Research progress of animal models on orthodontic tooth movement

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Abstract: Orthodontic tooth movement animal models are important carriers for studying orthodontic tooth movement. Experimental animals that can be modeled include: rats, mice, dogs, rabbits, etc. How to select suitable animal models for different scientific problems is very important. Therefore, this paper reviews the types and characteristics of orthodontic tooth movement animal models, and focuses on the similarities and differences of rodent anatomy, modeling methods and considerations. It is found that there is a lack of unified modeling standards for orthodontic tooth movement animal models. Thus appropriate animal models should be selected according to actual needs.

Keywords: animal models, orthodontic tooth movement, periodontal tissue, and mechanical stres

1. Introduction

In recent years, people's growing needs for a better life, especially in the oral field, are increasingly manifested in the pursuit of beauty and health. Dental and maxillofacial deformities can cause serious harm to the patient's facial appearance, oral function and physical and mental health. The prevalence varies in different regions. It has been reported to be 22.5%-93%.[1]

Orthodontic treatment aims at correcting dental and maxillofacial deformities, restoring the coordination and aesthetics of teeth, jaws and faces by applying mechanical stimulation to teeth and even jaws through appropriate appliances.[2,3] Among them, orthodontic tooth movement (OTM) is an important phenomenon in orthodontic treatment. OTM is the result of an adaptive, mildly reversible biological response to the physiological balance of the periodontal tissue after mechanical load.[4] Its biological basis is the reconstruction of periodontal tissue, mainly including the reconstruction of alveolar bone and periodontal ligament, involving changes in multicellular functions and levels of various substances.[5] However, the specific mechanism of this biological process has not been fully revealed. Therefore, it is important to elucidate the bio-cellular mechanisms and endogenous or exogenous influences in OTM [6], and to explain treatment differences and adverse effects in different patients. Since a large number of cell-to-cell interactions can only be observed at the in vivo level, animal experiments are necessary.
Although animal models are increasingly used in orthodontic-related research, the use of any animal model has its limitations.[7] How to choose suitable animal models for different scientific problems has become a question worthy of discussion. Therefore, this article will introduce the types and characteristics of common OTM animal models, and focus on the similarities and differences of rodent anatomy, modeling methods and considerations, and review their research progress.

2. Otm animal models

The OTM animal models are the most common type of orthodontic-related animal models, which can study OTM phenomena [5], promotion or intervention mechanisms [8-13], mechanisms of orthodontic adverse reactions[14-16], and the impact mechanism of orthodontic treatment and other diseases.[17,18] The OTM animal models also provide important in vivo experimental evidence functional evaluation after periodontal defect reconstruction [19].
To establish OTM animal models requires the following requirements: ①It is necessary to establish animal models as close as possible to the structural and functional state of human periodontal tissue. Since the biological basis of OTM is periodontal tissue reconstruction, the animals which can be applied to periodontal-related research (Table 1) can also be used to establish OTM models, especially rats, mice, dogs, and rabbits. Although they are different

from humans in terms of dental formula, tooth morphology, etc., they have similarities in OTM mechanism, that is, under the mediation of mechanical stress, alveolar bone resorption on the "pressure side" and new bone formation on the "tension side".[20] ②The OTM animal models should be reproducible, that is, the interference of experimental animals and environmental factors must be strictly controlled. ③On the compressed side of the periodontal tissue, OTM consists of three stages: the initial stage, the teeth are displaced in the PDL space, the PDL is compressed and deformed, the cell death occurs due to insufficient blood supply; the delayed stage, At this time, the osteoclasts did not reach the PDL compression area, and the tooth movement stopped, which may last for 2 weeks; the post-lag period is characterized by the direct absorption of the alveolar bone by the osteoclasts, so that the teeth continue to move. On the tension side, when the PDL is stretched, blood vessels proliferate, and osteoblast differentiation and mineralization are stimulated.[21] Therefore, experimental animals should be able to tolerate mechanical stimulation for a certain period of time to complete the OTM process. ④Experimental animals should be able to endure other interventions or disease states based on OTM to study the mechanisms that promote or inhibit OTM, and explore the impact of complex systemic or local factors on OTM.

Table 1 animal models used in periodontal research[22]

Animal	Advantage	Disadvantage
Nonhuman primate	① Comparable dental anatomy ② Natural occurring plaque and calculus Comparable periodontal wound healing ③ Suitable for studying furcation defects ④ Experimentally induced defects do not spontaneously regenerate	① High purchase and maintenance costs ② Hard to operate ③ Potentially infectious ④ Ethical debate
Rat	① Most histological features of epithelium and connective tissue similar to humans ② Cheap purchase and maintenance, many related reagents	① Occlusal plane wear can changes tooth position ② Continuous eruption ③ Small dimensions, potential surgical difficulties because of the size ④ Number and size of defects limited
Mouse	① Most histological features of epithelium and connective tissue similar to humans ② Cheap purchase and maintenance, many related reagents ③ Sterile mouse models can be established, and oral microorganisms can be humanized ④ Transgenic mouse model establishable	① Occlusal plane wear can easily lead to changes in tooth position ② Continuous eruption ③ Small dimensions, potential surgical difficulties because of the size ④ Number and size of defects limited
Canines	① Susceptible to periodontal disease ② Reasonable number and size of defects ③ Suitable for studying furcation defects ④ Simple morphology of the roots ⑤ Docile temperament	① Purchase and maintenance expensive ② Much faster bone turnover rate and different architectures and thickness of bone ③ Great interanimal variability ④ Ethical debate
Rabbit	① Relatively easy to operate	① Continuous eruption ② rootless bifurcation structure ③ Much slower bone turnover rate
Minipig	① Histologically, the inflammatory process is similar to human situation ② Suitable for studying furcation defects	① Purchase and maintenance expensive ② Much faster bone turnover rate and different architectures and thickness of bone
Ferret	① Spontaneous calculus formation ② Course of periodontal lesions similar pathway as in human	① Expensive purchase and maintenance ② Limited research has been done ③ Potential surgical difficulties because of

the size

3. Rats

Sprague Dawley rats and Wistar rats are common closed colony, which can simulate the effects of intervention factors on OTM under the condition of polygenic confounding. Furthermore, larger sample sizes can be obtained using rat models because the cost of feeding is relatively inexpensive. They are larger than mice, thus the surgical operation is relatively easy. Additionally, the histological preparation of rat is easier than the histological preparation of canine. More importantly, most of the antibodies needed for cellular and molecular biology techniques are only available in rats and mice.[23] Thus, 70% of the studies are performed in rats.[24]

However, rodents still face multiple challenges as a model for OTM. Due to the small size of rat teeth, creating an effective force application device is complex. It's more complex to exert a constant and continuous or designed mechanical stress within an acceptable range.[25] It is reported that the alveolar bone of rats has no marrow cavity, and the extracellular matrix contains relatively little acidic mucopolysaccharide, so its bone density is larger than that of humans.[25] Periodontal tissue remodeling in rats is faster than in humans during orthodontic treatment, although the main mechanisms are the same.

The dental formula of rats and mice are both: 1-0-0-3/1-0-0-3, that is, there are 2 incisors and 6 molars in the upper and lower jaws. Since the shape of rat incisors is completely different from that of humans, the roots of the teeth are long and erupt throughout life, and the bone mass at the front of the upper and lower jaws is very limited.[25] Therefore, the teeth used for OTM are generally the maxillary or mandibular first molars, and the ipsilateral incisors can be used as anchorages. However, the eruption of the incisors may lead to poor retention and, at the same time, change the direction of the traction stress, hampering the interpretation of the data to some extent.[25] The choice of mini-implant can avoid these problems. However, the cost of micro-screws is higher. In addition, rodents are obligate nasal breathers and aspiration of blood could lead to death[7]. Therefore, it is necessary to be alert to the complications of bleeding in the nasal cavity when placing mini-implants in the maxilla.

Since the center of resistance of the first molars of rodents is closer to the root apex than that of dogs, the tooth movement is often inclined, and it is difficult to achieve parallel movement.[7,26] The moving direction of the first molar is usually mesial. It is worth noting that the amount of movement is limited. It is easy to move out of the alveolar bone when moving a first molar mesially by 3-4 mm.[7] It has not been reported so far that moving the tooth to the extraction site, for example, extracting the first molar and moving the second molar mesially, or extracting the second molar and moving the first molar distally, probably because it causes unilateral Inability to chew. There are few reports on the vertical depression or elongation of molars. The posterior teeth will continue to erupt, so it is hard to depress them. For elongating molars, it is difficult to apply vertical stress exactly. Moreover, the elongated molars raise the occlusion, which destroys the overall occlusal relationship, which is not conducive to animal welfare.

The specific modeling method is as follows: generally, 6-12-week-old rats are selected. The younger the rat, the faster the recruitment of osteoclasts.[27] After intraperitoneal injection of mixed anesthetics, the head of the rat is fixed. A 0.5mm groove is prepared for the neck of the incisor, and a ligature wire is placed and fixed with glass ionomer cement. Subsequently, a nickel-titanium coil spring is placed between the first molar and the incisor. Then ligation wires are fixed distally to the first molar and pull the spring mesially. It is worth noting that, in terms of diet, a standard diet with feed pellets should be softened to mash.[28,29] The experiments usually last for 14 days.

In terms of mechanical force selection, 27% of studies used elastic bands with unknown force, 20% of studies used the force below 20g [30], and 37% used the force ranging from 20g to 50g[30-33], 12% used the force ranging from 50g to 100g [25,34], and the rest used the force over 100g.[35] It is reported that human molars are approximately 50 times larger than rat molars [7], which means that the force of 20g acting on rat molars is equivalent to a force of 1000g acting on human molars. It is showed that increasing orthodontic force does not linearly increase OTM rate.[36] Therefore, the selection of the mechanical force should refer to the estimation of the root surface area and the purpose of the experiment, and a pre-experiment should be carried out if necessary.

In order to explore the impact of other diseases on OTM, an animal model of the disease is often established before an animal model of OTM is established. Ferreira [17] and Santamaria [18] randomly divided male Wistar rats into 4 groups: OTM group, periodontitis + OTM group, diabetes + OTM group, and diabetes + periodontitis + OTM group. Among them, the diabetes model is induced by taking alloxan, and the periodontitis model is induced by ligating the gum retraction cord for 7 days.

4. Mice

C57BL mice and ICR mice are the most commonly used mice to study OTM.[37,38] It is worth mentioning that the alveolar bone of mice, like rats, has no bone marrow cavity, so quantitative analysis of histology cannot be performed.[7] Mice are also different from humans in the arrangement of periodontal ligament fibers and the growth and development of tooth roots.[23] However, the mice are considered a good model for studying OTM because they have similar advantages to the rat. In addition, the biggest advantage of mice models is the ability to establish transgenic models, and inbred lines are often used to ensure genotype consistency, making it possible to analyze the effects of single genes in vivo.[10,16]

Undoubtedly, placing the appliance in the mouth of the mouse is more difficult. Moreover, compared with rat models, the total amount of tooth movement that can be performed by the first molars of mice is small, usually less than 1mm [7], so it can only be used to study the initial stage of OTM.

The specific modeling method: generally, 8-10-week-old mice are selected, and their heads are fixed after intraperitoneal injection of mixed anesthetics. The first molars and incisors are etched with 37% phosphoric acid gel for 30s, and the acid is removed with a small brush. Then clean and dry the tooth surface with a small bristle brush dipped in ethanol. The distal end of the nickel-titanium coil spring is placed on the first molar and fixed with light-cured composite resin. The spring is pulled mesally until a predetermined mechanical stress is reached, and the light-cured composite resin secures the proximal end of the spring to the incisor. After surgery, mice are transferred to a heat pad and monitored until they fully recover from anesthesia. Orthodontic treatment generally last for 12-14 days. It is worth noting that nickel-titanium coil springs are used for applying stress, because the elastic stress of elastic bands and elastic power chains will continue to decay, and its ability to induce OTM can only last for 7 days [16], which is only suitable for short-term experiments. However, the ease of placement of the elastic bands and elastic power chains reduce the burden on the animal by reducing the dose required for anesthesia, increasing the welfare and survival of the animal.[5] In terms of mechanical force selection, most studies use 10g.[39] Some experiments use 25g[5] or 35g[16,40], which may be related to the study of root resorption.

5. Canines

Canines, such as the beagle, are also widely used to study OTM. However, the use of canines and other large animal models has become increasingly difficult due to ethical concerns. Some countries prohibit the use of some large animal models for medical research.[7] Therefore, when using canines, the 3Rs should be more strictly followed, namely replacement, reduction and refinement.

The dental formula of Canines are: 3-1-4-2/3-1-4-3, that is, the upper and lower jaws have 6 incisors, 2 canines and 8 premolars, 4 molars on the upper jaw, and 6 molars on the lower jaw. Canines are very similar to humans in anatomy, biology and tooth type (dental formula of human are generally 2-1-2-3/2-1-2-3). Thus, orthodontic appliances for humans can be placed in dogs without redesign or downsizing.[7] Using canines, OTM can be used for up to 3-4 months to study the sustained response of periodontal tissue to mechanical stress. The orthodontic force is generally 100-200g, which can be generated by a coil spring. During modeling, extraction of premolars or root cutting of premolars is often chosen to create OTM space.[41]

6. Rabbits

The New Zealand White Rabbit is a common variety for rabbit model of OTM. The bone and tooth root structure of rabbits is quite different from that of humans, so the experimental results may not be representative of humans. The dental formula of rabbits is 2-0-3-3/1-0-2-3. Generally, the first premolar is used for mesial traction. All the teeth of the experimental rabbits will continue to grow. If the bite is not appropriate and the teeth wear unevenly, it is easy to cause eating disorders.

The bone turnover rate of experimental rabbits is about 2%/year.[7] A low rate of bone turnover implies a slower rate of alveolar bone remodeling and a higher likelihood of OTM recurrence. AlSwafeeri [42] performed active traction on

10 New Zealand white rabbits to move the teeth for 21 days, and then took out the appliance. The experimental group was given local injection of simvastatin in the relapse phase of the following 21 days. However, it could not be concluded that the drug inhibited conclusion of recurrence.

In addition, experimental rabbits are not conducive to the construction of alveolar bone defect models.[22] Due to its low bone turnover rate, the implanted biomaterials often cannot be transformed into new bone tissue in a short period of time. During the functional evaluation of periodontal defects, the teeth move to the defect regeneration area, and the rate is often accelerated.[19] If the study considers the factor of low bone turnover rate, or explores the law of low bone turnover rate and OTM, then the rabbit model of OTM should be selected.

7. Conclusions and perspectives

At present, many researches focus on promoting or intervening OTM mechanism through the study of stress, physical and chemical stimulation factors, and biological factors, and have achieved certain research results. In addition, there are many studies on the mechanism of orthodontic adverse reactions, such as alveolar bone resorption and root resorption.

As research progresses, clinicians and researchers pay more and more attention to oral and systemic diseases, such as periodontitis, diabetes, etc, because these diseases hinder the performance of orthodontic treatment. Periodontitis often leads to periodontal defects. It has been found that it is not enough to focus on gene expression, morphology and other indicators for the reconstruction of periodontal defects, and functional evaluations represented by OTM should also be considered. Therefore, the model of OTM will be more widely used in similar studies.

Although there are various kinds of animals that can be used for OTM modeling, and different factors in modeling methods have been discussed in the literature, the modeling scheme is still single. There is also a lack of unified modeling standards and comprehensive analysis methods. Therefore, the coming decades, the animal models of OTM need to be further based on the human OTM mechanism to form a consistent OTM modeling standard.

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