannot synthesize its own endogenous vitamin C (Chatterjee *et al.*, 1975; Jenkins, 2010) due to the lack of the hepatic enzyme L-gulonolactone oxidase, which converts dietary glucose into vitamin C (Jenkins, 2010; Yarto-Jaramillo, 2011). This has made the guinea pig particularly popular in studies assessing dietary supplements that include vitamin C as one of the active agents (McFadden *et al.*, 2005; Le Prell *et al.*, 2007a; Le Prell *et al.*, 2011a). Second, the ototoxic side effects of noise, aminoglycosides, and cisplatin are increased in animals fed diets that have nutrient deficits, including for example low protein, low iron, and reduced vitamin A diets (Biesalski *et al.*, 1990; Lautermann *et al.*, 1995b; Lautermann and Schacht, 1996; Yu *et al.*, 2016).

With respect to guinea pig digestion, food typically has left the stomach within 2 h of consumption and total duration of gastrointestinal processing is approximately 20 h [for review see Grant (2014)]. For otoprotective agents that are delivered orally, it is important to understand digestion and absorption rates for active agents [for detailed discussion of drug absorption and related issues, see Cousins (2019)]. Additional brief discussion of the importance of pharmacokinetic and pharmacodynamic data in studies on noise injury and its prevention is available in Lynch *et al.* (2016); oral dosing via food supplements can make the collection of such data more challenging.

It has been suggested that fresh greens, such as cabbage, kale, spinach, chicory, dandelion and beet greens, and parsley, as well as broccoli, yams, and carrots, should be provided to supplement food pellets (Quesenberry, 1994; Yarto-Jaramillo, 2011; Grant, 2014). These foods are all nutrient dense, with many of the vitamins and minerals they contain hypothesized to provide protection against ototoxic injury (Haase *et al.*, 2009; Le Prell and Spankovich, 2013). Thus, potential confounds that may be introduced by nutrient dense food supplements that support endogenous antioxidant activity should be carefully considered as part of study design and discussed with animal husbandry to assure careful control of relevant scientific variables.

As described by Grant (2014), guinea pigs are strict herbivores, typically consuming short grasses in open grasslands in the wild; in captivity, grass hay is important for adults, and a mix of grass hay and alfalfa is necessary for juvenile guinea pigs and lactating females. Clover and alfalfa hays should be avoided for adult animals as they may damage the renal system (Yarto-Jaramillo, 2011). The highly fibrous diet in the wild wears down guinea pig (and chinchilla) teeth and, thus, their teeth grow continuously across their lifespan; dental issues in captive animals are common and access to appropriate chewing materials is necessary [see Jenkins (2010), Yarto-Jaramillo (2011), and Grant (2014)]. While these issues are not likely to directly affect hearing per se, laboratory animals that lack chewing materials and suffer from dental issues may not be able to consume chow and may suffer from nutritional deficits that influence vulnerability to noise injury.

D. Health concerns

Animals that are ill may have concomitant nutritional deficits if they are not consuming daily chow requirements, and may be predisposed to other injury. A primary health concern in guinea pigs is thus the prevention of respiratory disease (Quesenberry, 1994; Yarto-Jaramillo, 2011). Respiratory disease can result from overcrowding and other housing-related issues such as poor ventilation, temperature changes, inappropriate (too warm, too cold) temperatures, dust in the environment, and changes in humidity; pneumonia is common when housing conditions are damp or drafty [for review, see Yarto-Jaramillo (2011)]. Another leading cause of respiratory disease in guinea pigs is pathogen exposure, with bacterial, viral, and fungal pathogens all inducing respiratory issues [for review, see Yarto-Jaramillo (2011)]. Infections are particularly likely to be transferred from dogs and rabbits, if multiple species are maintained in close proximity or by the same husbandry personnel. Antibiotic management is possible, but penicillin and macrolide antibiotics are to be avoided (Quesenberry, 1994) and antibiotics (aminoglycosides) leading to hearing loss must not be used for infection control in animals in which hearing function serves as a study outcome.

A second key concern is lesions on the surfaces of the feet and injury to the feet, which can be caused by wire floors or rough bedding, as well as dirty bedding and inappropriate sanitary control (Quesenberry, 1994; Jenkins, 2010). Hair loss and superficial dermatitis secondary to biting or self-trauma are possible (Quesenberry, 1994). Biting and self-trauma can also occur subsequent to injections, particularly when intra-muscular injections are delivered to the quadriceps muscle in the hind legs. If an agent of interest

must be delivered using intra-muscular injection, the needle and volume should both be as small as possible; although individual animal care units may have different specific guidance, current guidance should also be sought from relevant oversight and regulatory agencies [see, for example, the information posted on the NIH Office of Intramural Research Office of Animal Care and Use (https://oacu.oir.nih.gov/sites/default/files/uploads/training-resources/rodentinjection.pdf) or the Canadian Council on Animal Care (CCAC) (Canadian Council on Animal Care, 1993)]. Parasites such as fur mites and fungal infections can also cause hair loss with scaly or crusty lesions (Quesenberry, 1994).

E. Social behavior

Guinea pigs are highly social and herd formation has been observed in domesticated and wild guinea pig populations [for discussion, see Donnelly and Brown (2004) and Brewer *et al*. (2014)]. Thus, there have been some efforts to explore potential social enrichment using open-field arenas that allow herd-like interactions (Brewer *et al*., 2014). Guinea pigs have a diverse range of social behaviors, and a detailed review is available in Harper (1976). In brief, approach behaviors commonly include nose to nose contact, but may also include contact of the snout with the ears or perineum of other animals. At rest, guinea pigs commonly show huddling behavior in which they lie side to side, in contact with each other; however, mutual grooming is not a common social behavior within adult guinea pigs (see Harper, 1976). Female pairs typically can be housed together for social enrichment, but male pairs should be avoided to reduce the risk of fighting (Raje and Stewart, 2000). Male/female pairs are typically to be avoided as guinea pigs can start breeding as early as 4–6 weeks of age.

When guinea pigs and other rodents are group housed, study designs have sometimes employed *ad libitum* access to supplemented food (Le Prell *et al*., 2011b; Le Prell *et al*., 2014c) or supplemented water (Davis *et al*., 2007), foregoing monitoring of intake and losing the ability to estimate dosing or dose equivalence across animals. When group housing is used, potentially aggressive behaviors should be monitored during daily health checks. Aggressive postures include the head raised, mouth partially open, forelegs extended, and back legs crouched; during an attack the head is thrust forwards and biting of the nose and lips can occur if neither backs down [see Harper (1976)]. If one of the guinea pigs flees, the other may chase the fleeing animal and deliver deep bites to the retreating animal. It is possible for death to occur when males vie for dominance, although it is also possible for evenly matched males to reach a standoff limited to aggressive posturing [see Harper (1976)].

F. Vocal behavior

The guinea pig has a rich vocal behavior system which has made them a species of interest for investigating the processing of vocal communication in the central auditory system (CAS), including inferior colliculus (Suta *et al*., 2003; Suta *et al*., 2013; Lyzwa *et al*., 2015), thalamus (Philibert *et al*., 2005; Suta *et al*., 2007; Suta *et al*., 2013), and auditory cortex (Syka *et al*., 2005; Wallace *et al*., 2005; Grimsley *et al*., 2011; Suta *et al*., 2013). Early observations of vocal behavior by adult and infant guinea-pigs housed within a large colony revealed 11 call types belonging to 5 functional categories (Berryman, 1976). As per the detailed review and discussion by Harper (1976), whistles, screams, and squeals are generally higher frequency vocalizations with energy up to 16–32 000 Hz whereas chutt, chutter, whine, tweet, low whistle, purr, and drr calls generally are lower frequency calls that do not include significant energy above 4000 Hz. The whistle has been suggested to serve as a distress call (Suarez and Gallup, 1982). There is an extensive literature on changes in guinea pig vocal behavior as a tool in pharmacological research and development (Groenink *et al*., 2015).

There is ongoing discussion of the extent to which neurons in the medial geniculate body of the thalamus and the auditory cortex of the guinea pig are selective for complex acoustic features specific to vocalizations and thus the extent to which guinea pigs provide a good model of the specialized processing that occurs in the non-human primate and human auditory systems (Suta *et al*., 2008; Suta *et al*., 2013). There is also a significant body of research establishing the changes in CAS processing of acoustic signals that occur as a consequence of noise exposure (Mulders and Robertson, 2013; Heeringa and van Dijk, 2018). These paradigms could be readily exploited for use assessing the extent to which otoprotective agents prevent changes in processing complex signals at the level of the CAS, particularly with the significantly increased interest in the effects of noise on supra-threshold function, such as the processing of speech stimuli in quiet and in noise (Bramhall *et al*., 2019; Le Prell, 2019).

III. SENSORY FUNCTION IN THE GUINEA PIG

A. Sensory function

Guinea pigs have sensitive hearing and good vision. The guinea pig has better hearing at higher frequencies, relative to humans. The human hearing range is typically defined as 20–20 000 Hz, whereas the guinea pig hears sounds from 150 to 50 000 Hz. For humans, hearing is best from about 1000 to 4000 Hz, whereas for guinea pigs, hearing is best from about 8000 to 16 000 Hz. Early work using classical conditioning techniques revealed relatively good sensitivity to tones at frequencies up to about 40 to 50 000 Hz, with sharply decreasing performance through as high as 80 to 100 000 Hz (Wever *et al*., 1963). Subsequent work using operant conditioning techniques confirmed and extended these results (Heffner *et al*., 1971; Walloch and Taylor-Spikes, 1976). A comparison of the human and guinea pig audiogram is shown in Fig. 1. As noted above, the guinea pig has been previously suggested to be one of the most useful species in which to assess the effects of noise on the inner ear, based on both overlap with the human with respect to audible frequency range (which may drive overlap in vulnerability to injury), and the relative ease of training guinea pigs to perform detection and discrimination tasks [see Stebbins *et al*. (1982)]. Although psychophysical data provide powerful direct comparison with human results, two of

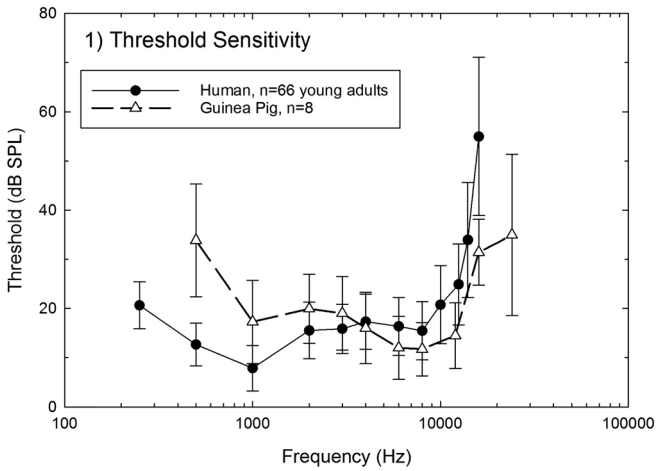

FIG. 1. Average audiometric thresholds measured from 66 normal hearing young adults who participated in the study by Spankovich *et al.* (2014) are illustrated in combination with average audiometric thresholds measured from eight young adult guinea pigs (unpublished data collected at the University of Florida). All data are mean ± standard deviation of the mean.

the most commonly used methods of assessing auditory function in the guinea are non-behavioral tests, including otoacoustic emissions (OAEs) and the sound evoked auditory brainstem response (ABR).

B. Otoacoustic emissions (OAEs)

OAEs do not measure hearing per se; rather, they provide a sensitive and objective measure of how well the outer hair cell (OHC) population is functioning. One of the most commonly measured emissions is the distortion product otoacoustic emission (DPOAE); DPOAE thresholds and DPOAE response amplitude are routinely used to assess the integrity of the OHC active process both before and after noise exposure, with tests completed in control animals and animals treated with potential otoprotective agents. Prevention of noise-induced DPOAE deficits provides evidence of drug-mediated hair cell preservation. Because DPOAEs are not influenced by the status of the ascending neural pathway, they are not sensitive to damage to or protection of the neural pathways. Thus, DPOAEs are commonly measured in combination with the sound-evoked ABR. An example of the DPOAE measure is shown in Fig. 2.

C. Auditory brainstem response (ABR)

The ABR provides a sensitive and objective measure of the transmission of auditory information from the auditory periphery (cochlea) to the auditory nerve and across the auditory brainstem. The ABR reflects the synchronous discharge of multiple neurons induced by short tone pips. There are multiple "waves" in the ABR and each wave represents synchronous discharge of neurons at discrete locations in the peripheral and central auditory systems. For many years, ABR thresholds have been considered a gold standard measure for the recovery of auditory function after noise exposure, and the documentation of permanent noise-induced threshold changes. Although thresholds are typically about 10–15 dB higher when measured using ABR techniques instead of psychophysical detection thresholds based on behavioral detection responses, this is readily explained by reduced opportunity for temporal integration when brief tone pip signals are used instead of the longer tones used in

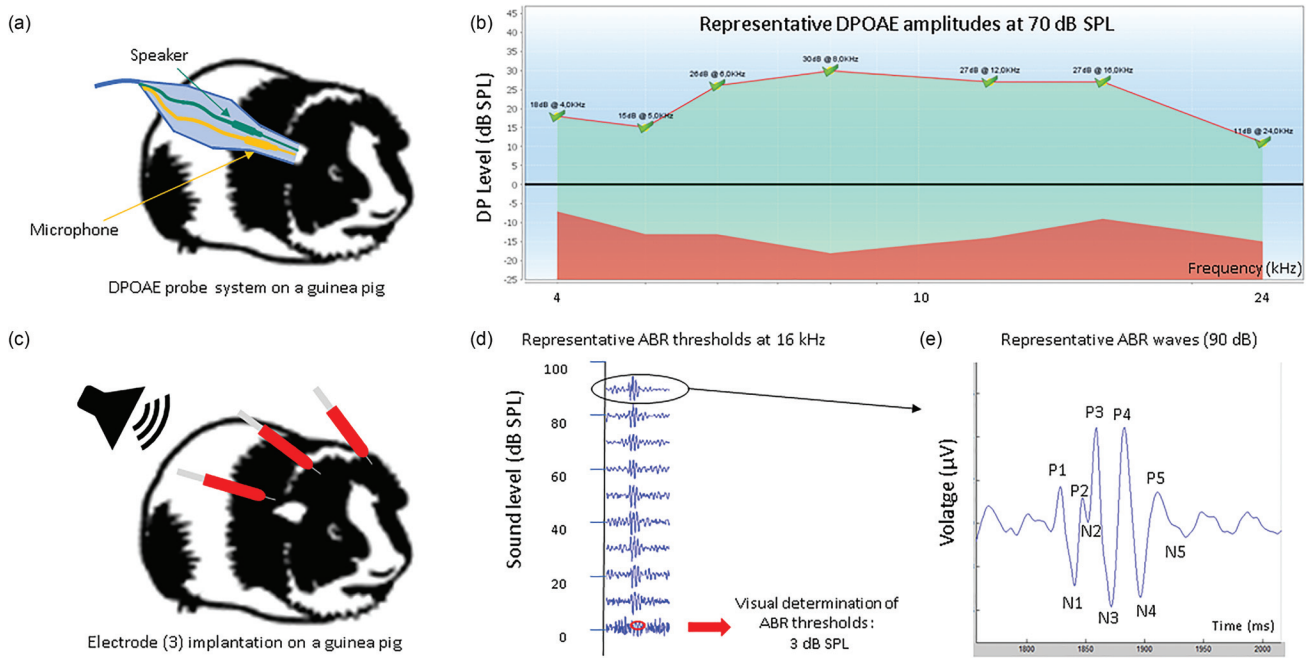

FIG. 2. (a) Schematic cartoon of the probe microphone assembly entering the ear for distortion-product otoacoustic emission (DPOAE) measurement; tones are delivered via the speaker (green) and emissions are measured using the microphone (yellow). (b) Normal DPOAE amplitude in the guinea pig is shown for test signals of 70 dB SPL. (c) Schematic cartoon illustrating three electrode locations used to record the ABR. (d) Tones are presented at decreasing levels from 0 to 90 dB SPL and ABR threshold is determine based on visual inspection of waveforms. (e) Typical ABR waveforms (16 kHz, 90 dB SPL) illustrating the peaks (P) and troughs (N), defining each wave amplitude. The five marked waves (P1–P5) reflect specific central activity. P1: auditory nerve; P2: cochlear nucleus; P3: superior olivary complex; P4: lateral lemniscus; P5: inferior colliculus. (Unpublished data collected at CILcare.)

psychophysical detection studies (Le Prell *et al.*, 2004). More recently, ABR wave I response amplitude has emerged as a metric of interest, as decreases in the amplitude of this neural evoked response, occurring in the absence of permanent threshold shift (PTS), are highly correlated with damage to the synapses connecting the inner hair cells (IHCs) to the auditory nerve (Sergeyenko *et al.*, 2013; Kujawa and Liberman, 2015). Prevention of noise-induced ABR threshold and amplitude deficits would provide evidence of drug-mediated protection of not only the OHCs but also the ascending neural pathway. Illustration of ABR thresholds and waves is provided in Fig. 2.

With the easy availability of equipment that facilitates the collection of OAE and ABR data in laboratory animals, the number of laboratories routinely using behavioral techniques to collect threshold data has decreased. Nonetheless, behavioral techniques provide a powerful opportunity to assess noise-induced tinnitus, and noise-induced deficits in other auditory processing domains, such as detection of intensity differences, frequency differences, and changes in vocalization signals. Thus, the sensory test paradigms that have been used to probe auditory function in guinea pigs are briefly reviewed in the following sections.

D. Positive reinforcement

Guinea pigs can be trained to push buttons or levers when they detect sound, or changes in sound, and they have therefore been widely used in psychophysical studies employing behavioral testing (Petersen *et al.*, 1977; Stebbins *et al.*, 1984). Many of these investigations have used positive reinforcement paradigms, with food used as a reward for correct responses in guinea pigs maintained on restricted diets. Careful investigation of the effects of food restriction and reinforcement paradigms by Hirsch and Collier (1974) reveals a need for caution with respect to the strategy used for limiting guinea pigs' access to food. Although guinea pigs compensated for limited access to food by eating either more quickly or for a longer period of time when food was available, guinea pigs with access to only a single meal per day did not achieve normal adult body weights; the significantly lower body weights were attributed to an inability to process large volumes of food in a short period of time (Hirsch and Collier, 1974). Relevant to acquired sensorineural hearing loss, operant techniques have been leveraged to assess the effects of ototoxic drugs (Prosen *et al.*, 1978a; Prosen *et al.*, 1978b) and excitotoxic agents (Le Prell *et al.*, 2004) on threshold sensitivity in the guinea pig. Whereas ototoxic aminoglycoside antibiotics induced PTS, excitotoxic agents induced temporary threshold shifts (TTS) that recovered subsequent to infusion of the excitotoxin. The ability to reliably measure threshold sensitivity using positive reinforcement procedures has also resulted in extensive use of guinea pigs for evaluating the perceptual consequences of parametric manipulation of cochlear implant programming parameters (Miller *et al.*, 1995a; Miller *et al.*, 1995b; Miller *et al.*, 1999; Miller *et al.*, 2000; Su *et al.*, 2008; Kang *et al.*, 2010; Pfingst *et al.*, 2011; Zhou *et al.*, 2015).

E. Conditioned avoidance

In conditioned avoidance paradigms, animals perform a trained response in order to avoid a punishment—typically, a mild foot shock stimulus. A classic paradigm is the use of a shuttle box, in which animal subjects must move to a different compartment when an auditory stimulus is presented to avoid the delivery of the foot shock. Guinea pigs have been described as more likely to freeze than to perform the desired avoidance behavior in such paradigms (Webster and Rabedeau, 1964; Webster *et al.*, 1965). Careful manipulation of the response window to allow avoidance behaviors to emerge subsequent to stereotypical freezing behavior has allowed some success within this paradigm (Evonic and Brimer, 1967). However, this freezing response has limited the use of the guinea pig in conventional shuttle box studies. Opportunities to use avoidance behavior as a tool within the guinea pig model are perhaps increasing given a number of recent successful efforts to use an aversive air stream in place of foot shock. The use of this less stressful stimulus has resulted in the ability to induce avoidance behavior rather than freezing behavior (Philippens *et al.*, 1992; Agterberg *et al.*, 2010; Agterberg and Versnel, 2014). This shuttle box-based approach has been used to investigate tinnitus in guinea pigs (Heeringa *et al.*, 2014), and it is possible that additional work could be initiated, particularly with respect to noise-induced tinnitus.

F. Reflex inhibition

For paradigms using reflex inhibition, acoustic ("pre-pulse") stimuli are used to modify the strength of subsequent reflexive startle responses induced by a "pulse" stimulus, such as a loud acoustic signal. Acoustic pre-pulse inhibition (PPI) protocols were largely developed using rats (Ison and Hammond, 1971; Ison *et al.*, 1973; Ison and Krauter, 1974; Parisi and Ison, 1979; Ison, 1982) with later development in mice (Ison *et al.*, 2002; Ison *et al.*, 2005), but there has also been some application of this technique to the guinea pig. By manipulating the frequency and level of the preceding (pre-pulse) inhibitory signal, Young and Fechter (1983) generated guinea pig audiograms that closely paralleled audiograms generated using positive reinforcement paradigms (Prosen *et al.*, 1978a). Although thresholds were about 10–15 dB higher when measured using pre-pulse inhibition techniques, this is readily explained by reduced opportunity for temporal integration when brief pre-pulse signals are used instead of the longer tones used in classic studies (for discussion see Young and Fechter, 1983).

In a more recent variation on this task, an airpuff is used in place of the loud acoustic signal as experimental protocols that damage the ear (i.e., noise exposure, ototoxic drug treatment) can compromise sound-induced startle reflexes (Lobarinas *et al.*, 2013; Lobarinas *et al.*, 2017). Another significant permutation of the task is the replacement of the acoustic pre-pulse signal with a silent gap, termed Gap-Prepulse Inhibition of the Acoustic Startle Reflex (GPIAS) (Turner *et al.*, 2006; Turner *et al.*, 2012; Galazyuk and Hebert, 2015; Schilling *et al.*, 2017). Although GPIAS has been successfully applied in studies of tinnitus using guinea

pigs (Mulders *et al*., 2014; Zhang *et al*., 2019), GPIAS is not fully understood within guinea pigs as GPIAS results were variable in a comparison of subjects drawn from two colonies of outbred tri-colour guinea pigs (Leggett *et al*., 2018). The laboratory rat remains the most prominent species used for investigating tinnitus at the behavioral level, although there are some data from guinea pigs trained to distinguish silent intervals from sound intervals (Moody, 2004). Because there is not a wide range of genetically modified rat strains, mice are also highly used in tinnitus studies (von der Behrens, 2014).

G. Schedule-induced polydipsia

In schedule-induced polydipsia paradigms, food-restricted animals are given access to both food and water during test sessions. When food pellets are delivered on a fixed time schedule, excessive drinking is observed. This phenomenon is well established in rats and mice, including development of a novel schedule-induced polydipsia avoidance conditioning paradigm for use assessing tinnitus percepts in rats (Lobarinas *et al*., 2004). The evidence is less consistent in guinea pigs, however, with two small studies showing the development of exaggerated drinking in either 2 of 3 guinea pigs (Porter *et al*., 1977) or 0 of 3 guinea pigs (Urbain *et al*., 1979). There has been little additional literature on schedule-induced polydipsia in guinea pigs since these early reports, and it seems unlikely that this technique will be used to further understanding of noise injury and its prevention, using the guinea pig as a model.

H. Supra-threshold processing

The above techniques, particularly operant training techniques that rely on positive reinforcement, have been used to measure supra-threshold auditory function, providing insight into intensity discrimination in guinea pigs (Prosen *et al*., 1981; Stebbins, 1982), interactions between acoustic and electro-acoustic stimulation (Le Prell *et al*., 2006), and frequency discrimination in chinchillas (Prosen *et al*., 1989). In a unique approach modeled after these classic psychoacoustic investigations, simple acoustic stimuli were replaced with noise-like non-harmonic broadband sounds as targets, with manipulated versions of these sounds and sound sequences used to assess recognition and discrimination (Ojima *et al*., 2012). Although powerful techniques for investigation of the effects of noise on auditory function are clearly available, there has been only limited collection of behavioral data after noise exposure [see, for example, Prosen *et al*. (1990)]. Given the significant current interest in the effects of noise on human supra-threshold function (Bramhall *et al*., 2019; Le Prell, 2019), it is indeed worthwhile for researchers to be familiar with the behavioral techniques that can be used to measure supra-threshold effects of noise exposure in the guinea pig model.

IV. REGULATORY ISSUES

A. National regulations

In the United States, the treatment, care and use of animals in research is regulated by the Animal Welfare Act (AWA), a federal law signed in 1966. The AWA defines the guinea pig as a protected species; hamsters (Cricetinae) and gerbils (Gerbillinae) are also protected, whereas mice (Mus) and rats (Rattus) are excluded from the protections. Compliance with AWA standards is intended to ensure the humane care and treatment of animals, including housing standards. Other nations have their own national guidance, but there are a number of commonalities across documents.

In the AWA, some specifications are defined for each species, in particular space for housing (i.e., size of the cage and the floor, see Table I) and feeding. In addition to the parameters in Table I, wire-bottom cages must be designed to provide sufficient support for the animals' feet, and the space between the wires in the floor grid must be small enough to preclude entrapment of animals' feet. The CCAC (Canadian Council on Animal Care, 1993) advocates that guinea pigs not be individually housed, but housed in groups consistent with their natural environment. Consistent with safety guidance in the AWA, they recommend that solid bottom cages be chosen to create a safe and healthy microenvironment with plastic "shoe box" or "drawer-style" cages being the preferred choice; if cages have wire mesh floors, the mesh must be smooth and hole sizes small such that injury is prevented. The cleaning of the cage requires pretreatment by acid, due to the urine of guinea pigs, produced in large volume and which contains proteins (National Research Council, 1996).

With respect to feeding, the feeder must not be suspended; a J-shape feeder placed on the floor is the best device, as this prevents guinea pigs from nesting in the feeder. As noted above, guinea pig diets must be fortified with vitamin C, directly provided in the drinking water or via food supplements including vegetables as kale (National Research Council, 1996). As per the CCAC, automatic watering devices are to be avoided as guinea pigs often play with these devises, potentially resulting in wet bedding or flooding (Canadian Council on Animal Care, 1993). Human caretakers are encouraged to pay attention to the vocalization of guinea pigs, as vocalizations are an important part of their social behavior (as described above).

The European Union (EU) also uses legislation to protect the welfare of animals. Directive 2010/63/EU (European

TABLE I. Comparison of recommended space for Guinea pigs in US, Canada and Europe.

Countries	Weight (g)	Minimal height (cm)	Floor area/animal (cm^2)	Comments
U.S.	<350	17.8	387	Larger animals may require more space to meet the performance standard
	>350	17.8	651.5	
Canada	<350	18	300	—
	>350	22	650	
Europe	<200	23	200	—
	Over 200 to 300	23	350	
	Over 300 to 450	23	500	
	Over 450 to 700	23	700	
	>700	23	900	

Parliament, 2010) follows the Replacement, Reduction, and Refinement (3 R) principles specified in other national guidelines. Like other guidance noted above, the Directive provides general guidelines for the facility, environmental controls including temperature and lighting, housing, enrichment and feeding requirements for rodents, guinea pigs and non-human primates, and specific guidelines for minimum enclosure area measurements for guinea pigs. There are many other national regulations. Researchers working in different countries must of course comply with their own national regulations and ethical committee rules and guidance; however, many journals require that research published within their journal comply with specific ethical guidance documents. For example, the Journal of the Acoustical Society of America requires that studies be in compliance with the Council for International Organizations of Medical Sciences (CIOMS) document: "International Guiding Principles for Biomedical Research Involving Animals-1985") (Acoustical Society of America, 2004). Other auditory journals that commonly publish otoprotection research have different requirements. For example, the journal Hearing Research requires compliance with the ARRIVE guidelines originally published in PLOS Biology, in addition to requiring compliance with the U.K. Animals (Scientific Procedures) Act, 1986, EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health Guide for the Care and Use of Laboratory animals (NIH Publications No. 8023, revised 1978). Those working in non-U.S. and non-U.K. locations should be aware of the U.S. and U.K. requirements and should assure compliance with these commonly cited compliance requirements. Broad compliance with common standards will improve reproducibility of scientific outcomes, by decreasing the variability in housing and animal care factors that may influence animal health, stress, and nutritional status, all of which may influence study outcomes.

B. Anesthesia

Anesthesia of guinea pigs and other laboratory animals is regulated by national standards; moreover, there are basic effects of anesthesia on auditory function that should be additionally considered as part of the scientific design of studies assessing auditory function. Isoflurane, a commonly used anesthetic, can impair the morphology of the ABR waveform in a dose-dependent manner in rodents.

Investigations, mainly conducted in rats, have shown that dose and duration of this volatile anesthetic can induce inconsistent changes in latency and amplitude of the ABR (Santarelli *et al.*, 2003; Bielefeld, 2014). Comparison between ABR measures obtained under isoflurane and those obtained under ketamine/xylazine anesthesia has revealed increased ABR thresholds under isoflurane with concentration-dependent effects (Ruebhausen *et al.*, 2012). Similarly, isoflurane dose-dependently reduced the amplitude and increased the latency of the ABR in guinea pigs (Stronks *et al.*, 2010). More recently, isoflurane has been shown to significantly reduce DPOAE amplitudes compared to ketamine/xylazine, and to increase variability of DPOAE responses (Sheppard *et al.*, 2018).

Additional attention must be paid to the use of anesthesia when anesthesia is administered during noise exposure, as anesthesia can modify noise injury (Rubinstein and Pluznik, 1976). A protective effect of chemical or volatile anesthetics administered during noise exposure has been shown in other rodent species (Kim *et al.*, 2005; Chung *et al.*, 2007). These protective effects could be explained by intrinsic properties of anesthetics and the involvement of stress processes in awake animals. When xylazine alone or ketamine together with xylazine were used as anesthesia during noise exposure, TTS was reduced compared to that in awake animals (Giraudet *et al.*, 2002). At least for the ketamine plus xylazine anesthetic protocol, this may be related to ketamine's action as an N-methyl-D-aspartic acid (NMDA) receptor antagonist, which could reduce both glutamate excitotoxicity and sympathetic activity (Giraudet *et al.*, 2002). Xylazine blocks noradrenaline release from the sympathetic system through its actions as a presynaptic alpha2-adrenoreceptor agonist and thus mediates the protective effects through other mechanisms (Giraudet *et al.*, 2002). There is also a protective effect of propofol against NIHL and hair cell loss induced by noise (Wen *et al.*, 2017). In addition, the use of gas during noise exposure of animals, for example, when using isoflurane anesthesia, reduces NIHL, at least in mice (Kim *et al.*, 2005; Chung *et al.*, 2007).

Administration of general anesthesia to the guinea pig can be difficult since they often maintain their pedal reflex; some oversight committees may recommend or require monitoring of heart rate or other physiological measures during periods of anesthesia.

V. USE OF THE GUINEA PIG IN AUDITORY RESEARCH

Guinea pigs were commonly used in early studies assessing the normal structure and function of the cochlea and auditory pathways. Based on the wealth of information from such early studies, they have also been highly utilized in studies of the pathological auditory system, after damage induced by noise exposure, ototoxic drug treatment, or other insults including aging. Interestingly, one of the experiments investigating early "rate" and "place" theories of hearing was actually a noise exposure study using guinea pigs as subjects and noise exposure at different intensities. The results were interpreted as suggesting that more intense exposure resulted in wider regions of damage, with damage centered at a specific place along the basilar membrane corresponding to the pitch of the exposure tone (Upton, 1929). Additional related studies using guinea pigs as a model further clarified place-based tonotopic cochlear stimulation using stimuli that varied in both frequency and level, in combination with sound evoked potential measurements collected in both the base and the apex (Tasaki *et al.*, 1952; Suga *et al.*, 1967). The remainder of this section provides a brief overview of historic major findings regarding normal structure and function, providing context for pathologies described and discussed below.

A. Outer hair cell (OHC) research

The guinea pig has commonly been used in efforts to understand the active electromotile expansion and contraction of OHCs in response to voltage change (Dallos, 1985;

for discussion see Kakehata *et al.*, 2000). Detailed reviews of the OHC active process are available for interested readers (Brownell, 1990; Manley, 2001; Hudspeth, 2008; Reichenbach and Hudspeth, 2014; Goutman *et al.*, 2015; Brownell, 2017); in brief, this active process provides approximately 40-dB of threshold gain, increasing the sensitivity for detection of acoustic signals. The phenomena of OHC electromotility was first identified in OHCs dissected from the guinea pig cochlea (Brownell, 1984; Brownell *et al.*, 1985; Rabbitt *et al.*, 2005; Hakizimana *et al.*, 2012). Subsequent *in vitro* manipulation of isolated OHCs has allowed in-depth insight into the biochemistry and biomechanics of OHC electromotility (Dallos and Evans, 1995; Gitter and Zenner, 1995; Sziklai *et al.*, 1996; Dallos *et al.*, 1997; Lue and Brownell, 1999; Frolenkov *et al.*, 2000; Sziklai *et al.*, 2001; Szonyi *et al.*, 2001; He *et al.*, 2003; Zhang *et al.*, 2003; Matsumoto *et al.*, 2010; Park and Kalinec, 2015). Additional *in vivo* investigation of OHC electromotility that builds on this substantive *in vitro* body of work has largely been completed using the guinea pig as a model (Nuttall and Ren, 1995; Nilsen and Russell, 1999; Nuttall *et al.*, 1999; Grosh *et al.*, 2004). The DPOAE tests discussed above provide a highly specific objective tool for quickly and easily measuring the overall integrity of the OHC active process using non-invasive *in vivo* procedures that do not require direct access to the cochlea.

B. Auditory nerve research

Some of the earliest efforts to understand the neural innervation of the cochlea were completed in guinea pig (Fernandez, 1951; Tsuji and Liberman, 1997), including early investigations of spontaneous and sound-evoked auditory nerve discharge (Tasaki, 1954) and adaptation (Sorensen, 1959). Noise exposure paradigms have served as a helpful tool for probing the contributions of the OHC active process to auditory nerve tuning (Cody, 1992). Although use of the guinea pig in early auditory nerve research was significant, extensive parallel activities using the cat as a model must also be noted (Gerstein and Kiang, 1960; Kiang and Peake, 1960; Kiang *et al.*, 1962; Peake and Kiang, 1962; Rodieck *et al.*, 1962; Kiang *et al.*, 1967; Sachs and Kiang, 1968). A number of later studies provided insight into the coding of speech-like sounds at the level of the auditory nerve in both guinea pig (Palmer *et al.*, 1986; Palmer, 1990; Steadman and Sumner, 2018) and cat (Kiang, 1980; Delgutte and Kiang, 1984d; 1984c; 1984b; 1984a; Le Prell *et al.*, 1996; May *et al.*, 1996). The effects of noise on the auditory nerve and its response properties are also described in detail in both guinea pig (Thomsen and Pakkenberg, 1962; Pakkenberg and Thomsen, 1964; Hallen *et al.*, 1965; Brown and Abbas, 1987) and cat (Kiang *et al.*, 1970; Kiang *et al.*, 1976; Liberman and Kiang, 1978; 1984; Pettigrew *et al.*, 1984; Bruce *et al.*, 2003). This extensive literature provides guidance and insight into study design for use in otoprotection research.

Auditory nerve recordings in guinea pigs have recently been used in an effort to understand the coding of high-frequency spectral notches that importantly contribute to sound localization (Alves-Pinto *et al.*, 2014). In other recent work, auditory nerve response measurements in the guinea pig have been used to identify the increased vulnerability of nerve fibers that have low and medium spontaneous rates of firing (Furman *et al.*, 2013), findings that have significant implications regarding the potential for deficits in the processing of supra-threshold signals (Kujawa and Liberman, 2015; Liberman and Kujawa, 2017; Kujawa and Liberman, 2019). With the wealth of data on auditory nerve response in the guinea pig, they are an ideal model with which to probe the earliest effects of noise on the inner ear, as well protection of neural function using otoprotective agents.

C. Auditory evoked potentials

Much of our understanding of the brainstem generators of the ABR came from studies completed in guinea pigs (Gardi and Bledsoe, 1981; Wada and Starr, 1983a; 1983c; 1983b; Harrison and Palmer, 1984; Palmer and Harrison, 1984) although parallel work in cat again closely followed (Jewett, 1970; Buchwald and Huang, 1975; Fullerton *et al.*, 1987; Fullerton and Kiang, 1990; Melcher *et al.*, 1996a; Melcher and Kiang, 1996; Melcher *et al.*, 1996b). Binaural interaction components within the ABR have been investigated in guinea pigs (Dum *et al.*, 1981; Gardi and Berlin, 1981; Wilson *et al.*, 1985; Ozdamar *et al.*, 1986); binaural processing is critical to accurate localization of sound and can be compromised by noise injury. Differences between species are driven by factors such as the size of the brain stem nuclei and lengths of the connecting fiber tracts, but the overall physiology and response properties appear to be well correlated across species (Huang, 1980). As noted above, the ABR is the current gold standard used to measure the functional effects of noise on the inner ear, and there is no reason to assume it will not continue to be heavily utilized in guinea pigs and across laboratory animal models.

D. Neurochemistry research

Because the cochlea and round window are easy to access in the guinea pig, they have also been popular for use in studies employing round window based drug delivery and perilymph sampling for the purposes of measurement of neurotransmitters, neuromodulators, and the movement of chemical ions during transduction. A number of detailed reviews that discuss data collected across species are already available (Bledsoe *et al.*, 1988; Eybalin, 1993; Puel, 1995; Le Prell *et al.*, 2001). It should be noted that much of the early work establishing glutamate (Glu) as the putative excitatory transmitter was completed in guinea pigs (Bobbin and Thompson, 1978; Bobbin, 1979; Bledsoe *et al.*, 1981; Jenison and Bobbin, 1985; Littman *et al.*, 1989). Detailed review and discussion of the Glu receptors located in the cochlea and the pathology observed during activation of these receptors are available [see Le Prell *et al.* (2001), Ruel *et al.* (2007), and Takago and Oshima-Takago (2018)] and this early work is highly relevant to the effects of noise on the inner ear given that noise-induced excitotoxicity has been a target in some otoprotection research (Yamasoba *et al.*, 2005). Much of the early work on adenosine

triphosphate (ATP) as a neuromodulator was also completed within the guinea pig cochlea (Skellett *et al.*, 1997; Chen *et al.*, 1998). More recent investigations in guinea pigs have now revealed the importance of P2X receptors (Sueta *et al.*, 2003; Thorne *et al.*, 2004; Yu and Zhao, 2008; Zhu and Zhao, 2012), and noise-induced changes in the receptor subunit distribution have been described (Szucs *et al.*, 2006). Chemical changes in the cochlea subsequent to noise exposure are not fully understood, and additional research is needed.

E. Olivocochlear efferent neuroanatomy and neurochemistry

Much of the work that established the ultrastructure (Satake and Liberman, 1996) and neurochemistry of the medial (MOC) and lateral (LOC) olivocochlear efferent systems was completed in guinea pigs, although the rat must also be acknowledged (White and Warr, 1983; Faye-Lund, 1986; Vetter *et al.*, 1991; Vetter and Mugnaini, 1992; Warr *et al.*, 1997). Transmitters investigated in the guinea pig model include acetylcholine (ACh), calcitonin-gene related peptide (CGRP), dopamine (DA), dynorphin (dyn), enkephalin (enk), and gamma-aminobutyric acid (GABA) [for detailed reviews and discussion see Eybalin (1993), Puel (1995), Le Prell *et al.* (2001), Ruel *et al.* (2007), and Wersinger and Fuchs (2011)]. Studies assessing the functional consequences of efferent stimulation have significantly relied on guinea pig as a model (Sridhar *et al.*, 1995; Kujawa and Liberman, 2001), and several investigations suggest a stronger MOC system is associated with decreased vulnerability to noise injury (Liberman and Gao, 1995; Reiter and Liberman, 1995; Maison and Liberman, 2000). More recent data extending insight into the LOC system continue to emerge from studies employing lesions of the LOC pathway (Le Prell *et al.*, 2003; Le Prell *et al.*, 2005; Le Prell *et al.*, 2014a), electrical stimulation of the LOC system (Groff and Liberman, 2003), and neurochemical manipulation of the guinea pig cochlea (Garrett *et al.*, 2011; Lendvai *et al.*, 2011; Le Prell *et al.*, 2014b; Wang *et al.*, 2014). The role of the MOC and LOC transmitter systems in mediating vulnerability to noise injury are not fully understood, but the guinea pig is an ideal model for continued research efforts given the wealth of information about these pathways in the guinea pig model.

F. Noise conditioning

Noise does not always cause trauma; there is a phenomena in which exposure to lower level noise can prevent later damage that occurs during a subsequent exposure to louder, more hazardous sound. This conditioning, or toughening, phenomena has been well investigated in the guinea pig, and is evident across species [for review see Niu and Canlon (2002)]. Data collected in the guinea pig model indicate that conditioning may mediate vulnerability by changing the OHC cellular cytoskeleton protein composition (Zuo *et al.*, 2008) and presynaptic vesicle content (Canlon *et al.*, 1993). However, other data in this animal model have shown upregulation of bcl-2 in the OHCs (Niu *et al.*, 2003), decreased levels of systemic malondialdehyde (suggesting decreased metabolic stress) (Liu *et al.*, 2000), and an upregulation in tyrosine hydroxylase positive neurons in the lateral superior olive (LSO) and dorsolateral periolivary nuclei (Niu *et al.*, 2004), suggesting other potential mechanisms of conditioning mediated protection. Other data have implicated the MOC system, based on conditioning induced changes in MOC neuron firing rates (Brown *et al.*, 1998) and protection of the MOC terminals (Canlon *et al.*, 1999).

Increases in DPOAE amplitude post-conditioning appear to be fairly consistent, whereas the direction of change in MOC reflex strength post-conditioning has varied across studies (Canlon and Fransson, 1995; Kujawa and Liberman, 1999; Peng *et al.*, 2007). Interestingly, when the MOC system is lesioned using strychnine, conditioning still confers protection, suggesting the MOC system is not necessary for conditioning (Yamasoba *et al.*, 1999a). Given mixed evidence for MOC effects with surgical transection of the efferent bundle (Kujawa and Liberman, 1997), it may be the case that the completeness of the lesion and method of lesion influence conditioning outcomes.

In some cases, conditioning is highly specific with respect to frequency, with protection observed when the conditioning stimulus and traumatic stimulus are at the same frequency, but no protection when there is a mismatch between the stimulus frequencies (Pourbakht and Imani, 2012). The temporal pattern of the noise matters as well, with intermittent conditioning noise suggested to be more effective than continuous exposure to the conditioning noise (Skellett *et al.*, 1998). In addition, longer post-conditioning delays reduce the effectiveness of the conditioning exposure (Canlon and Fransson, 1998). This continues to be an active research area. In an interesting recent investigation, for example, it was reported that gentamicin conditioning could be used in place of noise conditioning in order to toughen the ear and reduce vulnerability to noise injury (Strose *et al.*, 2014).

G. Perilymph sampling

Early efforts to sample cochlear perilymph in the guinea pig revealed a significant increase in potassium (K^+) and chloride (Cl^-) concentrations, and a decrease in sodium (Na^+) concentration, in noise exposed animals compared to control animals; this was interpreted as reflecting a change in the permeability of the barrier separating endolymph-filled and perilymph-filled compartments (Konishi *et al.*, 1979). Since then, new protocols for perilymph sampling have been developed (Salt *et al.*, 2006; Salt and Plontke, 2009). These new protocols have allowed the kinetics of drug movement within perilymph to be carefully investigated, with the guinea pig as the primary model, allowing new insights into the exchange of fluids across the cochlear aqueduct (Hunter *et al.*, 2003; Mynatt *et al.*, 2006; Plontke *et al.*, 2008; Salt *et al.*, 2012; Salt *et al.*, 2015; Salt *et al.*, 2016). In addition, the movement of systemically injected drugs into the cochlea has also become possible to quantify using this guinea pig model (Pierre *et al.*, 2009; Hahn *et al.*, 2013; Hellberg *et al.*, 2013).

VI. THE DAMAGED AUDITORY SYSTEM

Early investigations providing detailed insight into specific noise-induced histopathological changes in the guinea pig cochlea after noise exposure revealed damage to hair cells, supporting cells (including phalangeal cells and Deiters' cells), Reissner's membrane, and the reticular lamina (Covell *et al.*, 1957). As reviewed below, the guinea pig has continued to be a primary model of interest ever since, not only for studies on noise injury, but also for studies assessing DIHL, ARHL, and prevention of acquired sensorineural hearing loss subsequent to these diverse injuries.

A. Noise-induced hearing loss (NIHL)

Different noise paradigms have been used to induce NIHL in guinea pigs, with noise exposures differing in the frequency spectrum, intensity, duration, and chronicity (single or repeated exposure) (see Table II). Different types of noise have been used as traumatic insults in studies assessing otoprotective effects of pharmacological treatment [impulse noise, see Bielefeld *et al.* (2019); octave band noise, see Gittleman *et al.* (2019); blast, see Zhang (2019)]. Although some noise exposures are intended to mimic real-world exposure, such as impulse noise trauma intended to correspond to gunshot exposure affecting the military population, there are typically differences in impulse duration and frequency spectrum that decrease real-world relevance of the laboratory-generated signals.

Depending on the intensity and duration of the sound exposure, either a transient TTS or a lasting PTS will result [for review see Ryan *et al.* (2016)]. Threshold shifts that recover to baseline in the hours, days or weeks following exposure are termed TTS, whereas PTS is hearing loss that does not recover to pre-exposure levels. After some noise exposures, a compound threshold shift (CTS) is observed, including a large TTS which only partially recovers, such that a smaller PTS remains at the end of the recovery window. In addition, repeated exposures to noise that initially induce only a TTS may induce PTS subsequent to later exposures to the same noise stimulus (Wang and Ren, 2012). In animal models, the recovery window has sometimes extended up to 3 weeks and thus it may not be possible to fully distinguish TTS and PTS in animal models until a minimum of 3 weeks post-exposure [for review see Ryan *et al.* (2016)]. As an example, baseline and shift data measured using DPOAEs and ABRs are provided in Fig. 3. In this NIHL paradigm, guinea pigs were exposed to 115 dB sound pressure level (SPL) noise (1/3 octave band centered at 8 kHz) for 45 min, with PTS showing little recovery across a three week post-noise recovery window.

Young (2-month-old) albino guinea pigs appear to be more vulnerable to noise injury than young pigmented control animals (Conlee *et al.*, 1986). The decreased vulnerability of pigmented animals was attributed to the finding that stria vascularis in the pigmented guinea pig cochlea contains melanocytes that produce melanin with otoprotective effect. Protection of the pigmented guinea pigs was similarly observed following impulse noise (Xiong *et al.*, 2011). However, this protection did not extend to ARHL as pigmented guinea pigs had greater ARHL than albino animals at the age of 14-months old. When these 14-month old animals were exposed to noise, threshold shifts displayed by the pigmented animals (with poorer baseline hearing) were smaller than those of the albino animals, presumably because the pigmented animals had already lost cells during the aging process and these could not be lost again when exposed to noise (Conlee *et al.*, 1988).

Noise exposure induces the development of reactive oxygen species (ROS), as well as stress pathway signaling and apoptosis, commonly resulting in OHC loss [for review see Le Prell *et al.* (2007b), Abi-Hachem *et al.* (2010), and Poirrier *et al.* (2010)]. Noise exposure can also damage the synaptic connections between the IHCs and the primary afferent neurons, a pathology termed cochlear synaptopathy [for review see Kujawa and Liberman (2015)]. The phenomenon of noise-induced cochlear synaptopathy has now been demonstrated in several species and there is significant interest in the extent to which this pathology is present in the human inner ear [for recent review and discussion, see Bramhall *et al.* (2019) and Le Prell (2019)]. Although the majority of research has used mouse as a model [see Kujawa and Liberman (2015) and Liberman and Kujawa (2017)], the guinea pig has also now been used in several studies assessing the potential for cochlear synaptopathy (Lin *et al.*, 2011; Liu *et al.*, 2012; Furman *et al.*, 2013; Song *et al.*, 2016). One of the important advances in understanding of the loss of synapses after noise exposure was the documentation of a decrease in the proportion of low and medium spontaneous rate fibers in guinea pigs exposed to noise that induced a TTS (Furman *et al.*, 2013). Given interest in therapeutics for amelioration of such injuries (Wan *et al.*, 2014; Wan and Corfas, 2015; Suzuki *et al.*, 2016), it seems reasonable to predict that additional work in guinea pig will continue to emerge. One of the major emerging issues in synaptic regeneration research, however, is the unexpected finding of recovery of the synaptic ribbons over a one-month period following noise exposure in the guinea pig (Liu *et al.*, 2012; Shi *et al.*, 2013), a finding that has not been observed in mouse models. As discussed by Liberman and Kujawa (2017), additional research will be necessary to reconcile the differences in results across studies.

B. Effects of noise on cochlear blood flow

The cochlea is highly vascularized, and noise exposure constricts blood vessel diameter and decreases the velocity of cochlear blood flow [e.g., Perlman and Kimura (1962), Axelsson and Dengerink (1987), Thorne and Nuttall (1987), Meyer *et al.* (1991), Quirk *et al.* (1991), and Quirk *et al.* (1992)]. These effects appear to be both frequency and level dependent (Okamoto *et al.*, 1992; Scheibe *et al.*, 1993). Although cochlear blood flow is now well known to be decreased as a consequence of noise exposure [for reviews, see Axelsson and Dengerink (1987), Quirk and Seidman (1995), and Nuttall (1999)], recent data from blast exposed animals contrast in that an increase in cochlear blood flow was detected after blast (Chen *et al.*, 2013). The decreases in cochlear blood flow observed during and after short-term

TABLE II. A variety of noise exposure models used in the Guinea pig; for comprehensive systematic review of exposures used in otoprotection research see Hammill (2017). M: male; F: female; ND: Not Discussed; ket: ketamine; xyl: xylazine; ace: acepromazine; med: medetomidine; pent: pentobarbitol; CAP: compound action potential; DPOAE: distortion product otoacoustic emission.

Strain	Sex	Sedation/anesthesia	Noise	Intensity (dB SPL)	Duration	Final test time	Test metric	Anatomical metrics	Author
Pigmented	ND	ND	blank shots from FAMAS F1 rifle	170 peak SPL	3 shots	14 days	CAP threshold	Hair cell counts	Sendowski *et al.* (2006a)
Hartley	F	"lightly anesthetized"	blank shots from FAMAS F1 rifle	170 or 176 peak SPL	3 shots	14 days	CAP threshold	Hair cell counts	Sendowski *et al.* (2006b)
Pigmented	F	None (awake)	impulse noise (20 Hz to 6 kHz)	114	2 or 5 h	30 days	ABR threshold	ND	Franzé *et al.* (2003)
Pigmented	ND	None (awake)	repeated impulse noise	165	60 impulses	4 weeks	ABR threshold	Hair cell counts	Zhou *et al.* (2009)
Albino	ND	ND	2 kHz pure tone	120 or 125	10 min	7 days	CAP threshold; DPOAE amplitude	ND	Tabuchi *et al.* (2005)
Hartley	F	ket: 60 mg/kg xyl: 2 mg/kg ace: 0.2 mg/kg	6 kHz pure tone	120	0.5 h	7 days	CAP threshold	Hair cell counts	Fetoni *et al.* (2009b)
Pigmented	ND	Pent: dose not provided	6 kHz pure tone	120	0.5 h	7 days	CAP threshold and amplitude	Hair cell counts	Wang *et al.* (2003b)
Hartley	ND	ket: 25 mg/kg xyl: 5 mg/kg ace: 1.5 mg/kg	6 kHz pure tone	120	1 h	21 days	ABR threshold	Hair cell counts	Fetoni *et al.* (2010)
Hartley	ND	ket: 25 mg/kg xyl: 5 mg/kg ace: 1.5 mg/kg	6 kHz pure tone	120	1 h	21 days	ABR threshold	Hair cell counts	Fetoni *et al.* (2011)
Hartley	ND	"General anesthesia"	6 kHz pure tone	130	15 min	7 days	ABR threshold	Hair cell counts	Tona *et al.* (2014)
Hartley	ND	pent: 33 mg/kg	center frequency of 4 kHz; bandwidth ND	130	3 h	14 days	ABR threshold	Hair cell counts	Takemoto *et al.* (2004)
Hartley	M and F	None (awake)	narrow band noise centered at 2.5–3.5 kHz	130	1h	14 days	ABR threshold; DPOAE amplitude	Hair cell counts	Chen *et al.* (2014)
Pigmented	M and F	ket: 40 mg/kg xyl: 4 mg/kg	one-third octave band noise centered at 6.3 kHz	110	1 h	7 days	ABR threshold	ND	Chen *et al.* (2003)
Pigmented	M	None (awake)	Octave band centered at 4 kHz	100	8 h/day for 3 days	8 days	ABR threshold	Hair cell counts	Hou *et al.* (2003)
Hartley	F	ket: 40 mg/kg xyl: 10 mg/kg ace: 0.75 mg/kg	Octave band centered at 4 kHz	105 or 110	2h	10 days	ABR threshold	ND	Harrop-Jones *et al.* (2016)
Hartley	ND	med: 1 mg/kg xyl: 2 mg/kg pent: 24 mg/kg	Octave band centered at 4 kHz	110	3h	14 days	ABR threshold	Hair cell counts; synaptic ribbon density	Kanagawa *et al.* (2014)
Pigmented	M	None (awake)	Octave band centered at 4 kHz	110	4h	7 days	CAP threshold	Hair cell counts	Le Prell *et al.* (2011a)
Hartley	M and F	ND	Octave band centered at 4 kHz	114	6 h	21 days	ABR threshold	Hair cell counts	McFadden *et al.* (2005)

TABLE II. (*Continued*)

Strain	Sex	Sedation/anesthesia	Noise	Intensity (dB SPL)	Duration	Final test time	Test metric	Anatomical metrics	Author
Hartley	M	None (awake)	Octave band centered at 4 kHz	115	3 h	7 days	ABR threshold	Auditory nerve dendrite swelling	Yamasoba *et al.* (2005)
Pigmented	ND	None (awake)	Octave band centered at 4 kHz	115	5 h	7 days	ABR threshold	Hair cell counts	Shoji *et al.* (2000a)
Pigmented	ND	None (awake)	Octave band centered at 4 kHz	115	5 h	7 days	ABR threshold	Hair cell counts	Shoji *et al.* (2000b)
Hartley	F	None (awake)	Octave band centered at 4 kHz	115	5 h	10 days	ABR threshold	Hair cell counts	Ohinata *et al.* (2000)
Hartley	F	None (awake)	Octave band centered at 4 kHz	117	24 h	7 days	ABR threshold	Hair cell counts	Shibata *et al.* (2007)
Pigmented	F	None (awake)	white noise (20 Hz to 8 kHz)	120	2 or 5 h	30 days	ABR threshold	ND	Franzé *et al.* (2003)
Hartley	M	ND	Octave band centered at 4 kHz	120	3 h	21 days	ABR threshold	Hair cell counts	Inaoka *et al.* (2009)
Pigmented	M	ND	Octave band centered at 4 kHz	120	5 h	10 days	ABR threshold	Hair cell counts	Minami *et al.* (2007)
Pigmented	M	None (awake)	Octave band centered at 4 kHz	120	5 h	10 days	ABR threshold	Hair cell counts	Yamashita *et al.* (2005)
Hartley	F	None (awake)	Octave band centered at 4 kHz	125	5 h	14 days	ABR threshold	Hair cell counts	Pourbakht and Yamasoba (2003)
Pigmented	M	None (awake)	Octave band centered at 4 kHz	120	5h	10 days	ABR threshold	Hair cell counts	Le Prell *et al.* (2007a)
Hartley	M	None (awake)	Octave band centered at 4 kHz	120	6h	15 days	ABR threshold	ND	Mohammadian *et al.* (2017)
Hartley	M	None (awake)	Octave band centered at 4 kHz	120	24 h	7 days	ABR threshold	Hair cell counts	Takemura *et al.* (2004)
Hartley	ND	med: 1 mg/kg xyl: 2 mg/kg pent: 24 mg/kg	Octave band centered at 4 kHz	130	3h	7 days	ABR threshold	Hair cell counts; synaptic ribbon density	Kanagawa *et al.* (2014)
Hartley	M	Pent: 33 mg/kg	Octave band centered at 4 kHz	130	3 h	7 days	ABR threshold	Hair cell counts	Mikuriya *et al.* (2005)
Pigmented	F	None (awake)	broadband noise	102	3 h/day for 5 days	3 weeks	ABR threshold	Hair cell counts	Yamasoba *et al.* (1998)
Hartley	M	ND	broadband (white) noise (.125-15 kHz)	105 ± 2	10 min	7 days	ABR threshold	NA; enzyme analyses completed	Cheng *et al.* (2008)
Hartley	ND	None (awake)	broadband (white) noise (.125-15 kHz)	105	6h	14 days	ABR threshold	ND	Lo *et al.* (2013)
Pigmented	M and F	ND	broadband noise (8-16 kHz)	115	3h	21 days	CAP threshold	Hair cell counts; spiral ganglion counts	Landegger *et al.* (2016)

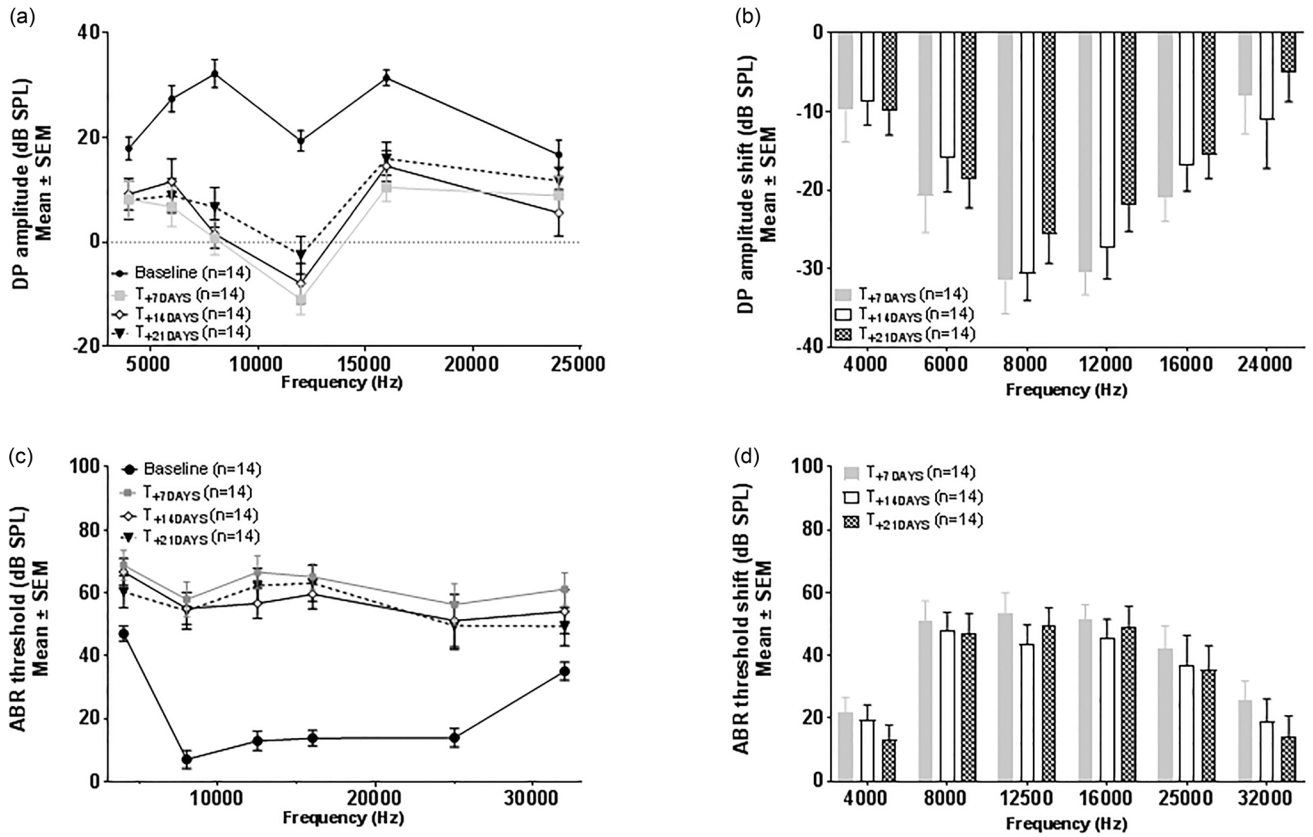

FIG. 3. Distortion Product Otoacoustic Emission (DPOAE) amplitude (3 A) and Auditory Brainstem Response (ABR) threshold (3 C) were measured bilaterally in seven young adult Hartley albino guinea pigs before and 7, 14, and 21 days after noise exposure; changes in DPOAE amplitude (3B) and ABR threshold (3 D) were calculated as shift from baseline at each post-noise time. Noise exposure was 115 dB SPL for a 1/3 octave noise band centered at 8 kHz; exposures were 45 min in duration and applied under anesthesia. All data are mean ± standard error of the mean (SEM). This noise exposure induces a rapid decrease of DPOAE amplitudes [(a) and (b)] and increase of ABR thresholds [(c) and (d)], which are still present 21 days post-noise, with the greatest noise injury at frequencies at and within one octave above the exposure frequency of 8 kHz. (Unpublished data collected at CILcare.)

noise (i.e., exposures lasting minutes to hours) can be prevented by vasodilating agents such as dilazep dihydrochloride (Okamoto *et al.*, 1990) or magnesium (Haupt and Scheibe, 2002); drugs that decrease blood viscosity, such as penoxifylline (Coleman *et al.*, 1990; Latoni *et al.*, 1996); or, the angiotensin receptor antagonist Sarthran (Goldwin *et al.*, 1998). Nitric oxide has been broadly implicated in cochlear blood flow and homeostasis [for review see Fessenden and Schacht (1998)]. Inhibition of nitric oxide using the nitric oxide synthase inhibitor N-nitro-L-arginine-methyl ester (L-NAME) attenuates noise induced decreases in cochlear blood flow (Ren *et al.*, 1997). Interestingly, L-NAME similarly prevented the blast-induced increase in cochlear blood flow (Chen *et al.*, 2013). Another potentially effective intervention assessed in the guinea pig model includes inhibition of TNF-alpha using etanercept to preserve cochlear microcirculation in strial capillaries and prevent NIHL (Arpornchayanon *et al.*, 2013). Inhalation of carbogen—a mixture composed of 90%–95% oxygen and 5%–10% carbon dioxide–increases blood vessel diameter and blood flow velocity, and decreased NIHL (Dengerink *et al.*, 1984; Zhao *et al.*, 2012). Another study using 100% oxygen as an additional experimental intervention found 100% oxygen to be even more beneficial than carbogen (Hatch *et al.*, 1991).

C. Age-related hearing loss (ARHL)

Although the focus of this review is noise injury and its prevention, there are changes in vulnerability to noise injury over the course of the lifespan (Kujawa and Liberman, 2006), and it is thus worthwhile to understand the changes in hearing that occur with aging in the guinea pig. Studies conducted in guinea pigs reveal age-related changes in hearing as observed in other mammalian species, with higher frequencies showing threshold elevations prior to the development of deficits at lower frequencies (Ingham *et al.*, 1998a). In addition, more hearing loss is observed in pigmented strains than albino strains (Dum *et al.*, 1980a, 1980b; Dum, 1984). With advancing age in guinea pigs (from 2 to 25 months old), there is a gradual elevation of thresholds [measured using ABR and compound action potential (CAP)] that is accompanied by prolonged ABR latencies for waves I, II, III, and IV, a finding that is generally common across species, including humans. Interestingly, although the ABR waveform amplitudes decreased, response latency (i.e., neural conduction time) associated with the individual potentials remained unchanged between old and young animals in a subset of studies (Dum *et al.*, 1980b; Proctor *et al.*, 1998). Individual differences in threshold elevation and latency prolongation may suggest individual differences in

degenerative aging processes of the auditory system (Nozawa *et al*., 1996; Nozawa *et al*., 1997).

Age related hair cell loss (Ingham *et al*., 1999) and changes in microtubules (Saha and Slepecky, 2000) in the guinea pig organ of Corti suggest age-related changes in micromechanical properties of the sensory epithelium. Age-related changes in guinea pig superior colliculus have also been described (Ingham *et al*., 1998b). In addition, recordings from the primary auditory cortex of pigmented guinea pigs aged from 6 months to 2 years old have demonstrated an age-related "cortical hearing loss" as shown by changes in both threshold and frequency response in the cortex (Gourevitch and Edeline, 2011). Taken together, these data are consistent with the involvement of both peripheral hearing loss and biological aging in the central auditory system in presbycusis. Because the guinea pig has a longer life span than most other rodents, increasing the duration and cost of ARHL studies, the preferred model for studying ARHL has been the mouse, which has the added benefit of many genetically modified strains being available [for review, see Ohlemiller (2006) and Bowl and Dawson (2015)].

D. Drug-induced hearing loss (DIHL)

More than 150 drugs are currently known to be ototoxic. These include aminoglycosides, glycopeptides and macrolide antibiotics, platinum-based anticancer drugs, loop diuretics, quinine, and salicylate analgesics. The effects of ototoxic drugs, such as loop diuretics, macrolide antibiotics, quinine and salicylate, tend to be temporary whereas the effects of other drugs, such as cisplatin and aminoglycoside antibiotics, are generally permanent [for review, see Lanvers-Kaminsky *et al*. (2017) and Campbell and Le Prell (2018)]. Ototoxic drug and chemical effects can be divided into categories of cochleotoxicity, defined as damage affecting the auditory system resulting in tinnitus and/or sensorineural hearing impairment, and vestibulotoxicity, defined as injury to the vestibular system resulting in dizziness, vertigo, and loss of balance.

Although the focus of this review is noise injury and its prevention, there is tremendous overlap in the mechanisms through which noise and ototoxic drug agents injure the ear, and there is extensive overlap in the protective effects of various drugs in preventing both noise-induced and drug-induced acquired sensorineural hearing loss. Perhaps equally important, however: patients that are prescribed ototoxic medications are often exposed to noise, and there can be synergistic interactions through which the combination of drugs plus noise increase the risk of acquired sensorineural hearing loss. Data from animal models suggest that treatment with cisplatin may result in long-lasting vulnerability to the effects of subsequent noise exposure, suggesting that patients should be counseled to avoid noise exposure during and after treatment with this chemotherapeutic (Gratton *et al*., 1990; DeBacker *et al*., 2017). As discussed above for prevention of noise injury, there is tremendous interest in the potential for prevention of DIHL [for review and discussion, see Anderson and Campbell (2015), Laurell and Pierre (2015), Rybak and Brenner (2015), and Hammill and Campbell (2018)].

Several ototoxic drugs have been studied in guinea pigs. Highlighting the importance of nutrition with respect to the vulnerability of the inner ear, the ototoxic side effects of aminoglycosides and cisplatin are increased in animals fed a low-protein diet (Lautermann *et al*., 1995b; Lautermann and Schacht, 1996). It should be noted that protein intake will be indirectly reduced in animals that are not maintaining sufficient food intake during aminoglycoside or cisplatin therapies; weight loss during such therapies is common, including in guinea pig models (Ekborn *et al*., 2003; Le Prell *et al*., 2014c). Nutritional supplements may be necessary, and should be reported in study descriptions when they are used to treat animals in ototoxicity and otoprotection research (Spankovich and Le Prell, 2019).

VII. OTOPROTECTION: PREVENTION OF COCHLEAR INJURY AND HEARING LOSS

The guinea pig has been a preferred model to test new therapies in part due to the ease of delivering drugs into the inner ear. It has also been used in safety studies, to define the best route of administration. The assessment of otoprotective agents has used not only different investigational agents but also different administration routes, dose, and duration of treatment, which has created challenges comparing the relative benefits of different drugs studied in diverse pre-clinical models [for discussion see Le Prell and Miller (2016) and Lynch *et al*. (2016)]. Both preventive (prophylactic, pre-noise) and curative (rescue, post-noise) effects have been assessed. The rest of this article briefly identifies diverse agents that have been assessed for prevention of NIHL, DIHL, and ARHL in guinea pigs. Efforts to induce regeneration using stem cell and gene therapies are not discussed; readers should see the review by Lee and Park (2018) for an introduction to these approaches.

A. Neuromodulators

Glutamatergic excitotoxicity has been well studied in the guinea pig (Pujol *et al*., 1993; Puel *et al*., 1995; Pujol and Puel, 1999) and antagonizing NMDA and/or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the guinea pig cochlea significantly decreases hearing impairment after noise trauma and ototoxins (see Table III). Exposure to noise trauma and ototoxins also affects the viability of sensory hair cells via the MAP kinase (MAPK) cell death signaling pathway that incorporates c-Jun N-terminal kinase (JNK) (Zine and van de Water, 2004). Blocking the MAPK-JNK signal pathway in the guinea pig cochlea also prevents hair cell death and hearing loss induced by noise and ototoxins (see Table III). Caspases mediate kinase cleavage, driving apoptotic cell death (Kurokawa and Kornbluth, 2009). Intracochlear perfusion with caspase- inhibitors prevents hearing loss induced by noise exposure and ototoxins (see Table III). For further details on mechanisms leading to hearing loss see Furness (2015) and Waters (1999).

TABLE III. Neuromodulators assessed in guinea pig hearing loss models.

Drugs	Target	Effect	Reference
Glutamate antagonists			
—	Glutamate	Attenuation of noise-induced TTS	Khan *et al.* (2000)
Kynurenate	AMPA	Protective effect on NIHL	Puel *et al.* (1998)
Caroverine	NMDA & AMPA	Reduction of hearing impairment in NIHL	Chen *et al.* (2003)
			Chen *et al.* (2004)
MK801	NMDA	Protection in amikacin-induced hearing loss	Duan *et al.* (2000)
Memantine	NMDA	Prevention of toxic damage to hair cells in amikacin-induced hearing loss	Pavlidis *et al.* (2014)
Kinase			
D-JNKI-1	Blocking of MAPK-JNK signal pathway	Prevention in a dose-dependent manner of hair cell death and permanent hearing loss induced by neomycin after cochlear application	Wang *et al.* (2003b) see Eshraghi *et al.* (2007).
		Prevention of noise-induced permanent hearing loss by a direct cochlear application	Wang *et al.* (2003b)
		Prevention of hair cell death and PTS induced noise by RWM application	Wang *et al.* (2007b)
Caspase inhibitors			
z-DEVD-fmk	caspase-3	Prevention of cisplatin-induced hearing loss by intracochlear treatment	Wang *et al.* (2004)
z-LEHD-fmk	caspase-9		
z-VAD-FMK	caspase	Hearing recovery and reduction of hair cell loss after NIHL	Abaamrane *et al.* (2011)
Enzymes			
MDL28170	gamma-secretase inhibitor	Protective effect on NIHL by direct delivery into the cochlear fluids	Tona *et al.* (2014)
Calpain inhibitors			
BN82270	calpain	Prevention of hair cell degeneration induced by noise by application in cochlear fluids or onto the RWM	Wang *et al.* (2007a)
leupeptin	calpain	No effect after a gunshot noise-induced trauma by cochlear infusion	Abaamrane *et al.* (2011)
Adrenocorticotrophic Hormone (ACTH)			
ORG 2766	ACTH analogue	Protection against hair cell loss and hearing loss induced by cisplatin	Hamers *et al.* (1994); Smoorenburg *et al.* (1999); Cardinaal *et al.* (2000)

TABLE IV. Anti-inflammatory agents assessed in guinea pig hearing loss models. DHEA-S: Dehydroepiandrosterone sulfate; TNF: Tumor necrosis factor.

Drugs	Effect	Reference
Glucocorticoids		
Dexamethasone (DEX)	Reduction of noise-induced OHC loss and ABR threshold shifts after cochlear delivery	Takemura *et al.* (2004)
	Prevention of hearing loss induced by acoustic trauma after application into RW niche	Chi *et al.* (2011)
	Protective effect in NIHL by trans-RWM delivery	Shih *et al.* (2019)
	No hearing recovery of late intratympanic injection (48 h) after a mild noise trauma	Mamelle *et al.* (2018)
OTO-104 (DEX)	Effective protection against NIHL by transtympanic administration	Harrop-Jones *et al.* (2016)
Methyl-prednisolone	Reduction of hair cell loss in NIHL by cochlear infusion	Sendowski *et al.* (2006a)
	Effective protection against NIHL by intratympanic administration	Zhou *et al.* (2009)
Prednisolone	Effective protection against acute noise trauma by RW administration	Muller *et al.* (2017)
DEX	Intratympanic administration in cisplatin-induced ototoxicity in guinea pigs	Daldal *et al.* (2007); Murphy and Daniel (2011); Shafik *et al.* (2013)
	Prevention of cisplatin induced hearing loss	Sun *et al.* (2015)
OTO-104 (DEX)	Protection against hearing loss induced by both acute and chronic administration of cisplatin	Fernandez *et al.* (2016)
DEX	No protection against cisplatin-induced ototoxicity by systemic delivery	Waissbluth *et al.* (2013)
	Protective effects against cisplatin-induced hearing loss by systemic administration	Sun *et al.* (2016)
Neurosteroids		
DHEA-S	Protective effect against injury of the cochlea induced by noise	Tabuchi *et al.* (2005)
Cytokines		
TNF-α inhibition (etanercept)	Prevention of NIHL by improvement of cochlear blood flow	Arpornchayanon *et al.* (2013)
Prostaglandin E receptor	Protection of cochleae against NIHL	Hori *et al.* (2009)
subtype EP4 agonist	Protective effect on cochleae against NIHL	Hori *et al.* (2013)
Histone deacetylase (HDAC) inhibitor		
Sodium butyrate	Attenuation of gentamicin-induced hearing loss	Wang *et al.* (2015)
	Attenuation of noise-induced PTS and OHC loss	Yang *et al.* (2017)

B. Anti-inflammatory agents

A common process observed in DIHL, NIHL, and ARHL is cochlear inflammation (Kalinec *et al.*, 2017). Reducing acute inflammation and related processes can be a therapeutic strategy to prevent hearing loss. This strategy has been successful in different hearing loss models in guineas pigs for several anti-inflammatory agents and inhibitors of inflammatory molecules, as listed in Table IV. A detailed review of the contribution of inflammation to NIHL is provided by Frye *et al.* (2019).

C. Free radical scavengers (anti-oxidants)

The generation of ROS is thought to be part of the mechanism underlying NIHL [for reviews, see Le Prell *et al.* (2007b) and Le Prell and Bao (2012)]. ROS not removed by antioxidant defenses could be expected to cause significant damage to the

TABLE V. Anti-oxidant agents assessed in guinea pig hearing loss models.

Drugs	Effect	Reference
D-Methionine	Prevention of ABR and ATPase activities induced by cisplatin	Cheng *et al.* (2005)
	Attenuation of threshold shifts induced by gentamicin	Sha and Schacht (2000)
	Reduction of kanamycin-induced ototoxicity	Campbell *et al.* (2016)
	Rescuing noise-induced permanent threshold shift	Lo *et al.* (2013); Alagic *et al.* (2011); Cheng *et al.* (2008)
	For further details in several species, against cisplatin-, carboplatin-, aminoglycoside- and noise-induced hearing loss and hair cell loss	see Campbell *et al.* (2007)
N-Acetylcysteine (NAC)	No protective effect on kanamycin-induced hearing loss, on the contrary, produced a more severe hearing loss and more severe cochlear damage	Bock *et al.* (1983)
	Preventive effect on cisplatin ototoxicity by NAC transtympanic administration	Choe *et al.* (2004)
	Otoprotection from cisplatin ototoxicity	Mohan *et al.* (2014)
	Protective effects on noise-induced hearing loss	Fetoni *et al.* (2009b)
Mitoquinone (MitoQ)	Prevention of ototoxicity induced by cisplatin	Tate *et al.* (2017)
	Attenuation of gentamicin-induced cochlear damage and hearing loss	Ojano-Dirain *et al.* (2014)
	Limited protection against amikacin-induced hearing loss and cochlear damage	Dirain *et al.* (2018)
NG-nitro-L-arginine methyl ester (L-NAME) (iNOS inhibitor)	Reduction of ABR threshold shifts induced by cisplatin	Watanabe *et al.* (2000)
	Reduction of noise-induced cochlear damage	Diao *et al.* (2007); Inai *et al.* (2012)
Aminoguanidine (iNOS inhibitor)	Prevention of hearing loss induced by gentamicin combined with furosemide	Liu *et al.* (2008).
Glutathione (GSH)	Attenuation of the progression of hearing loss and threshold shift induced by gentamicin, depending on nutritional status	Garetz *et al.* (1994); Lautermann *et al.* (1995a)
	Attenuation of hearing loss by GSH supplementation under low protein diet	Ohinata *et al.* (2000)
	Reduction of NIHL	Yamasoba *et al.* (1998)
Ebselen (2-phenyl-1,2-benzisoselenazol-3(2H)-one)	Attenuation of noise-induced cochlear damage, by prevention of noise-induced excitotoxicity and threshold shift	Pourbakht and Yamasoba (2003); Yamasoba *et al.* (2005)
Sodium thiosulfate	Chemoprotectant against carboplatin-induced ototoxicity	Neuwelt *et al.* (1996); Muldoon *et al.* (2000)
	Complete prevention of cisplatin-induced hearing loss by local delivery into cochlea or middle ear	Wang *et al.* (2003a); Stocks *et al.* (2004); Berglin *et al.* (2011)
Alpha-tocopherol	Protective effects against gentamicin ototoxicity	Fetoni *et al.* (2003); Fetoni *et al.* (2004a)
	Protective effects against cisplatin ototoxicity	Fetoni *et al.* (2004b)
	Attenuation of noise induced cochlear damage	Hou *et al.* (2003)
Radical scavengers (Edaravone and Tempol)	Inconsistent effects on aminoglycoside-induced ototoxicity	Song and Schacht (1996)
	Protection of the cochleae from acoustic trauma	Takemoto *et al.* (2004) Tanaka *et al.* (2005) Minami *et al.* (2007)
Iron chelators	Complete functional and morphological protection from gentamicin ototoxicity	Song and Schacht (1996); Sha and Schacht (1997); Song *et al.* (1997); Sinswat *et al.* (2000)
	Protection against ototoxicity induced by neomycin, kanamycin and streptomycin	Conlon *et al.* (1998); Song *et al.* (1998)
	Attenuation of NIHL	Yamasoba *et al.* (1999b)
Salicylate	Reduction of auditory threshold shifts and protection of auditory sensory cells against gentamicin	Sha and Schacht (1999).
	Protection of the OHC against cisplatin ototoxicity at low doses	Hyppolito *et al.* (2006)
Allopurinol	Otoprotective effect after noise exposure	Franzé *et al.* (2003)
Idebenone, a coenzyme Q10 analogue	Reduction of threshold shifts, apoptotic activation and hair cell loss induced by noise	Sergi *et al.* (2006); Fetoni *et al.* (2008); Fetoni *et al.* (2009a)
Ferulic acid (4-hydroxy 3-methoxycinnamic acid)	Protective effect on PTS in NIHL	Fetoni *et al.* (2010); Fetoni *et al.* (2011)

sensory cells of the cochlea. Studies over the last decade have left little doubt that ROS also participate in the cellular events leading to aminoglycoside-induced hearing loss (Rybak and Brenner, 2015) and cisplatin induced hearing loss as well (Laurell and Pierre, 2015). A list of anti-oxidant agents studied in the guinea pig are provided in Table V.

D. Trophic factors

Neurotrophic factors are secreted peptides that when interacting with specific classes of membrane receptors activate intracellular signaling cascades that prevent neuronal death during embryonic development and enable neurotrophic effects in adult. Brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), members of the neurotrophin family of neurotrophic factors that also include nerve growth factor (NGF) and neurotrophin-4/5 (NT-4), are important in development of the neuronal components of the inner ear. Several studies have aimed to assess the protectives effects of neurotrophin members in different models of hearing loss. In addition, other trophic or growth factors have also demonstrated otoprotective effects. The agents in Table VI provide a list of trophic factors assessed in guinea pig models of hearing loss.

VIII. CONCLUDING COMMENTS

Stebbins *et al.* (1982) identified critical challenges in the investigation of the effects of noise on the inner ear as including (1) the use of diverse species across studies, (2) the use of diverse protocols for threshold measurement, (3) the use of diverse noise exposures, many of which do not necessarily model human exposures, and (4) overall lack of consideration of supra-threshold measures of sensitivity. Although they called for greater uniformity and standardization to drive more rapid progress, the systematic review by Hammill (2017) clearly documents that research assessing the effects of noise and potential benefits of different otoprotective agents continues to have tremendous diversity with respect to both species and noise exposure paradigms, with few, if any, efforts to assess supra-threshold measures of sensitivity. As reviewed in this article, there is a wealth of knowledge regarding the guinea pig auditory system, and the guinea pig has become one of the most common models used within noise injury and otoprotection research. The mouse (Ohlemiller, 2019), rat (Escabi *et al.*, 2019; Holt *et al.*, 2019), and chinchilla (Lobarinas *et al.*, 2019; Radziwon *et al.*, 2019) also continue to be commonly used, and new data using nonhuman primates as subjects in noise injury research are also emerging (Burton *et al.*, 2019). Otoprotection research designs have most commonly relied on rodent models, with specific agents typically being assessed in only one or sometimes two rodent species. To facilitate comparisons of efficacy across agents, we encourage a series of new investigations using the guinea pig as a common model based not only on the wealth of normative data from the cochlea to the auditory cortex for this species, but also the wealth of data across diverse octave band noise exposures—the exposure model that has been the most common across otoprotection research investigations (Hammill, 2017; Gittleman *et al.*, 2019). The importance of testing using a common model does not preclude the possibility of research using other models to extend and confirm hypotheses regarding drug effects and mechanisms of action. However, only with the collection of new data using a common species and a common noise insult will we begin to be able to make reliable inferences about the relative efficacy of different agents, and the relative likelihood of success in translation to humans. As part of this effort, it will be critical to collect dose-response data to assure that the "best" (most

TABLE VI. Trophic and growth factors assessed in guinea pig hearing loss models. GDNF: Glial-derived neurotrophic factor; rhIGF-1: recombinant human insulin-like growth factor 1; HGF: hepatocyte growth factor; bFGF: Basic fibroblast growth factor; G-CSF: Granulocyte colony-stimulating factor.

Drugs	Effect	Reference
Neurotrophins		
NT-3	Prevention of degeneration of spiral ganglion neurons, hearing loss induced by aminoglycosides	Ernfors *et al.* (1996)
	Protective effect in a dose dependent manner, enabling OHC survival and a decrease in ABR threshold shift after preventive treatment into the cochlea	Shoji *et al.* (2000a)
NGF	Protective effects on neomycin-induced auditory nerve degeneration	Shah *et al.* (1995)
BDNF	Prevention of hearing loss induced by cisplatin by intracochlear application	Meen *et al.* (2009)
	No protection on hearing and hair cell loss induced by noise after preventive treatment into the cochlea	Shoji *et al.* (2000a)
BDNF & NT-3	Reduction of IHC synaptopathy and recovery of high-frequency hearing in in NIHL when delivered together to the RW	Sly *et al.* (2016).
Other trophic factors		
GDNF	Otoprotective effect on hair cells against cisplatin or kanamycin and ethacrynic acid by local delivery—transtympanic injection into the middle ear or infusion into the scala tympani	Kuang *et al.* (1999).
	Prevention, in a dose-dependent manner, of cochlear sensory cell damage and hearing loss after acoustic trauma	Keithley *et al.* (1998); Shoji *et al.* (2000b).
rhIGF-1	Attenuation of functional and histologic damage induced by noise in guinea pigs after local application	Lee *et al.* (2007)
HGF	Reduction of ABR threshold shifts and loss of OHC induced by noise after RWM application	Inaoka *et al.* (2009)
bFGF	Protection of the hair cells from acoustic trauma and recovery of hearing by perfusion into the cochlea	Zhai *et al.* (2002)
	Protection of auditory neurons and hair cells from glutamate neurotoxicity and noise exposure by intramuscular injection	Zhai *et al.* (2004)
G-CSF	Attenuation of NIHL by preserving hair cells after intense noise exposure	Shi *et al.* (2014)

effective) doses and dose paradigms are able to be compared across studies with otherwise shared design features; with the large number of agents already assessed in the guinea pig, there are rational starting points for dose assessment for many agents. With cooperation to reach consensus on study design, scientific research findings will be better poised to support the translation of promising agents into human clinical testing for prevention of NIHL.

IX. DISCLOSURE

G.N. and M.P. are employed by CILcare, a preclinical provider of pharmacokinetics, preclinical efficacy, and GLP toxicology studies. C.L. has received contract funding from industry sources for clinical trials (Sound Pharmaceuticals, Inc., Edison Pharmaceuticals, Inc., and Hearing Health Science, Inc.) and is grateful for support from the Emilie and Phil Schepps Professorship in Hearing Science. C.L. is currently supported by USAMRAA W81XWH-19-C-0054, JPC-8/SRMRP W81XWH1820014, NIH-NIDCD 1R01DC014088, 3M Inc., and the Emilie and Phil Schepps Professorship in Hearing Science.

ACKNOWLEDGMENTS

The authors thank Dr. Yves Cazals for feedback on an earlier version of this manuscript.

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