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Animal Models of Relevance to Dentistry

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Abstract

Animal experiments are a source of an on-going scientific and non-scientific discussion. Since time immemorial utility of animals for the service of manhood has been practiced. These experimental animal models have distinct advantages because of their ability to reproduce *in vivo* cellular details and responses occurring in humans. This review addresses various animal models in use for periodontology, oral submucous fibrosis (OSMF) and oral squamous cell carcinoma (OSCC) research work.

Subject Areas

Animal Behavior, Dentistry

Keywords

Animal Experiments, Animal Models, Dental Research

1. Introduction

Use of animals for research as models of human anatomy and physiology began in ancient Greece [1]. Universally, we are enjoying a superior quality of life because of the advances and development of new medicines and medical treatments through animal research [2]. Most crucial element in animal-based research is the identification and selection of suitable animal models [3]. By using various animal models, the disease pathophysiology and human anatomy can be investigated [4].

The principles of "3 Rs" (replace, reduce and refine) proposes the carefulness needed for conducting research with animals. They are internationally accepted as principles for human animal use in research and testing [5]. The principles are: 1) Animals need to be replaced by alternate methods; 2) The figure of ani-

mals used should be condensed in order to surge the methodological quality and boost the statistical analysis of data; 3) The refinement of the technique used should lessen pain and discomfort of animals during experiments [5].

Animal models are particularly important in periodontal disease as they provide a scientific basis for understanding the pathological processes [6]. Periodontitis is linked with some systemic diseases including rheumatoid arthritis, cardiovascular problems, and adverse pregnancy outcomes [7].

Due to the reproducibility and surgical accessibility large animal models, are preferred experimental defects in the perspective of regenerative medicine using biomaterials [8].

Animal models have provided invaluable information in the pursuit of medical knowledge and alleviation of human suffering [4].

The goal of present review is to address several animal models in use for periodontology, oral submucous fibrosis (OSMF) and oral squamous cell carcinoma (OSCC).

2. Concept of Animal Models

What is an Animal? Etymologically, the word "animal" is derived from the Latin word meaning soul/spirit, thus describing living organisms that are animated [2].

What is a Model? A model is an object of imitation, something that accurately resembles something else, a person or thing that is the likeness or image of another[1]. The Holy Bible tells us that God said, "Let us make man in our image, so God created man in his own image." God made man out of the dust from the ground and then respired into his nostrils the breath of life to animate him. Therefore, humans are "animal models" of God [9].

Upon merging the two definitions, an "animal model" is an animated objective of imitation, an "image of Man" or other species, used to inspect a physiological or pathological condition in demand [9].

U.S. National Committee on Animal Models for Research on Aging defined "laboratory animal model" as "an animal in which normative biology or behaviour can be studied, or in which an unprompted or induced pathological process can be inspected, and in which the phenomenon in one or more respects bear a resemblance to the same phenomenon in humans or other species of animal [10]."

3. History of Animal Modelling

Physicians dissected animals for anatomical studies in ancient Greece because of the taboos concerning the dissection of humans [1]. Physicians from this period like Alcmaeon of Croton, Diocles, Praxagoras, Aristotle, Herophilus and Erasistratus performed "vivisections" *i.e.*, exploratory surgery of live animals [11]. Flemish anatomist Vesalius (1514-1564), a physician and surgeon, stated that many anatomical structures prevailing in humans, are absent in other ani-

mals [12].

During the late sixteenth and early seventeenth centuries, William Harvey (1578-1657) interminably studied and related the anatomic and functional properties of the heart and vasculature in various species like eels, Chicks, fish and pigeons [1].

French physiologist, Claude Bernard, published an introduction to the study of experimental medicine in 1865 that guided the physicians in experimental research [12].

His peers of the time Robert Koch from Germany and Louis Pasteur from France put forth concepts of "germ theory of disease" and specificity into medicine respectively [12]. Seven out of the last 10 Nobel Prizes in medicine have depended at least in part on animal research since 1901 [10].

4. Animal Models Used in Periodontology

4.1. Non-Human Primates

Numerous non-human primates species in use as models are: Howler monkey (Alloutacaraya), Cotton-top marmoset (Saguinus Oedipus), Cotton-ear marmoset (Callithrix jacchus), Cercopithecidae Baboon (Papio anubis), Rhesus monkey (Macaca mulatta), Squirrel monkey (Saimiri sciureus), Cynomolgus monkey (Macacafascicularis), Hominidae Chimpanzee (Pan troglodytes) Mountain gorilla (Gorilla gorilla beringei), Stump-tailed monkey (Macacaactoides) and Pig-tailed monkey (Macacanemestrina) [13].

Oral structures and teeth of non human primates are similar to humans and have naturally occurring oral microbial pathogens, dental plaque, calculus, and periodontal disease [8]. It is noteworthy that, rhesus monkeys (Macaca mulatta), cynomolgus monkeys (Macaca fascicularis) and baboons (Papio Anubis) are vulnerable to normally occurring periodontal disease [14].

Dental formula of Macaques, chimpanzees and baboons is the same as that of humans *i.e.*, I 2/2, C 1/1, Pm 2/2 and M 3/3. Their tooth size is smaller but anatomy and roots are similar to that of humans [8].

4.2. Dogs

Dogs are appropriate models for learning usually occurring gingivitis and periodontitis [15]. Beagle is most regularly used because of its extremely cooperative nature and size [15]. Size of the teeth and periodontal tissues is similar to that of humans [16]. Subgingival plaque of dogs predominantly consists of anaerobic gram negative cocci and rods such as F. nucleatum and P.gingivalis similar to human bacteria [17].

A surgical model was proposed by Wikesjo in 1994, a critical sized supra-alveolar defects measuring 6mm were created at the level of the mandibular premolars (**Figure 1**). More than one hundred publications were found for periodontal research involving dogs for healing defects with various biomaterials, membranes or with enamel matrix derivatives [18].

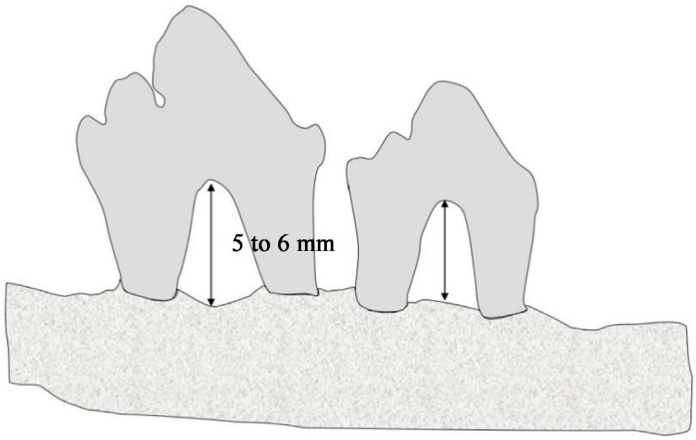

Figure 1. Supraalveolar critical size periodontal defects on dog mandibular premolars as described by Wikesjo *et al.* 1994 [18].

Major dissimilarities between dogs and humans are the presence of open contacts between teeth, lack of lateral movements and no occlusal contacts for all the premolars [17]. All dogs are diphyodont with deciduous, permanent dentition and I 3/3, C1/1, Pm 4/4, M 2/3 is formula for permanent dentition [19].

4.3. Ferrets

Domestic Ferret scientifically known as Mustelaputoriusfuro is derived from the wild polecat [20]. King *et al.* in 1940s first described its use as animal experimental model in periodontics and they also stated that the incidence of periodontal disease in ferrets was alike to humans [20].

Ferrets have a primary and permanent dentition *i.e.*, they are diphyodonts and Dental formula of permanent dentition is I 2/2, C 1/1, Pm 4/4, M 2/2 [8]. As the disease progressed gingiva revealed signs of inflammation and calculus amplified both in amount and extent [20]. Alveolar bone resorption was severe up to 50% [21].

4.4. Rats

Rat is extensively studied rodent to know the pathogenesis of periodontal diseases and its dentition is I 1/1, C 0/0, Pm 0/0, M 3/3 [8]. Incisor in rats is rootless with the structure of the gingival area comparable to that of in humans [22].

There are certain differences like relationship between the gingival and junctional epithelium with desmosomal contact between the most superficial cells of the gingival epithelium, non keratinized cells of the junctional epithelium and keratinisation of crevicular epithelium in rats [23].

The fruitful approach for studying oral disease in rats is application of the gnotobiotic or germ-free rat [24]. Germ free rats of the Spraque-Dawley strain are being used to validate the capacity of numerous filamentous bacteria to procedure plaque and bring periodontal disease in the non-attendance of other bacteria [24]. When compared to humans the occurrence of periodontal diseases is less common in rats [25].

There is clear evidence suggesting horizontal bone damage in rats infected with Aggregatibacter actinomycetemcomitans or Porphyromonas gingivalis [15].

Experimental animal models have been developed in a range of species using a variety of methods to induce hydrocephalus or through genetic mutations in rodents [26].

4.5. Hamsters

In hamsters, periodontal disease needs to be obtained experimentally and does not occur spontaneously [27]. The formula for permanent dentition is I 1/1, C 0/0, Pm 0/0, M 3/3 [8]. Unprompted periodontal disease was achieved using a suitable diet comprising high concentrations of carbohydrates in particular sucrose [28].

The mechanism of alveolar bone resorption in hamsters seems to be quite akin to those detected in rats infected with Gram-positive bacteria [20].

4.6. Minks

Permanent dentition formula of mink is I 3/3, C 1/1, Pm 3/3 and M 1/2 [8]. Padgett *et al.* in 1963 reported that the incidence of a panleukocytic abnormality of Aleutian type mink seems to be morphologically indistinguishable to that of Chediak-Higashi syndrome (CH-S) of man [29].

In minks, neutrophils play an vital role in periodontal destruction because of the insufficiencies in chemotactic response, enormous release of proteases and lysosomal enzymes into periodontal tissue [20].

4.7. Miniature Pigs

Miniature pigs possess oral structures comparable to humans and periodontitis is stimulated in 4 - 8 weeks using ligatures, and with bacterial inoculations of *S. mutans, P. gingivalis*, and *A. actinomycetemcomitans* [30].

Minipigs are appropriate models for both periodontal and dentofacial investigations but they are comparatively expensive, with husbandry issues and a small number of studies supporting their use [15].

4.8. Mice

Mice usually develop periodontitis at 9 months of age which further rises as a function of age, similar to human periodontitis. Dental formula for permanent dentition is I 1/1, C 0/0, Pm 0/0, M 3/3 [22].

Mice and other small rodents have long been important model animals for basic research and have contributed greatly to our understanding of human disease pathogenesis [31].

4.9. Baker Mouse Model

The Baker mouse model of periodontitis is used to measure alveolar bone resorption triggered by oral bacterial inoculums as a consequence for the clinical

appearance of periodontitis in humans [32].

Alveolar bone loss was spotted after 10 weeks and it was speculated that P. gingivalis began experimental periodontitis, at least in part, by adapting the endogenous subgingival biofilm to obtain improved virulence [33].

4.10. Other Animals

4.10.1. Rabbit

Rabbits are used for making of surgically induced periodontal defect and to study periodontal regeneration, but they are less appropriate for regeneration of periodontal ligament [34].

Tyrrell KL *et al.* in 2002 stated that the cultures from a set of 12 rabbits yielded pathogenic bacterial species that are consistent with the flora of periodontal disease in humans [35].

4.10.2. Horses

Well known commonest cause of tooth loss in small animals and humans is periodontal disease [32]. The experimental observations indicate the same is true in the case of horses [36].

Commonly happening oral diseases in horses include gingival recession, Buccal abrasion and periodontal pockets [37]. But because of their hefty size and husbandry considerations, horses are not a practical model for basic science studies of periodontitis [37]. **Table 1** summarizes the different animal models used in periodontal research [38].

5. Animal Models in Oral Cancer Research

Head and neck squamous cell carcinoma is the sixth most commonly occuring cancer worldwide. It accounted for 49,260 new cancer identifies and 11,480 deaths in the United States in the year 2010 [39].

Several animal models like hamster, rat and mouse are used for oral squamous cell carcinoma research, and every model has its own advantages and disadvantages [40]. New treatments can be explored both *in vitro* and *in vivo* but the

Table 1. Different animal models are used in periodontal research.

Pertinence of the model	Research Based on Pathogenesis of Periodontal Disease		
	Disease etiology	Calculus	Immunology and Micriobiology
Non Human Primates	Excellent	Medium	Excellent
Dog	Good	Good	Good
Minipig	Low	Low	Low
Rabbit	Low	Low	Low
Ferret	Medium	Good	Low
Rat	Low	Medium	Good
Hamster	Low	Medium	Good

disadvantage of *in vitro* studies is the difference between the cell culture and the physiological processes giving deceptive results [40].

Spontaneous oral squamous cell carcinoma (OSCC) rarely occurs in domestic and laboratory animal's hence artificial induction is necessary for oral cancer research [40].

In previous experiments, tumours were induced by mechanical injury to the jaws of mice [41].

Numerous agents including oncogenic viruses, physical and chemical carcinogens and some other microorganisms are capable of initiating genetic damage there by persuading malignant transformation [42].

5.1. Carcinogen Induced Model

Animal models have been restricted to chemically induce oral carcinomas since long time, possibly because the chemical constituents of tobacco and alcohol were rapidly recognised as accountable for most human OSCC [40]. Many of the initial attempts to bring malignant tumours were largely unsuccessful because the oral mucosa is more unaffected by action of chemicals when compared to skin [43]. This alteration in susceptibility is due to the presence of saliva in oral cavity providing defensive effect [44].

There are several methods of oral cancer instigation in animals using carcinogenic agents. The initial DMBA model proposed by Salley utilises the administration of polycyclic hydrocarbon 9, 10 dimethy-1,2 benzanthracene (DMBA), dissolved in benzene or acetone and applied to the cheek pouch of hamsters [45].

For the duration of the first 2 weeks, there was an inflammatory phase with necrosis and sloughing of the distal part of the pouch, followed by healing and shrinkage [46]. The mucosa consequently passed through four histologically identifiable stages such as hyperplasia, papilloma, carcinoma in situ and squamous cell carcinoma (SCC) [46].

Most descriptive model to study OSSC is chemical carcinogenesis induced locally or systemically by 4-nitroquinoline-1-oxide (4NQO) [42]. The mechanism of action of 4NQO is through the generation of reactive oxygen species (ROS) and nitrogen (RNS) including superoxide radicals, nitric oxide and hydrogen peroxide causing intracellular oxidative stress [42].

Depending upon the dose and duration of treatment, 4NQO causes a spectrum of dysplastic and neoplastic lesions in the oroesophageal epithelium, with morphological and molecular changes alike to those occuring in human oral epithelial preneoplastic and neoplastic lesions [47].

5.2. Orthotopic Models

Orthotopic xenograft models of oral squamous cell carcinoma (OSCC) was initially defined by Fitch *et al* in which SCC cells aspirated from subcutaneous ectopic xenografts were injected into the tongues of nude mice [48].

Orthotopic murine models revealed the fruitful growth of primary tumors histologically comparable to oral SCC of tongue with metastasis to the cervical lymph node (LN) and hence, they were ideal for *in vivo* study of the genetic changes accountable for metastasis [49].

5.3. Transgenic Models

The transgenic mouse models of oral cancer have been proposed that use the keratin 5 (K5) or keratin 14 (K14) promoter to overexpress the oncogene K-ras in oral epithelium of mice [50].

Ras gene mutations are commonly observed in human cancer [50]. A notable variation in ras mutation rates, because of exposure to different carcinogens, has been detected in human oral cancer therefore two animal models for oral cancer have been built by targeting the gene [40].

A transgenic mouse model that caused squamous cell carcinoma exclusively within the oral cavity has also been described using the K-*ras*G12D oncogene [50]. In this particular model, the mice carrying K-*ras*G12D oncogene construct under the control of K14 promoter and tamoxifen-inducible Cre recombinase were crossed with p53 conditional knockout mice [48]. The resultant progeny mice developed squamous cell carcinoma in the oral cavity in two weeks of tamoxifen treatment [48].

Redman *et al.* monitored and inspected the growth of hyperplasia, neoplasia and other anomalies in 10 Smad4 ± mice [51]. Three animals developed SCC invading half or more of the mandible where as in one mouse invasion of maxilla was noticed [51].

Newly described transgenic model of employed constitutive activation of Akt along with down regulation of Trp53 [52]. In this model put forth by Moral *et al.*, the K14 promoter was utilised to target the expression of active Akt to the oral cavity. The mice developed pre-neoplastic lesions which slowly advanced to squamous cell carcinoma [52].

6. Animal Models in Research of Oral Submucous Fibrosis

Oral submucous fibrosis (OSF) is a premalignant disorder linked to the chewing of areca nut with and without tobacco. The use of areca nut with tobacco has led to a sharp upsurge in the frequency of OSF in Indo China [53].

There is insufficient *in vivo* experimental data suggesting the capacity of areca nut extract to produce oral sub mucous fibrosis [54]. There has not been any reproducible animal model of OSF restricting further research into the understanding of the pathogenesis and development of therapeutic agents to switch the progression of this disease [54].

Components used for induction of OSF in animal models include capsaicin, arecoline, lime to aqueous extracts of areca nut, pan masala and gutka (areca nut + tobacco) [55]. The type of animal model used varies from region to region and based on accessibility and previous experiences of the investigator and most reg-

ularly used models are Wistar rats, albino mice and Sprague-Dawley rats [55].

Among a number of theories proposed for the development of OSF, growth factors and cytokines found in chronic inflammation play a major role in the induction and advancement of the disease [54]. Khrime *et al.* [56] in 1991 reported a marked surge in submucosal collagen contents in 88.2% of rats treated with panmasala for 6 months [56].

Maria S *et al.* [52] in 2015 did a study on Sprague-Dawley (SD) rats as a potential model in the initiation and progression of OSF [56]. Buccal mucosa of SD rats was injected with areca nut and pan masala solutions on alternate days for a period of 48 weeks and the control group was treated with saline [56]. On light microscopic observation oral submucous fibrosis-like lesions were seen in both the areca nut and pan masala treated groups and the histological changes witnessed included: Atrophic epithelium, juxta-epithelial hyalinization, partial or complete loss of rete ridges, inflammation and deposit of dense bundles of collagen fibers subepithelially bearing a resemblance with that of humans. Hence, they serve as inexpensive and effectual models for initiation and development of OSF [56].

7. Conclusion

The anatomy, physiology and pathogenicity of experimental models should relay as much as possible to those of patients in order to determine the safety and efficiency of new biomaterials or treatments. Although many animal models have been proposed in dentistry there is no unique animal model for all the dental diseases listed above. Hence a suitable animal model needs to be selected carefully for future research in dentistry. More systematic use of these small animal models appears evident for future research, especially from a surgical point of view.

Conflicts of Interest

The authors declare no conflicts of interest.

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