Animal models in Periodontology: a review

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Abstract

Non-human primates have been extensively used in periodontal research to investigate the pathogenesis of periodontal disease, use of dental implants, guided tissue regeneration and other surgical procedures. Rats and hamsters are best suited for caries and calculus research. Ferrets may be a promising new model for studying periodontal disease and calculus formation. Beagle dogs are best suited for periodontal disease models than for caries or calculus formation. The purpose of this review is to evaluate animals as models for studying various aspects of human periodontal disease, including the disease process, its prevention and treatment.

Key words: Animal models; Experimental animals; Periodontal diseases.

Introduction

To achieve an understanding of the life process, animals are experimented since long. There are around 4500 mammalian species and 9000 species of birds. For over hundred years, periodontal diseases have been studied in many species and a wealth of dependable data about periodontitis in species other than human exists. In the field of periodontics, the first report appears to be that of Talbott(1899), who described periodontitis in Mongrel dogs. Human longitudinal studies of periodontal diseases pose many problems such as determining the individuals at risk, the level of disease activity and susceptibility to disease progression (1).
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Thus, animal models have been used to evaluate the pathogenesis of periodontal diseases and various periodontal treatment modalities. Animal data can provide us with models of biologic trends before proceeding to human application. It is important to choose a laboratory animal model that has similar characteristics of human anatomy and periodontal disease.

Classification
Animal models are classified as follows (2):
Experimental Model- one in which the experimentally reproduced condition mimics a human disease.
Negative Model- (Non model) – are animal species in which a particular disease cannot be produced.
Spontaneous Model- is an animal species that has a disease which occurs naturally and mimics a human disease at least in some way.
Orphan Model- is an animal species that does not mimic a human disease. Even though the animal disease pathogenesis is well understood, the similar disease is not, therefore, the animal disease model may not be recognized as a true model.

Rationale for using animal model in Periodontics
- Animal models for testing periodontal regenerative procedures are necessary because controlled quantitative histological analysis is required to evaluate the quality and extent of newly formed supporting tissues (3). These studies are not possible in man because of the need to retrieve teeth and surrounding periodontium in large blocks appropriate for histological analysis.
- Proper evaluation of a new therapy necessarily involves the use of treated and untreated controls which are difficult to obtain in the human.
- The testing of potentially harmful new devices and drugs may be unethical in man prior to thorough evaluation in higher animals (4).

Criteria for selection of proper animal models (2)
- Appropriateness as an analog
- Transferability of information
- Genetic uniformity of organisms, where applicable
- Background knowledge of biological properties
- Cost and availability
- Generalizability of the results
- Ease of and adaptability to experimental manipulation,
- Ecological consequences and
- Ethical implications.

Advantages of animal experiments
- By comparison with human subjects, animal models have several advantages:
  - Constant environmental conditions can be maintained over long periods of time, greatly increasing the power to detect genetic effects (5)
  - Different environmental conditions can be imposed sequentially on individuals to characterize genotype-environment interactions (5)
  - Complex pedigrees that are much more powerful for genetic analysis than typically available human pedigrees can be generated (5)
  - Genetic hypotheses can be tested prospectively by selective matings (5)
  - Essential invasive and terminal experiments can be conducted (5)

An obvious advantage of experimentation in animal systems is the possibility of creating paired defects of equal size, which simplifies statistical handling of data (6).

Limitations of animal experiments
- Not all human diseases can be reproduced in animals.
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- All the conclusions derived from animal experiments may not be strictly applicable to human beings. Difficulties are encountered in extrapolating findings from animal experiments in man.

Non-human primates

The majority of non-human primates have similar deciduous and permanent dental formulas as man with closely related dental anatomy, although the size of teeth is dramatically smaller (i). The various non-human primates species used as animal models are: Howler monkey (Alouatta caraya), Squirrel monkey (Saimiri sciureus), Cotton-ear marmoset (Callithrix jaccus), Cotton-top marmoset (Saguinus oedipus), Cercopithecidae Baboon (Papio anubis), Rhesus monkey (Macaca mulatta), Cynomolgus monkey (Macaca fascicularis), Stump-tailed monkey (Macaca fascicularis), Pig-tailed monkey (Macaca nemestrina), Hominidae Chimpanzee (Pan troglodytes) and Mountain gorilla (Gorilla g. beringei). Among the species of non-human primates, squirrel monkeys and marmosets are small in size and relatively easy to handle, but unfortunately do not exhibit an inflammatory profile characteristic of human periodontal disease. Periodontal tissue specimens from these animals, unlike humans, exhibit very limited numbers of lymphocytes and plasma cells (7-10). Monkeys have been used widely as an animal model for studying periodontal surgical procedures. Periodontal lesions in these animals are also suitable for evaluating periodontal regenerative procedures, especially since histometric analysis need to quantify the amount of new cementum, periodontal ligament and alveolar bone formed as the result of regenerative periodontal surgery (4). Fritz et al., (11) suggested that ligature-induced periodontitis around teeth and ligature-induced peri-implantitis follow similar destructive patterns, namely alteration of microbiological flora. Non-human primates have naturally occurring periodontal disease, but it occurs late in life and the lesions are asymmetrical. Non-human primates are expensive to obtain and house, hard to handle and may be infectious (1).

Hamsters

Hamsters have been used to demonstrate the transmissibility of periodontal disease with plaque bacteria (12). The type of periodontal disease hamsters develop is similar to rats in that there is primarily gingival retraction with horizontal bone loss and the interdental septum being too narrow to induce infrabony defects. Inflammation is not a prominent feature, as it is in humans.

When a cariogenic streptococci strain BA1 was inoculated with a plaque-producing filament (strain T6), the hamsters developed both caries and extensive periodontal disease. This is of special interest because caries and periodontal disease could be evaluated in vivo at the same time. Hamsters have been used primarily for caries research due to the capability of the cariogenic microorganisms to form profuse amount of plaque and quickly develop carious lesions (1).

Dogs

The etiologic factors of periodontal disease seem to be identical in humans and dogs (13). Gingival recession is an outstanding feature in dogs with periodontitis. The subgingival microflora in Beagle dogs with relatively healthy gingiva is different from humans with a high percentage of gram-negative bacteria. In disease, there is an increase in catalase-positive Prevotella melaninogena, which is not seen in humans, and a decrease in gram-negative facultative rods isolated from ligated sites (14).

In view of their docile temperament and natural susceptibility to periodontal disease, dogs, particularly Beagles, are used
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in dental research for the study of periodontal disease progression, guided tissue regeneration, tissue wound healing, and dental implants.

Ferrets

The domestic Ferret (Mustelaputoriusfuro) is believed to be derived from the wild (European) polcat. Use of the domestic ferret as an animal study model in periodontics was originally described in the 1940s by King et al., who documented that the occurrence of periodontal disease in ferrets was similar to that occurring in humans (15). The ferret is a suitable model for the study of calculus because of its resemblance to human calculus and the fact that formation of calculus is not diet dependent as in the rat and hamster.

Rodents

Rodents, belonging to the cohort Glires, such as mice, rats have been used widely for periodontal research because of specific advantages such as small size, low cost, known age and genetic background, controllable microflora, and ease of handling and housing. However, anatomical structures of periodontal tissues and histopathological features of periodontal disease of rodents are different from those of humans. For example, oral sulcular epithelium is keratinized in rodents, but not in humans. Neutrophils appear to be the only infiltrating cells in periodontal lesions of rodents. In contrast, periodontally involved human tissues show a complex infiltrate of lymphocytes, plasma cells, macrophages and neutrophils. Suggested reasons for these histological variances include the possibility of some fundamental differences in host responses and divergence in the reaction of tissues to specific challenges between rodents versus humans (16, 17).

Application of animal models in periodontology (17)

- Periodontal tissue regeneration studies: Animal models can be used in the studies considering growth factors, bone grafts/materials, guided tissue/bone regeneration, Enamel Matrix Derivative (EMD) application, collagen/synthetic membranes, Bone Morphogenetic Proteins (BMPs) application, periodontal tissues, regenerative factors and osteogenesis by means of biological cells.

- Bone Healing Investigations: Various animal models can be used in the studies considering bone healing of artificial defects.

- Periodontitis Model Descriptions: Ferrets can be used as models to evaluate the assessments in periodontal defects, experimental/induced periodontitis or gingivitis, inflammatory mediators in gingivitis or periodontitis,
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comparisons between human and animal in terms of periodontal pathogenesis and oral pathology investigations. Since the course of the periodontal lesion in ferrets follow a similar path as in humans (15).

- Calculus formation studies: Beagle dogs, rats and ferrets could be suitable for calculus formation and research studies (1).
- Implant Studies: Various animal models can be used in the studies considering evaluation of different types of dental implants.
- Bone Regeneration Investigation: Non-human primates can be used in the studies considering bone inducing materials.
- Peri-implant Tissue Studies: Rhesus monkey, cynomolgus monkey and baboons have been used to study osseointegrated oral implants due to the possibility of obtaining block biopsies (1).
- LASER Application: Animal models can be used in the studies considering all applications related to laser.

Conclusions

Non-human primates have been extensively used in periodontal research to investigate the pathogenesis of periodontal disease, use of dental implants, guided tissue regeneration and other surgical procedures. Some species such as cynomolgus monkeys have similar dental formulas, root morphology and periodontium as in humans. Non-human primates have naturally occurring periodontal disease, but it occurs late in life and the lesions are asymmetrical. Rats and hamsters are best suited for caries and calculus research. Ferrets may be a promising new model for studying periodontal disease and calculus formation. Beagle dogs are best suited for periodontal disease models than for caries or calculus formation. Thus, in designing any dental animal study, it is often advantageous to select an animal that is phylogenetically similar to humans. The wide range of animal species allows appropriate selection of bio-models for different investigations. Each species has unique similarities and dissimilarities to humans. Choosing a gold animal model which suits all fields of application is a current goal in research though seems to be very difficult or impossible.

References

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