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Stereotactic surgery and its application in Alzheimer's disease rat models

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Abstract

Stereotactic surgery is a technique that can be used to locate small targets in the body and administer interventions and/or treatments, such as injections, to the specific target. Stereotactic surgery is frequently used to create neurological disease models in experimental research in addition to clinical practice. The injection is administered with appropriate glass injectors using the rodent brain coordinate atlas after the specific brain region is determined. Alzheimer's disease (AD), the most common cause of dementia, has no curative treatment yet. AD models can be created in rodents through stereotactic surgery and injections of different substances. These AD models represent the disease and are frequently used especially for drug development studies. AD-like models seem to examine different and unidirectional developmental mechanisms according to the creating way. However, AD is a multidirectional disease. AD rodent models created using different methods have specific properties. This review aims to explain the basic aspects of stereotactic surgery and to discuss AD rodent models created with this surgical technique and also with alternate methods.

Keywords: stereotactic surgery, Alzheimer's disease, animal models, rat

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Introduction

Stereotactic surgery is used to locate small targets in the body and administer surgical interventions and/or treatments, such as injection, stimulation, ablation, biopsy, implantation, and/or radiosurgery, to these targets. This surgery uses a three-dimensional coordinate system to apply such interventions while causing minimal damage to the targets [1]. Stereotactic applications are frequently used in neurological research, pharmacological evaluations, and experiments on central nervous system diseases to eliminate, disrupt, or increase the function of certain regions of the brain [2].

Alzheimer's disease (AD) is a neurodegenerative disease that causes cognitive loss, personality changes, and speech disorders. AD, which is the most common cause of dementia, currently does not have a definitive treatment [3]. Rodents are the animals most often used in neuroscience studies. Studies are being conducted using the AD models created in rodents, and treatment options are being developed for the disease [4–6]. In these studies, transgenic rodents can be used, and AD models can be created using stereotactic surgery [7,8].

Stereotactic surgery is a method that is frequently used in rats to create AD models. Stereotactic methods used to create models of AD allow injections of substances to be administered to certain parts of the brain [9]. Appropriate coordinates are set in the stereotactic device to generate AD models. The injection area is determined using the brain coordinate atlas for rats. These coordinates may include the brain ventricles to ensure the distribution of the applied substance in the brain in addition to the hippocampus, which is an important brain region involved in the development of AD [10,11]. Therefore, the injection can be performed intracerebroventricularly or intrahippocampally.

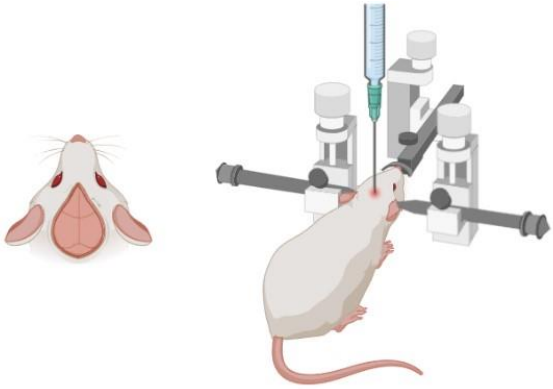
Chemicals to be injected to induce AD include various forms of amyloid or streptozotocin and also agents that will promote tau accumulation [12–14]. It is also known that metal ions play a role in AD development. Therefore, injections of substances associated with metal cations are also used to induce a model of AD [15].

In this traditional review, stereotactic surgery and its application in AD models was defined along with its basic features. This review also aims to discuss the rodent models of AD created by methods other than stereotactic surgery.

Application Steps of Stereotactic Surgery

First, the head of the experimental animal under anesthesia is shaved. The rats are placed in the stereotactic device so that the dental apparatus grasps the upper incisors, the ear bars fit into the external ear canal, and the head ceiling is in the horizontal plane. The movable apparatus of the device is compressed so as not to damage the ear and chin and to obtain a stable plane during the application (Figure 1). After this stabilization process, an incision is made in the scalp using a scalpel. After cleaning the periosteum in the skull, the lambda and bregma, which are reference points that allow us to determine the coordinates, are exposed. After the brain region to be injected with the substance is determined from the stereotaxic coordinate atlas [16], a hole is drilled into the skull in this region after which the desired coordinates are injected using a micro-injector. It is appropriate to slowly administer the chemical infusion and then remove the injector after waiting for a while (approximately 5 min) so that the chemical is absorbed after the infusion. The skin incision is then closed with sutures. Attention to maintaining asepsis during the surgical procedure positively affects the survival of the experimental animal after the procedure.

Figure 1: Stereotactic neurosurgery in rats



For example, in the rat brain atlas of Paxinos and Watson [16], the coordinates of the region we want to inject should be 3.6 mm posterior to the bregma, 2.4 mm lateral to the sagittal suture, and 2.8 mm ventral to the rat skull surface. In this case, after bringing the micro injector needle to the bregma, it should be moved 3.6 mm posterior and 2.4 mm lateral from the midline sagittal suture through the apparatus of the stereotactic device. After making a mark with a pencil perpendicular to this point, a hole is drilled into the skull at this point. The micro injector is brought to the appropriate coordinates and the syringe needle is advanced 2.4 mm ventrally in the vertical direction by means of stereotactic device apparatus after which the substance is injected.

Before starting the experiment, practicing with a preliminary study is useful. During this preliminary study, it is beneficial for experimental accuracy to inject a dye (for example, methylene blue) and then take sections from the rat brain and make sure that the stained area is the one we wish to study.

AD Models Created by Stereotactic Surgery

Since no agent is available that can provide a definitive treatment for AD, experimental models are necessary both to better understand the disease pathogenesis and develop a treatment agent. In addition to AD models created by stereotactic surgery, AD models created with transgenic animals have also been applied in recent years [17–20]. AD models created in different ways have their own distinctive features. It should be emphasized that transgenic models are established via a non-physiological process that reflects only certain pathological features. This drawback is most likely the cause of clinical failure of therapeutic agents that show positive effects in transgenic preclinical studies [21]. In addition, both transgenic and surgical AD models target only one developmental mechanism. However, since AD is a multifactorial disease, treatments targeting only one of the several developmental stages do not produce clinical success [21].

The most studied step in animal models for AD involves amyloid deposition. Triggering amyloid deposition in animals often results in cognitive impairment [22]. However, many pathways, such as neuronal loss, deterioration in both synaptic plasticity and long-term potentiation, pericyte dysfunction, metal dyshomeostasis, mitochondrial distress, blood–brain barrier

dysfunction, and pathologies associated with tau hyperphosphorylation, have been described in the development of AD [23–26]. Therefore, the reason why these models cannot fully reflect AD seems to be that they do not include the entire pathogenesis. On the other hand, the pathogenesis of AD has not yet been fully elucidated.

Stereotactic injection of amyloid derivatives is often preferred for creating a model of AD. Behavioral tests have shown that intracerebroventricular injection of amyloid β 1-42 peptide leads to impairment of learning and memory function [27]. In a previous study, it was shown that learning and memory were impaired in behavioral tests after intracerebroventricular injection of amyloid β 1-42 peptide, and hippocampal neuronal survival was impaired in histological analyses [28].

In a different study, the effect of amyloid β injected intracerebroventricularly via stereotactic surgery in rats was examined, and it was shown that infusion causes impairment of learning and memory. It was also found that amyloid β expression in the cortex and hippocampus increased in the group that received amyloid infusion compared to the control [29].

In a different rodent study in which stereotaxic injection was performed intrahippocampally, AD model was induced by amyloid β 1-40. It was shown that spatial learning and memory were impaired in rats after the injection [30].

Conclusion

AD models that are established via the use of stereotactic surgery reflect the disease in terms of learning and memory impairment and pathological accumulations of several kinds of proteins. However, models established via stereotactic surgery seem to represent the disease in terms of only one pathway depending on the substance injected and the pathway triggered. Injection of amyloid derivatives is frequently used to create an AD model via stereotactic surgery. Amyloid injection produces results that mimic AD in aspects of amyloid plaque formation and hippocampal amyloid deposition. However, the multidirectional pathogenesis of AD does not produce the expected results in pre-clinical studies conducted with AD models as these models reflect only a single pathway. Transgenic animal models of AD also present only one pathological pathway. More studies are needed to elucidate the unknown mechanisms of AD, to develop models covering the entire pathogenesis of the disease, and to develop treatment agents as a result.

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