WJO World Journal of Otorhinolaryngology

Online Submissions: http://www.wjgnet.com/esps/
wjotorhinolaryngol@wjgnet.com
doi:10.5319/wjo.v3.i3.71

World J Otorhinolaryngol 2013 August 28; 3(3): 71-88
ISSN 2218-6247 (online)

REVIEW

Systematic review of animal models of middle ear surgery

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Received: May 21, 2013 **Revised:** August 9, 2013
Accepted: August 20, 2013
Published online: August 28, 2013

Abstract

Animal models of middle ear surgery help us to explore disease processes and intervention outcomes in a manner not possible in patients. This review begins with an overview of animal models of middle ear surgery which outlines the advantages and limitations of such models. Procedures of interest include myringoplasty/tympanoplasty, mastoidectomy, ossiculoplasty, stapedectomy, and active middle ear implants. The most important issue is how well the model reflects the human response to surgery. Primates are most similar to humans with respect to anatomy; however, such studies are uncommon now due to expense and ethical issues. Conversely, small animals are easily obtained and housed, but experimental findings may not accurately represent what happens in humans. We then present a systematic review of animal models of middle ear surgery. Particular attention is paid to any distinctive anatomical features of the middle ear, the method of accessing the middle ear and the chosen outcomes. These outcomes are classified as either physiological in live animals, (*e.g.*, behavioural or electrophysiological responses), or anatomical in cadaveric animals, (*e.g.*, light or electron microscopy). Evoked physiological measures are limited by the disruption of the evoking air-conducted sound across the manipulated middle ear. The eleven identified species suitable as animal models are mouse, rat, gerbil, chinchilla, guinea pig, rabbit, cat, dog, sheep, pig and primate. Advantages and disadvantages of each species as a middle ear surgical model are outlined, and a suggested framework to aid in choosing a particular model is presented.

Key words: Otologic surgical procedures; Middle ear; Animal models; Electrophysiology; Microscopy

Core tip: Animal models provide an invaluable insight into physiological and anatomical responses to middle ear surgical interventions. The choice of which animal model to use depends on the question which needs to be answered and on the available resources. Acute terminal experiments permit greater access and exposure of the middle ear structures, but the behavioural and long-term outcomes are not available. Chronic experiments conversely have more limited options for exposure, but allow long-term observation of tissue recovery and tolerance of the surgery. Both options are considered in this review.

Bergin M, Vlajkovic S, Bird P, Thorne P. Systematic review of animal models of middle ear surgery. *World J Otorhinolaryngol* 2013; 3(3): 71-88 Available from: URL: http://www.wjgnet.com/2218-6247/full/v3/i3/71.htm DOI: http://dx.doi.org/10.5319/wjo.v3.i3.71

REVIEW AIM

This review aims to assess the strengths and weaknesses of different animal models of middle ear surgery by noting particular anatomical features; methods of surgical access to the middle ear; middle ear surgical outcomes, with particular attention to the hearing frequency spectrum; and advantages or disadvantages of each animal model. Unless otherwise indicated, the hearing frequency spectra are taken from work by Fay[1] and Warfield[2].

DEFINITION AND ANATOMY

Middle ear surgery is a broad term which encompasses any manipulation of the structures of the middle ear and adjoining air spaces. The human middle ear, or tympanum, is bounded laterally by the tympanic membrane (TM); medially by the promontory of the cochlea; anteriorly by the Eustachian (auditory) tube; and posteriorly by the aditus ad antrum and subsequent entry into the mastoid air cells. Superiorly is the tegmen, a bony roof on the other side of which is the middle cranial fossa; and, inferiorly is another plate of bone which separates the middle ear from the jugular fossa[3]. On the lateral aspect, the tympanic cavity is only partly bordered by the TM and so the cavity is partitioned into the mesotympanum, which is directly medial to the TM; the hypotympanum and the epitympanum (attic) which are below and above the mesotympanum respectively.

The middle ear is an air-filled space with specialised features to transmit acoustic energy from the terrestrial air environment to the fluid filled space of the inner ear. This is referred to as the middle ear transformer and in mammals consists of the malleus, incus and stapes; a chain of three articulating bones, which joins the TM to the oval window of the cochlea[4]. Several other structures of note are also present and include muscles and nerves. The tensor tympani muscle attaches to the TM, and the stapedius muscle to the neck of the stapes. The facial nerve courses along the medial wall of the tympanic cavity while the chorda tympani passes across the middle ear between the malleus and incus.

Disease processes of the middle ear manifest with symptoms of hearing impairment, otalgia (pain), otorrhoea (discharge), tinnitus, aural fullness, imbalance and vertigo due to the proximity of the vestibular system in the inner ear[5]. The aetiologies of these processes may be infective, neoplastic, traumatic, congenital, degenerative, metabolic or iatrogenic. The role of surgery in these processes is primarily to provide a safe and dry ear, and secondarily to improve hearing[6]. Other indications include access to other structures (inner ear, posterior or middle cranial fossa) or tissue biopsy[7]. In this regard the concept of a safe ear is one in which any destructive tissue such as tumour, cholesteatoma, or other nidus of infection has been removed and the middle ear is sealed off from the external environment[8].

Surgical access to the human middle ear is commonly gained either directly down the ear canal with reflection aside of the TM (transcanal), or by drilling away the mastoid air cells and entering from behind (posterior tympanotomy or facial recess approach). Any operation upon the tympanum is generally referred to as a tympanoplasty and was classically categorised by Wullstein into Types Ⅰ-Ⅴ, depending on how medial the reconstruction proceeded[9]. In tympanoplasty Type Ⅰ the TM is patched, whereas a Type Ⅴ operation requires fenestration of the inner ear due to an immobile stapes footplate. This classification has now been largely abandoned in favour of terms which describe the procedures performed in any given operation. An ossiculoplasty is any procedure which endeavours to restore sound conduction from the TM to the oval window either by direct opposition or with coupling *via* a prosthesis or tissue. Special note is made of the situation previously encountered in a Type Ⅴ tympanoplasty, where the stapes footplate is immobile. Since John Shea's popularising of oval window fenestration, this procedure is referred to as a stapedectomy[10].

WHY ANIMAL MODELS?

The primary goal of modelling middle ear surgery is to improve outcomes in humans. The outcomes of interest are improvement in hearing, resolution of disease and safety of the procedure. As discussed later, there are several limitations to hearing assessment in animal models, but safety evaluation of an intervention is where models offer much utility. Even before interventions are assessed, animal models can aid in understanding disease aetiology and natural history[11-13]. While there are many differences between humans and other animals, it is possible to compare specific disease states in animals with their human counterparts through transgenic or knockout models or gene expression[14-16]. Animal models also allow researchers to investigate the impact of concomitant diseases on surgery outcomes[17]. With careful experimental design, variable extremes not possible in humans can also be studied[18,19]. If the animal has a shorter life cycle than humans, it is possible to see the effects of these diseases or interventions from many individual animals over a shorter and more practical timeframe.

Middle ear surgical animal models enable operators to gain experience, confidence and competence with procedures, thereby reducing complications from the learning curve on human patients. In stapes surgery, live animal models expose operators to complications found in human surgery. For example, a floating or depressed footplate, incus dislocation, overhanging or dehiscent facial nerve, excessive bleeding, or perilymph drainage with a dry vestibule are all possible findings[20]. Animal research explores the foundations of treatments, reinforces surgical techniques and brings advances to patient care[21].

Artificial temporal bones have been available since 1998[22] and provide an additional way for operators to refine their skills without the need for human or other temporal bones. These bones may be used where human temporal bones are unavailable[23], and offer the advantage over animal models in that they may be fashioned with equivalent dimensions to human temporal bones. They may be constructed from synthetic resins[22], polyurethane[24], three dimensional printing with a cast powder and bonding agent[25], or selective laser powder sintering[26]. However, resin does not look or handle like bone[24], some processes leave construction materials in the finished product[26], the detail from artificial bones is less than bones from animals and may miss structures such as the chorda tympani or round window[25] or other soft tissue structures such as skin and subcutaneous tissues. Furthermore, artificial temporal bones do not model complications such as bleeding, or leaking of cerebrospinal fluid or perilymph which are possible in live animal models.

INTERVENTIONS

The scope of this review specifically pertains to middle ear surgical interventions. These include materials used for tympanoplasty and their bio-tolerance in the middle ear mucosal environment[27], as well as their impact on hearing. Such experiments include different tympanoplasty reconstruction techniques[28,29], middle ear packing[30-32], support materials[33,34], tissue glues[35-37], and active middle ear implants[38-48]. The impact of mastoid surgery has been modelled with noise[49,50], vibration[51,52], and ossicular contact[19] interventions. Examined variables include drilling duration and speed, burr size and composition (diamond or cutting). Stapedectomy is a very reproducible procedure in terms of pathology and outcomes; however, there are several variables which have been examined in animal models[53-55]. These include the degree and method of footplate removal[56-66], choice of prosthesis and graft material[67-72], and effects of tensor tympani tendon transection[20].

Complications are also able to be closely evaluated in an animal model. These include blood in the vestibule[20,69,73], and induction and effect of infection[74-77]. Noise induced injuries were not included in this review unless the noise was specifically related to middle ear surgery, such as from drilling or the blast wave and cavitation effects of the erbium-doped yttrium aluminium garnet laser[61,62]. Noise injury is distinct from, but analogous with the acoustic injury which comes from the impact of excessive surgical forces applied to the middle ear and transmitted down the ossicular chain to the cochlea[56,62,69,78]. Laser surgery avoids acoustic injury by virtue of its no-touch method, but other laser complications may include perilymph temperature elevation or direct cochlear injury[58,59,61,63,64,79,80].

OUTCOME MEASURES

The outcomes of interest in models of middle ear surgery can be broadly classified as either physiological and behavioural in live animals or anatomical in cadaveric studies. The importance of these outcome measures is to provide information on changes in middle or inner ear function as a consequence of the manipulation and which is relevant to human surgery. Measurements of changes in hearing as an outcome can be performed with behavioural tests of auditory threshold or other behavioural tests. Physiological methods, such as auditory brainstem responses (ABR), electrocochleography (ECochG) or otoacoustic emissions provide information on sound transfer through the middle ear and inner ear function, while more specific techniques, such as using laser Doppler vibrometry (LDV) gives information on the integrity of middle ear structures.

Behavioural measures of auditory threshold have an advantage that they can be more directly applied to humans, but these tests are difficult to perform, costly and require considerable specialised expertise in behavioural animal testing. The advantage of physiological methods is that they do not require any training and can be performed in anesthetised animals during or soon after the middle ear manipulation. The physiological methods, apart from LDV are also ones that can be routinely used in human ear function assessment. A limitation of all techniques, however, is the ability to differentiate the influence of the middle ear manipulation on middle ear and inner ear function using air conducted (AC) sound. When the middle ear is surgically manipulated, such as by experimental stapedectomy or ossiculoplasty, sound conduction through the middle ear will potentially change. When AC-evoked auditory thresholds are measured, the magnitude of any post-intervention conductive hearing loss (CHL) or threshold shift is confounded by a potential surgically-induced sensorineural hearing loss (SNHL). This inner ear trauma from middle ear surgery is frequently cited as a cause of SNHL in humans[81-87]. Studies which only assess AC-evoked thresholds and note a hearing loss after the intervention are therefore not able to differentiate whether this loss was due to a conductive, sensorineural or mixed pathology[54]. Some authors have attempted to define a SNHL on AC by decreased waveform amplitude or latency[88], while other authors have tried galvanic stimulation of the cochlea to bypass the middle ear[89].

The conventional method for direct stimulation of the cochlea is with a bone-conducted (BC) stimulus which bypasses the middle ear to give an indication of cochlear function. Bone conduction thresholds are routinely measured in humans using calibrated bone vibrators in audiometry, but as conventional BC transducer performance significantly deteriorates at frequencies greater than 5 kHz[90] bone-conduction thresholds are not routinely measured at higher audiometric frequencies. Measuring physiological responses with BC stimuli in smaller animals which have a higher hearing frequency spectrum, is therefore impractical and studies with BC stimuli are generally limited to the lower frequency spectrum[91]. Unfortunately it is the high-frequency basal region of the cochlea which is most susceptible to trauma, whether due to noise[92,93], chemotherapy[94] or surgical aetiologies[95]. Being unable to investigate this region significantly limits the sensitivity of BC-evoked auditory potentials to detect cochlear injury in small animals.

Because of this difficulty in accurately assessing cochlear function in small animals undergoing middle ear surgery, histopathological outcomes of cadaveric tissue have been favoured. This may involve light microscopy or transmission (TEM) or scanning electron microscopy (SEM). These outcomes have the advantage of directly assessing tissue injury, such as hair cell loss or saccule perforation, and also allow assessment of the middle ear at the same time. Biocompatibility studies of exogenous material rely on this outcome for signs of rejection, extrusion or dissolution. The disadvantages of this approach are that the animal must be euthanised to gain access to the tissue and so many animals are needed for longitudinal studies of the development and recovery of any injury.

Histology may not be a sensitive enough indicator of structural or functional injury after middle ear surgery. For example, Ikeda *et al*[66] showed that cochlear histology remained unchanged when vestibular perilymph was removed during stapedectomy, even though the endocochlear potential (EP) was substantially reduced, which would have caused a significant loss of auditory threshold as reduction in EP is strongly correlated to loss of auditory sensitivity[96].

A more recent indicator of middle ear function is LDV[43,97,98]. As with evoked auditory potentials, LDV has the advantage of being performed on live animals, but it is also able to use AC evoking sound to directly visualise TM and ossicular displacements without having to rely on the cochlea for the outcome measure[99]. While LDV is not a direct measure of auditory function, acoustic correlates of surgical interventions are possible[100].

LIMITATIONS

The key limitation with any animal model is that it is the extent of comparability to humans. Animal models only approximate humans and have their inherent limitations. Results of animal studies may not directly apply to humans due to anatomical, physiological or pathological differences between species[17,80,101]. This fallibility is inherent with all basic scientific research[102] but valuable information is still obtained when animals are exposed to the same conditions as human surgery. Tissue healing and repair of the delicate inner ear can be studied in great detail[21].

Sometimes the outcome differences between animal and human studies may be explained by anatomical differences in the middle ear, or the ossicular chain structure and its transformer properties. For example, the lever ratio of the malleus and incus in humans is significantly smaller than in cats; a human stapes weighs more than four times that of the cat; humans have a wider anterior annular ligament *vs* posterior, whereas the cat's is symmetrical; and, the rotational component of stapes motion is more prominent in humans than cats[72,103]. Removing an extensively diseased otosclerotic footplate in humans is likely to be more traumatic than removing than the mobile footplate in the catV. The anatomical differences between the squirrel monkey and human mean the tympanic cavity is much smaller in the monkey and therefore more likely to develop adhesions due to the proximity of structures[78]. Clinically, this means the results of experimental surgery in a clean and dry monkey ear may not be relevant in the human with active infection.

Occasionally, however, the differences between animals and humans are advantageous. Laser assisted middle ear surgery offers excellent results in humans[104-106] but the reported success of argon laser stapedotomy in patients contradicts the poor results anticipated by animal experimentation[64]. This was thought to be due to differences in footplate pigmentation or mineralisation, and variations of vestibular anatomy. Bellucci *et al*[21] found fibrosis invading the inner ear occurs in cats in stapes surgery, and later studies suggested it was due to invasion of the middle ear through the defect in the atticotomy. But Fee did not note any significant cases in humans and concluded this was not clinically important in human stapes surgery[107]. Foreign body giant cells were seen within 3 wk on aluminium oxide ossicular prostheses in a rabbit model, but this was not a consistent finding in human studies[108]. And the human TM can tolerate capped polyethylene prosthesis when reinforced with vein much better than in feline models[109].

Difficulties also arise when attempting to compare results from different animal models. Hydroxyapatite has been used as a substrate for crafting ossicular reconstruction prostheses, however, early animal studies produced conflicting accounts of biodegradation[110]. It was recognised that this divergence may be due to using different animal species. Audiometric differences between species have also been noted and are due to differences in configuration of the pinna and external auditory canal (EAC), the bulla size and the middle ear transformer ratio, and potentially the cross sectional area of the helicotrema at the cochlea apex[111]. Conflicting reports about the safety of cyanoacrylate tissue glues in the middle ear were in part due to different compounds being used, but even with a single compound, butyl cyanoacrylate (Histoacryl), there were different outcomes across six species used to test this glue[37].

Some species have particular anatomical features which limit their usefulness as a middle ear surgical model. The anatomy of smaller animals poses particular challenges, both in terms of access and tissue response to intervention. For example, models of myringoplasty with iatrogenic TM perforation are limited by the excellent intrinsic reparative ability of the TM[78,112]. The rat stapedial artery, a branch of the internal carotid artery, passes across the stapedial footplate and limits access to the oval window[54,113], although it is possible to cauterise this vessel and proceed[114]. Sheep have an adipose-filled and poorly pneumatised mastoid cavity which restricts a postauricular approach and cortical mastoidectomy[48,115]. Similarly, the mastoid in pigs is also poorly pneumatised and hidden by the atlanto-occipital joint[116]. For clarity, postauricular in relation to most animal models denotes a postauricular incision, soft tissue reflection, exposure and opening of the bulla. Non-human primates are the only animals which have a similarly developed mastoid air cell system and antrum to humans[20], and postauricular may denote either the skin incision or the subsequent transmastoid approach, or both. Non-human primates also have a cartilaginous EAC which approximates the human one, although the bony canal is too long and narrow in most species for a transcanal approach to the middle ear[20]. Other specific-species limitations are further identified later in this review.

Another limitation of animal models of middle ear surgery may come from researcher inexperience with new species or techniques, which can lead to inadvertent injury. This learning curve with new species or techniques may reduce the number of research subjects. In a study of nine baboon ears, Siedentop[117] accidentally opened the horizontal semicircular canal in three ears, three ears sustained bur injury to the facial nerve, and two cochleae promontory were injured. Following a monkey death from suppurative labyrinthitis and meningitis, Hohmann *et al*[20] advocated pilot studies for researchers to become familiar with new middle ear surgical techniques. Krupala *et al*[32] and Antonelli *et al*[118] both used three animals to refine study procedures and achieve technical skill. In such pilot studies it is possible to find safe operating parameters to guide further research. In examining the effect of the CO_2 laser on the middle ear, Lyons *et al*[58] found animals which received between 20 and 30 watt laser lesions did not recover from anaesthesia. While pilot studies are useful for reducing unintended injury, Rutledge *et al*[68] acknowledged that while operative experience reduced serious complications, it does not completely eliminate them.

Experimental injury may cause unnecessary distress when the animal wakes from anaesthesia and consideration should be given to acute non-recovery experiments[72]. Operative facial nerve injury may cause facial paralysis and have animals unable to maintain adequate nutrition or eye care, and even cause death[119]. Sometimes, however, this injury is unavoidable such as in the guinea pig where the facial nerve runs posteriorly over the oval window niche and needs to be sacrificed to widely expose this area[72,120], or in rat where the stapedial artery limits access to the oval windows[54]. An insensate guinea pig or rat auricle after a postauricular incision is at risk of being bitten though social activity, so animals may need to be kept separate for several days[120]. Injury to the vestibule may result in abnormal head tilt[120], or in extreme cases poor oral intake and death. However, acute experiments prohibit behavioural outcome assessment and intervention outcome follow up over time.

SEARCH

The Medline, Cochrane and Embase databases were searched for the terms model, middle ear and surgery. The search was expanded by searching for the interventions of ossicular replacement, stapes surgery, myringoplasty, tympanoplasty, mastoidectomy and active middle ear implant. 8250 articles were then limited to animal studies and the English language. The resulting 278 titles and abstracts were reviewed for inclusion. Studies of surgical anatomy of the animal middle ear were included, but studies not pertaining to surgical intervention of the middle ear were excluded. These included interventions to induce a medical model of disease, as it was only the treatment of such diseases which were of interest. The full text of 121 articles was sought and the references of these checked for further pertinent studies. A total of 176 articles were subsequently included in this review.

MOUSE

Anatomical features

The mouse EAC is 6.25 millimetres (mm) long and has a slight rostral curve as it approaches the TM. All rodents lack mastoid air cells. The malleus and incus are firmly joined by a synarthrosis. The ossicular system is of a microtype which has restricted mobility, *vs* the freely mobile synovial joints in humans[121]. The microtype system is better for high-frequency hearing[122].

Approach

Only one study was identified which used the mouse as a model of middle ear surgery, and as there was only need to access the TM to model the mitotic activity of TM healing, the transcanal route was chosen[123].

Outcomes

The mouse hearing frequency spectrum is 1000-91000 Hz. No mouse middle ear surgical models used hearing as an outcome. The only identified study used radio-identified mitotic repair of TM[123].

Advantages

Mice are relatively cheap to acquire and house, so mouse studies can have greater numbers of subjects. Fundamentally, there are no important differences of the structure of the TM between mice and humans, except the relatively large size of the pars flaccida in mice[123].

Disadvantages

The small size of the mouse middle ear makes access and exposure challenging. Their short lifespan may complicate longer term studies by presbycusis[121].

RAT

Anatomical features

The rat facial nerve exits the temporal bone more superficially and anterorostrally than in humans. The ossicles are thinner than human ones and are almost totally hidden in the epitympanic region[119]. The stapedial artery runs between the stapes crura[119].

Approach

The cervical approach to the ventrolateral wall of the tympanic bullae is the traditional method of accessing the middle, and inner, ear in rodents[27,88,113,124]. The postauricular approach is relatively straightforward, provides good access and is less invasive than the ventral approach[75,77,101,119,124-126]. Similarly, the supra-auricular approach exposes the middle ear above the TM, leaving this attached to the meatal skin. This approach gives full view of the incus and its articulations and has the advantage of not having to remove bone from the bulla or cavity wall[27,127]. The transcanal route is possible, but challenging due to the dimensions of the EAC[128].

Outcomes

The rat hearing frequency spectrum is 200-76000 Hz. This was audiometrically assessed with air-conducted ABR broadband clicks[88,126]. Pathological examination included: otomicroscopy; SEM and TEM; X-ray microanalysis and bone fluorescence; haematoxylin and eosin (HE) staining, autoradiography; and methyl green-pyronin staining which clarifies the ribonucleic acid content and allows a better differentiation between living and dead cells[27,75,77,110,127,128]. Perilymph temperature elevation has also been used as an outcome measure in laser studies[61].

Advantages

The rat middle ear ventilation and drainage system is similar to humans due to the Eustachian tube, middle ear and attic communication, so the rat middle ear might have advantages over the chinchilla or guinea pig in tubal occlusion research with associate middle ear infections, as these infections occur naturally in the rat[74,76,124,129]. The rat middle ear structures are more similar to humans than for guinea pigs, with the exception of the facial nerve which is more superficial and anterorostral in rats. The rat ossicles are clearly defined and can be removed separately, as in humans[113]. It is easier to open the tympanic bulla in rats than guinea pigs due to weaker bulla joints[74]. The Long-Evans rat is not known to have hearing deficits[88]. The Fat Sand rat is found in the deserts of the Middle East and northern Africa and provides easier access to middle and inner ear anatomy due to the large bulla cavity, a thin otic capsule, and an inner ear that clearly projects into the middle ear cavity[126,130].

Disadvantages

The rat stapedial artery runs through the stapes crura, making stapes and oval window manipulations extraordinarily difficult[54,124,130]. Exposing the oval window can cause haemorrhage, cochlear injury and death[113]. Rat ossicles are nearly a quarter the size of their human counterparts and are nearly completely hidden within the epitympanum[119]. Albuquerque *et al*[74] believed the rat is harder than the guinea pig to handle as it is less docile and also the tympanic bulla was more fragile, making handling more delicate[74]. Transcanal or intact TM exposure of the middle ear was impossible unless approached ventrally[119]. Following induced middle ear infection, the bone was stronger and so opening the tympanic bulla was more difficult which in turn facilitated damage to the cochlea, vestibular system and ossicles[74]. Wistar Albino rats have hearing deficits[88]. Rat middle ear packing with Gelfoam induces osteoneogenesis and connective tissue formation with adhesions[34,125].

MONGOLIAN GERBIL

Anatomical features

The Mongolian gerbil's enlarged bulla enhances low frequency hearing sensitivity, which allows it to detect approaching predators faster[131]. The pars flaccida is circular and relatively large, 10%-20% TM surface, compared with only 2%-3% in humans[132]. The anterior mallear process extends from the anterior process of the malleus to the temporal bone, and is not seen in humans[131]. The ossicular system is of micro type, whereby the handle of the malleus is fused to the tympanic ring[121].

Approach

Postauricular[133] and transcanal[33] routes have been used for middle ear surgical models, but as these studies were chronic experiments, no comment is able to be made about the suitability of the ventral approach which is commonly used in rodents.

Outcomes

The Mongolian Gerbil hearing frequency spectrum is 100-60000 Hz, but there were no studies identified which used hearing as an outcome. Pathological specimens were examined under TEM, HE or polychrome staining and examined under the light microscope with routine and polarized light[33,133,134].

Advantages

Similar to mice and rats, gerbils are small and easy to care for. The comparatively large bulla assists in dissection and exposure, in much the same way as in the Fat Sand Rat. Gerbils are naturally relatively free of otitis media[129]. Liening *et al*[33] used the gerbil in their model because it is the least phylogenetically advanced animal known to form retraction pockets, and it does this quickly in response to Eustachian tube cautery.

Disadvantages

The researchers in these studies did not identify any specific weaknesses to using gerbils as a middle ear surgical model, however, there were few reports and the general concerns with small animal external validity apply.

CHINCHILLA

Anatomical features

Similar to the gerbil, for its size the chinchilla has a comparatively large bulla and TM[135,136]. The ossicular system is freely mobile, whereby the bones are suspended on ligaments, as they are in humans[121]. The incus and malleus are fused with cartilage, functioning as a horizontal bar. Compared with humans, the crura are more central on the stapes footplate. A bony strut, the crista stapedis is persistent, as in the human embryo and guinea pig[136]. It passes through the stapes arch from the fallopian canal to the rim of the round window[137].

Approach

Browning *et al*[137] in their foundational work describe four surgical approaches to the labyrinth and ossicular chain. The dorsal, labyrinthine, and combined approach through the mastoid and labyrinthine parts of the bulla all go through the bulla, while the fourth approach is down EAC. No single approach demonstrates all of the middle ear, so the chosen approach is tailored to the kind of surgery required.

Outcomes

The hearing frequency spectrum of the chinchilla is 90-22800 Hz, which is remarkably similar to humans and reflects the enhanced hearing in the lower frequencies due to the proportionally large TM and bulla. Hearing measures included ABR[138], cochlear microphonics (CM)[44] and compound action potentials (CAP)[139]. The chinchilla can also be trained in behavioural audiometry[137]. Middle ear implant studies have used tone evoked CM[40,43,47], CAP and ABR[44]. The same studies also used LDV to examine stapes motion. Other outcomes of note were tympanometry and histology[140], and vestibular temperature[141].

Advantages

As noted with mice, rats and gerbils, the chinchilla is cheap to acquire and look after. The large bulla is thin and allows for easy immobilisation, middle ear access and histological preparation. After it is opened, the bulla heals firstly with fibrous tissue and then with bone so that recovery experiments are possible. The cochlea is also thin and projects into the labyrinthine bulla, so is easily accessed for electrophysiological measurements. The chinchilla's hearing is relatively susceptible to noise trauma[137]. As with gerbils, chinchillas are naturally relatively free of otitis media[129]. The life span of the chinchilla is 12 to 20 years[142], so they are useful for studies requiring normal hearing, but less good as a model of presbycusis.

Disadvantages

The chinchilla venous sinuses are within the skull bones, instead of the dura as in humans. As such, removing bone can be challenging due to the risk of haemorrhage[137]. It is difficult to identify the TM *via* the transcanal route due to the direction of the EAC, even following removal of the convoluted cartilaginous folds of the pinna[139]. The EAC runs dorsal-ventral where the lateral wall is continuous with, and in the same plane as, the lateral walls of the labyrinthine and mastoid bulla sections[137]. The chinchilla round window membrane is only one sixth the thickness as that of humans[139].

GUINEA PIG

Anatomical features

There is a foramen in the anteroinferior aspect of the EAC which resembles the foramen typanicum seen in the first few years of human life. The guinea pig TM is proportionally larger than in humans and only has *pars tensa*, above which is a bony area called the supratympanic crest. The cochlea has 3.5 turns and projects well into the middle ear, dividing it into bulla below and epitympanum above, the bulla corresponding to the meso- and hypotympanum of the human ear. The epitympanum is a slit like space which contains the fused malleoincudal complex. Compared to humans, there is a simplified air cell system of four large cells which do not have fine partitions. The oval window is orientated vertically while the round window sits horizontally. The stapes is identical to that in humans but has a bony bridge passing between the crura which is known as the crista stapedius. This structure is present in the human embryo, chinchilla and guinea pig and represents the calcified remnants of the stapedial artery. The guinea pig Eustachian tube consists entirely of cartilage. The facial nerve exits in a postero-superior position between the tympanic ring and the bulla[54,124,136,143].

Approach

There is a large body of literature on the guinea pig as a model of middle ear surgery, and this is reflected in the number of different methods of access to the middle ear. The head is strapped to table[144] or immobilised with a custom head holder. Most authors favoured a postauricular approach to the bulla[32,45,91,118], sometimes referring to retroauricular[31,145] or postaural[146] approaches. This gives excellent access to the round window with a slight turn of the animal's head, however, the stapes is hidden by an overhanding facial nerve and a shelf of bone medial to the nerve also obscures the incudostapedial joint (ISJ). Full access to the oval window therefore requires removal of the bony shelf, sacrifice of the facial nerve and removal of the crista stapedius[54]. Special care needs to be taken of animals with facial nerve sacrifice as they are liable to develop ocular complications or feeding problems[119,120]. As a slight variant, the supra-aural approach comes down onto the epitympanum first, before exposure of the rest of the ossicular chain, cochlear promontory, and the facial nerve[28,102]. This approach was particularly useful for homograft reconstruction which required removal of the TM from its annulus[28]. The transcanal approach[30,144,147,148] is facilitated by incision of the pinna base[58] or removal entirely, however, the incision leaves the pinna insensate and it is at risk of being bitten in social activity[120]. The inferior[143] or ventral[60,73] approaches give excellent exposure, but are more suited to non-recovery anaesthesia experiments.

Outcomes

The hearing frequency spectrum of the guinea pig is 54-

50000 Hz, of which the lower half of this spectrum is commonly interrogated with AC sound. Evoked potentials include tone[79,149] and click[52,63] evoked CAP[17,54,145], tone evoked CM[73,79], and tone[31,49] and click[19,63] evoked ABR[118]. Middle ear surgical implants are also capable of evoking ABR potentials with clicks[45,46] or tones[46] *via* coupling to the ossicular chain or round window[41,45,46]. EP changes correlate with hearing impairment, and are another physiological outcome measure which indicates cochlea injury[66]. The direct current extracochlear potential has also been measured, however this does not reflect underlying function of the cochlea, rather the heating influence of a laser[150]. Other studies have also examined thermal effects in a more conventional fashion[60,79]. Post-mortem analysis includes histology[32,148,151] with HE staining[146], hair cell counting[152] and SEM[50].

Advantages

The large tympanic cavity affords excellent exposure of the middle ear and the Eustachian tube is always patent[28]. This has the advantage of excellent postoperative middle ear ventilation to reduce the influence of infection or TM retraction. The facial nerve anatomy resembles that in humans, but the exit point is more superficial in the guinea pig[119]. Noise-induced hearing loss, which is thought to be analogous with surgical injury, is well established as an experimental model in the guinea pig which complements the surgical models[49]. The guinea pig is chosen in models of laser-assisted otosclerosis surgery because the basal turn of the cochlea is readily accessible and is of a similar thickness to the otosclerotic human footplate (150-200 μm)[62,63].

Disadvantages

Guinea pigs live to about 3 years. For the first half of their life ear infections are rare, but in later years they tend to have an increasing incidence of spontaneous infections[28]. Guinea pig anaesthesia is notoriously difficult for long operations with conventional techniques[28]. Such procedures benefit from a gaseous anaesthetic circuit, which increases complexity of the experiment. The fusion of the malleoincudal process limits the external validity of ossiculoplasty procedures to humans. The prominence of the cochlea is more suited to inner ear experiments[113]. Compared with rat, the guinea pig bulla is thicker and may require drilling away, whereas in rat the bulla can be gently taken apart in a piecemeal fashion[74]. Despite the relatively large bulla, simultaneous access to the oval window for interventions and the round window for ECochG may be difficult[73].

The guinea pig cochlea is more susceptible than humans to ototoxicity due to the thinner round window membrane in guinea pigs[145], and is also ten times more sensitive to acoustic trauma than humans[62]. Cochlear harm may also be overestimated in guinea pig stapes surgery because the structures most traumatised are the basilar membrane and the organ of Corti, whereas in humans it is the utricle and saccule which are most exposed[62]. Additionally, the guinea pig cochlear aqueduct is patent. This can lead to flow of cerebrospinal fluid from the subarachnoid to the perilymphatic space which may continue to leak through the oval window following stapedectomy[66]. The net effects of these features may overestimate the inner ear harm in guinea pigs from interventions.

Several authors have also noted the guinea pig possesses the ability to lay down new bone in the middle ear. Dost *et al*[120] found a control group of animals were apparently able to regrow crude stapes superstructures from the remnants of their crurae. This osteoblastic response was also seen in relation to generic middle ear bony trauma and with granulation tissue by Holzer[146]. He proposed this response was unique to the guinea pig and this notion was supported by Wells *et al*[102] who found bony overgrowth at the Histoacryl site in guinea pigs, whereas bony destruction was seen in the cat[153] and the rabbit[154], but not in the dog[155]. This finding limits the external validity of guinea pig ossiculoplasty surgery in humans, but also causes problems in the guinea pig where uncontrolled bony fixation between an implant and other middle ear structures complicated what may have been an otherwise successful operation[151].

RABBIT

Anatomical features

The rabbit bulla is larger than most mammals and has a longer EAC. The bulla is rounder and does not project past the level of the occipital bone, as found in the cat and dog[121].

Approach

The transcanal[108,156-159] route was most common and exposure was aided by a postauricular incision with reflection forward of the pinna and incision through the cartilaginous EAC, before raising the tympanomeatal flap[154]. While the postauricular incision was used for pinna control, the postauricular approach through the bulla was only advocated in one study which compared it to a human atticoantrostomy[157]. Another group did, however, advocate a combined transcanal and postauricular approach[160]. The ventral approach once again was better suited to non-recovery experiments[161].

Outcomes

The hearing frequency spectrum of the rabbit is 360-42000 Hz. Stieve *et al*[158] attempted to get around the problem of ossiculoplasty disrupting the AC stimulus by using BC click-evoked ABR, however, no comment was made as to the frequency response of transducer. Manual positioning of transducer may also provide inconsistent pressure and therefore energy transfer of stimulus. Another publication from the same group used click and 8 kHz pip stimulus ABR, traditional and SEM, but did not report their audiological findings[108]. In addition to SEM[162]; Giemsa[162,163], HE[157,159], von Gieson's stain and fibroblast growth factor stains[159] were also used with transmission and fluorescent light microscopy[164].

Advantages

As with rodents, the rabbit is cheap and easy to obtain[165], but being larger, the ear is much easier to examine perioperatively[166]. Rabbits provide a close model of human middle ear anatomy and have a standardised surgical approach[108,158]. Their response to middle ear surgery shares the same bone remodelling processes as in humans[166] without showing the ossicular osteogenic response seen in guinea pigs[156]. The anaesthesia depth can be better controlled with inhalational techniques rather than barbiturates which enabled mortality to be considerably reduced[158]. This was, however, complicated by bradycardia on endotracheal tube insertion and associated cardiac arrest. The tube effect was mitigated against with Glycopyrrolate[158].

Disadvantages

Gaining access to the rabbit middle ear is still more difficult than in humans due to the small dimensions involved[158]. There are differing opinions whether the facial nerve is dehiscent in the middle ear[162] or not[158]. A dehiscent nerve is at greater risk from middle ear surgery, but would only be a problem in non-acute experiments.

CAT

Anatomical features

The middle ear cavity of the cat is separated in two by a bony septum. This has a small hole in it so that the ear functions in a similar way to the mastoid, aditus, middle ear arrangement in humans, although the cavity effect is much greater in cats[103]. While the cat TM is smaller and thinner than in humans, the structure is essentially the same. There are two collagenous bundle layers in the middle layer of the pars tensa which are oriented radially and in a circular fashion respectively. The pars flaccida middle layer does not have a specific fibre arrangement. The lateral layer of the TM is covered by the same keratinising squamous epithelium as the EAC, and medially the TM is lined by the mucosa of the middle ear cavity[123]. The pyramidal process is bony in humans but in the cat it is cartilaginous, located next to the cartilaginous rim of the TM, and referred to as the pyramidal cone to reflect these differences[167]. The cat has the ability to regenerate its stapedius tendon[20].

Approach

Access to the cat middle ear was aided by removing the pinna[35], and by suitable head immobilisation, such as ear bars and a snout clamp[103]. Once again, the postauricular route was the most popular[20,21,29,57,70,80,124,168]. This entailed extending the postauricular incision to the posterior surface of the pinna cartilage to find the bony EAC, and then drilling posterior to the EAC until the middle ear space was blue lined and could be opened with picks[71,153]. This has also been referred to as the posterosuperior[13,132], retroauricular[123], transmastoid[65] or squamomastoid approaches[68]. In a similar way it was also possible to approach from above through the attic[69,72]. Davey began with a postauricular incision and drilled down the EAC to reach the middle ear *via* an attic approach[167]. The mediolateral approach is also possible, but requires removal of the parotid gland, digastric muscle, hyoid chain, ligature and cutting of the ICA and posterior facial vein[169]. As such, along with the ventral approaches[37,161], the mediolateral approach is better suited to non-recovery experiments. The transcanal approach was not used in any identified studies due to the narrow EAC in cats, and the excellent exposure afforded by other means[71].

Outcomes

The hearing frequency spectrum of the cat is 45-64000 Hz. Cats have been trained to behaviourally respond to tones for audiometric testing. Traditionally, this involved shock avoidance techniques[19], however, as the same information can be gained electrophysiologically[169] with CM[56,72,161], such techniques are now uncommon. Active middle ear implants were evaluated on cat stapes in the early days of this technology[39]. Histopathological studies used HE staining[29,65,68-70,80,123,170], inverted-phase and SEM[171,172], or other histology[55,67,168]. Vestibular temperature response to laser has also been investigated[64].

Advantages

As with guinea pigs, there is a large body of literature on feline middle ear surgical models, and researchers often chose cats as a model to allow comparisons with earlier work[103]. Being larger than rodents, the middle ear structures are more easily accessed and manipulated[21,72], while the cat is still cheaply acquired, housed and cared for[20]. Being larger also confers an anaesthetic survival advantage, sometimes for many months after surgery[35]. The cat middle ear also resembles the human ear much closer than the guinea pig in relation to ossicular orientation and shape, facial nerve, and middle ear muscles[119]. Cats are responsive and agile, so accurate postoperative clinical observations of hearing and balance are possible[21]. Anaesthesia can be difficult to titrate in other species, but barbiturate anaesthesia in the cat eliminates middle ear muscle activity when appropriately deep, and can be used as a guide to anaesthesia adequacy[103].

Disadvantages

The middle ear structures are robustly protected deeper in the temporal bone than rodents[119] and drilling is required for access, as the epitympanum cannot be exposed by the transcanal route due to the long, narrow and convoluted EAC[71]. The EAC can also harbour a large number of bacteria, fungi and parasites[20,173]. While the ossicles are larger than rodents, they are still smaller than in humans and surgery is therefore much more challenging with cochlear injury much more likely[71]. It would also appear that the cat TM is less robust than in humans as extrusion of a polyethylene strut was a common finding in cats[109]. A patent cochlear aqueduct was not infrequently found in cats[55] and may contribute to perilymph overflow not usually found in human stapedectomy[71].

The cat was also prone to osteoneogenesis, although this was in association with mucosal injury[29] and the significant fibrosis reaction which followed[65]. When the mucosa was not traumatised, fibrosis was not a significant problem[70]. It is likely that this repair process is influenced by the small epitympanic area and associated proximity of the middle ear structures to the wall of the cavity[174].

DOG

Anatomical features

As in the cat, the cartilaginous EAC of the dog is convoluted and can be a reservoir of bacteria and parasites[20].

Approach

Only two authors were identified who utilised a canine model of middle ear surgery. Siedentop[155] accessed the middle ear through the bulla, but does not describe his approach any further. Guilford *et al*[112,175,176] describe different approaches in their three publications. They used a postauricular incision with transection of the cartilaginous EAC and a transcanal approach with removal of the skin of the posterior EAC and overhanging canal roof in a study on incus repositioning[176], what appears to be a standard transcanal approach in a study on TM perforation repair[112], and a postauricular approach with opening of the bulla in a third study[175].

Outcomes

The canine hearing frequency spectrum 67-45000 Hz, however, none of the above studies assessed hearing as an outcome. Pathological evaluation was with HE, trichrome or Weigert's elastic tissue stains[91,112,140]. Siedentop[155] also used histological evaluation, but did not elaborate further.

Advantages

In these studies, mongrel dogs were apparently easily acquired and their middle ears are bigger than those in cats.

Disadvantages

In the perforation study it was observed that iatrogenic TM perforation would generally heal spontaneously within a few weeks[112]. This limits the utility of this model in tympanoplasty when the control group can do as well, or better, than the surgical intervention group. As there is very little data on the use of dogs as a middle ear surgical model, comparisons are difficult. Dogs are larger and more energetic than cats and rodents and so require more specialised care.

SHEEP

Anatomical features

The EAC of the sheep is highly curved and projects over the pars flaccida which is triangular and smaller than the circular pars tensa[177]. This leaves part of the lateral bulla under the bony shelf of the ventral EAC. Similarly, the inferolateral bulla extends laterally under the tympanic bone and annulus[115]. As such, the hypotympanum is particularly large. The pars tensa is proportionally large compared with other animals. The sheep middle ear is morphologically equivalent to the human middle ear[48], although the size is about two thirds smaller[115]. The long process of the incus is shorter, thicker, and closer to the body of the malleus[115]. As with the chinchilla and human, the ossicular system is freely mobile, being suspended by collagenous fibres or mucosal folds carrying blood vessels and nerves. The malleus head articular surface forms a diarthrosis with the incus body, whereas the ISJ is similar to the enarthrosis seen in humans[177]. Human and sheep round windows are similar, but sheep have no mastoid antrum and the mastoid cells are filled by adipose[177].

Approach

The only studies identified explored the potential of using sheep as a middle ear surgical model. Based on these studies, the postauricular approach was not recommended due to mastoid adipose[115], however, the transcanal route provides adequate exposure[53,115].

Outcomes

The sheep hearing frequency spectrum is 100-30000 Hz, however, no identified studies used hearing outcomes in sheep. The outcomes from stapedectomy training models focused on successful placement of the prosthesis, duration of procedure, and complications[53,115].

Advantages

Sheep easily managed in a laboratory as they do not need special care in confinement and are docile animals. They are more expensive to acquire than rodents, but tolerate surgical procedures well and have a longer lifespan. Sheep are specifically bred for human consumption so there is less objection from animal rights organisations to their involvement in research[178]. The smaller attic allows the ossicles to be accessed in the same axis as the EAC down the transcanal route, so there is no need to open the dorsal bone of the head[177]. Such a model is advocated for myringotomy, tympanotomy, ossiculoplasty and stapedectomy[53].

Disadvantages

The postauricular approach and mastoidectomy are precluded by mastoid adipose[48,53,115]. The facial nerve is thicker than in humans and often dehiscent in the tympanic cavity[115].

PIG

Anatomical features

The atlanto-occipital joint is faces posteriorly and partially overlaps the mastoid[179]. The mastoidectomy landmarks of the temporal line and suprameatal spine are not seen, and the pneumatised mastoid air cells are not found, rather there are pneumatised air cells inferior to the tympanic cavity[180]. The external ear canal of the pig is very long and orientated posterosuperiorly[179]. The body of the incus is shorter than in humans and has another process, perpendicular to the short process[179]. The remaining ossicles are approximately the same size as their human counterparts.

Approach

As with the sheep, the only studies identified explored the potential of using pigs as a middle ear surgical model. Based on these studies, the postauricular approach was not recommended due to the overhanging atlanto-occipital joint and lack of mastoid pneumatization. The transcanal technique requires drilling to enlarge the narrow EAC, modelling the human canalplasty[179].

Outcomes

The pig hearing frequency spectrum is 42-40000 Hz[181], and due to the small volume of literature is yet to be assessed as an outcome of middle ear surgery in this species.

Advantages

While the external ear is conspicuously different to humans, the middle ear is very similar, both in terms of structure dimensions and position[179,182].

Disadvantages

The pig temporal bone has a very different appearance to the human one, which leads to increased difficulty with middle ear exposure[179]. The temporal bone also has a significant amount of soft tissue coverage and mastoid adipose[48].

PRIMATE

Anatomical features

The squirrel monkey has a straight EAC[35], the bony portion of which is very short as it consists of only an exaggerated bony annulus[78]. The temporalis muscle is large and permits fashioning of a rotation flap[78]. As noted earlier, primates are the only animals which have mastoid air cell system and antrum which are similar to humans[20].

The cynomolgus monkey has a cartilaginous EAC which resembles the human, but the bony EAC is too long and narrow to permit the transcanal approach[20].

The baboon EAC is short and narrow with a diameter of less than 4 mm and length of approximately 25 mm[183].

Approach

The straight EAC facilitated the transcanal route similar to that used in humans, either with[35] or without[184] endaural releasing incisions. Paparella[78] initially used a postauricular incision in the squirrel monkey, but abandoned this because of the required length of incision and associated postoperative wound infection. They too moved to the transcanal approach with endaural incisions and the operation was well tolerated. The postauricular approach was, however, favoured for the cynomolgus monkey[20] and baboon[117] with drilling down of the posterior EAC wall[183].

Outcomes

The hearing frequency spectrums for the squirrel and cynomolgus monkeys are 100-43000 and 28-42000 Hz, respectively[185]. Pure tone auditory thresholds were assessed in squirrel monkeys with behavioural conditioning using the shock avoidance technique while employing a double grill box[78]. This study noted hearing losses of 30 to 40 dB and assumed this was a conductive loss as the inner ears were normal on histological examination. Hardcastle *et al*[186] also assumed hearing losses to be conductive in nature due to normal cochlea histology. Lima *et al*[184] assessed AC and BC thresholds up to 16 kHz with ABR and shock avoidance behavioural testing, but they make no comment about BC masking and the BC transducer they used was the Radioear B-70A bone vibrator, which artificial mastoid testing demonstrates a poor response for frequencies above 5 kHz[90].

The single cynomolgus monkey and 18 baboons only underwent histopathological review[20,117,183].

Advantages

In the squirrel monkey, the transcanal approach is straightforward and is the preferred method of middle ear exposure[20,78]. The squirrel monkey is small and manageable and can survive for extended periods after surgery[35]. It can be readily conditioned so that pure tone auditory thresholds can be established even more quickly than in cats.

Old World monkeys, including baboons, are phylogenetically closer to humans than most other living primates, the closest being anthropoid apes[183]. Results from baboons are expected to stand the best chance of being transferable to the human middle ear. Paparella[78] also notes that the phylogenetic proximity of the squirrel monkey to man may increase the external validity of experimental findings. The same may be said for the phylogenetic closeness of the cynomolgus monkey[20].

Disadvantages

The mastoid cavity is shallow so the semicircular canals may be inadvertently exposed and opened during surgery[78]. The TM possesses a remarkable ability to repair itself which makes myringoplasty modelling difficult as even large lesions heal spontaneously within a week[78]. The cynomolgus monkey has a weak annular ligament which made it difficult to remove the stapes crura and not the footplate[20]. The baboon transverse and sigmoid sinuses are close to the posterior EAC wall, which reduces the space for surgical manipulation. The horizontal semicircular canal and the facial ridge limit visibility of the stapes footplate[183], but the stapes head and some of the crura could usually be seen[117].

CONCLUSION

The choice of animal model to use when evaluating a

Table 1 Advantages and disadvantages of each animal model of middle ear surgery

Species	Advantages	Disadvantages
Mouse	Inexpensive to acquire and house. Genetic models of hearing loss	Small size makes access and exposure challenging
Rat	Relatively inexpensive to acquire and house. Anatomy bigger than mouse	Stapedial artery. Less docile than guinea pig
Mongolian Gerbil	Small and easy to care for. Comparatively large bulla. Naturally relatively free of otitis media. Able to form retraction pockets	Few published middle ear surgical models
Chinchilla	Inexpensive to look after. Large, thin bulla. Similar hearing frequency range to humans. Naturally relatively free of otitis media. Long lifespan	Venous sinuses within skull bones. Difficulty identifying the tympanic membrane *via* the transcanal route
Guinea Pig	Well established middle ear surgery and noise literature. Large tympanic cavity. Docile and easy to handle. Bigger than rodents	Middle ear infection common with age. Challenging anaesthesia. Fused incudomalleal complex. Osteoneogenesis after trauma
Rabbit	Larger anatomy than rodents. Close model of human middle ear anatomy and response to trauma	Challenging anaesthesia. Facial nerve frequently dehiscent
Cat	Well established middle ear surgery and noise literature. Anaesthesia tolerance. Behavioural outcomes easy to assess	Compared to rodents, drilling required to access structures. Many bacteria, fungi and parasites in ear canal. Patent cochlea aqueduct
Dog	Larger anatomy than cats and rodents. Behavioural outcomes easy to assess	Few published middle ear surgical models. More energetic animals require specialised care
Sheep	Docile animals. Easy to care for. Tolerate surgical procedures well. Long lifespan. Ossicles easily accessed *via* the transcanal route	More expensive than rodents. Mastoid adipose. Frequently dehiscent facial nerve thicker than humans
Pig	The middle ear is very similar, both in terms of structure dimensions and position to humans	Difficult middle ear access due to very different temporal bone with significant soft tissue coverage and mastoid adipose
Primate	Phylogenetically closest group of animals to humans. Mastoid air cell system and antrum present	Difficult to acquire and house. Ethical objections to research. Shallow mastoid cavity

middle ear surgical intervention depends on two key factors, the goals of the experiment and the local resources available. Table 1 summarises some of the key advantages and disadvantages of the species investigated.

The research question must clearly identify what the outcome measures are and what method is required to achieve this outcome. If only a few animals are needed to answer the research question, then larger animals may be considered as a model as they are likely to model the human response more closely. There are specific limitations identified for many of the above species which need to be considered when selecting an animal model. For example, if the stapedial artery cannot be worked around, then the rat should not be selected. Larger animals tend to be more robust and tolerate surgery and anaesthesia better than small animals, but the effect of bolus intraperitoneal anaesthesia may be less predictable in a larger animal and so gaseous anaesthesia may be required.

The experimental outcomes may be histopathological, functional or both. Either outcome may be assessed with acute or chronic experiments, but where chronic experiments permit observation over time, acute experiments have the ability to sacrifice key structures which impede surgical access. The ventral approach is more suited to acute experiments as it provides excellent exposure of the middle ear in most species, but this wider exposure is at the cost of greater tissue sacrifice which may not be compatible with animal survival beyond anaesthesia. Another limitation of the ventral approach model is that there is no equivalent approach in humans because of the destructive access. The postauricular approach is suited to most chronic experiments and provides adequate exposure of the middle ear, but is not possible in the sheep or pig due to the adipose filled mastoid and overhanging atlanto-occipital joint respectively[48,53,179]. The transcanal route provides the least invasive but technically most challenging exposure of the middle ear due to the narrow confines of the EAC and the limited visibility and access this provides to the middle ear. This is obviously an issue for smaller animals such as rodents, but even primates have a narrow bony portion of the EAC. Exposure may be enhanced by widening the EAC with a drill and both the postauricular and especially the transcanal approaches are facilitated by amputation of the pinna.

Middle ear surgery which manipulates the sound conducting apparatus limits audiometric outcomes by introducing a variable CHL. By itself this would not be a problem, however, middle ear surgery is also associated with SNHL from inner ear injury[8,187,188] and so it may be impossible to distinguish the cause of a hearing loss with conventional techniques. This is an issue with any model of hearing reconstruction surgery and may be overcome by direct stimulation of the cochlea electrically[89,189,190] or with BC[91]. No identified studies used galvanic stimulation in animals, and BC is problematic in animal models because of the mismatch between the frequency output capability of the transducer and the hearing frequency spectrum of the animal. There was no artificial mastoid for calibration of BC identified in animals, but when a human artificial mastoid was used there was a significantly sharp deterioration in transducer performance above 4 kHz[90,191]. This frequency response limit is satisfactory for assessing low frequency hearing structures located towards the cochlea apex, but the higher frequencies in the basal turn of the cochlea will be missed. Of the common animal models identified in this review, the upper hearing limits for guinea pig, cat and rat are 50, 64, and 76 kHz respectively[1,2]. Further compounding this problem is that injury from middle ear surgery is focussed on hearing in the basal turn[81,192-194].

The second significant consideration when choosing an animal model of middle ear surgery are the available resources. The choice of animal will be restricted by the animals available. While primates are the closest model of human middle ear anatomy, they are expensive to acquire and care for and legislation may significantly limit the kind of study permissible. Society may also deem certain species undesirable as research subjects. Research with the chinchilla and gerbil models are limited to places in the world where they occur naturally, as any advantage in importing the animal is likely to be offset by the cost differential with locally available rats or guinea pigs. Local facilities may also limit what kinds of animals are able to be cared for, and whether the animal unit has previous experience with that species. Anaesthetic modality may also influence the types of research able to be supported, as not all laboratories will have gaseous anaesthesia or perioperative support services. Choice of model is also influenced by the human resources available and experimenter experience as well.

This review has identified a significant body of evidence for tolerance of novel materials (packing, oval window graft, prostheses), and laser surgery, most of which has utilised histological rather than functional outcomes. Few studies were found which actually modelled surgery and investigated hearing outcomes. This is likely to be due to the inherent difficulty in assessing cochlear reserve in small animals when the middle ear has been disturbed. Further research is needed to develop models which are compatible with any disruption caused by middle ear surgical exposure or other intervention. Nevertheless, animal research has made a significant contribution to the development of middle ear surgical techniques and brought advances to treatments and patient care.

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