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Research Progress on Post-Traumatic Stress Disorder and Its Animal Model

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Abstract

Posttraumatic stress disorder (PTSD) is to a persistently severe mental disorder which is caused by individual exposure to some unusual threatening or catastrophic stressful events. Its essential clinical manifestations refer to repeated playback of traumatic experience, durative avoidance of related clues, mental numbness or affection paralysis, and persistent increase of vigilance level. At present, the pathogenesis of PTSD has not been fully elucidated, and the clinical therapeutic effect has not been ideal. Generally, the classical animal model of PTSD is mouse; the domestic and international researches in the animal model of PTSD in recent years remain active, which are summarized as follows.

Keywords

Post-Traumatic Stress Disorder, Animal Model, Review

1. Progress in PTSD Research

According to foreign data, for men, the incidence of high incidence of PTSD in human trauma is rape (65%), war (38.8%), sudden death of the lover (12.6%), harassment (12.2%); for women, rape (45.9%), harassment (26.5%), physical assault (21.3%), and sudden death of the lover (16.2%). Studies have shown that 50% - 70% of individuals are exposed to traumatic events [1] [2]. American civilians are 7% - 12%, and women are twice as many as men [3] [4] [5]. War veterans: The Gulf War was 10.1% [6] and the Iraq War was 13.8% [7]. Studies have shown that the lifetime prevalence of PTSD in the general population is 5% for

men and 10.4% for women, and about 1/12 of the population is affected [8]. Many studies have shown that the age of adult cancer patients is inversely proportional to the symptoms of PTSD [9] [10] [11]. It was also found that the age of children with cancer survivors was directly proportional to the PTSD score. The prevalence of women in the general population is twice that of men [12]. The time distribution of PTSD after different traumatic events is as follows: 1) Hurricane: incidence of PTSD in children 3 months, 7 months, 10 months after Andrew Hurricane.

They are 86%, 76%, and 69%, respectively [13]. 2) Terrorist attacks: Jehel *et al.* [14] [15] found in the study of bomb attacks in Paris, France, that the prevalence of PTSD was 6 months and 18 months after the explosion.

Don't be 41% and 34.4%. The incidence of PTSD at 1 month and 6 months after the US "911" incident was 7.5% and 0.6%, respectively [16]. 3) Floods: North *et al.* [17] reported that the incidence of PTSD among flood victims was 22% and 16% after 4 months and 6 months of flooding in St. Louis. 4) Cancer: the prevalence of PTSD in cancer patients is 3%-19%, and the lifetime prevalence is 10% - 22% [18]. Therefore, PTSD is receiving more and more attention.

China is a country with high natural disasters. In the 100 years from 1908 to 2008, four of the nine most destructive natural disasters in the Asia-Pacific region occurred in China. In recent years, major natural disasters such as the "Wenchuan Earthquake", "Yushu Earthquake" and "Zhuqu Debris Flow" have occurred in succession. In addition to major natural disasters, general man-made disasters are also common in our country. The China Injury Prevention Report shows that there are about 200 million injuries per year in the country, and the number of deaths due to injuries is about 700,000 to 750,000, with an average of 2000 per day. About 100,000 people die each year from traffic accidents in the country, and 480,000 people are injured. The direct economic loss is about 2.8 billion Yuan. Every year, about 15,000 people died in various industrial and mining business accidents, and about 2.6 million people in the country were disabled due to work-related injuries. There are about 150,000 fires in the country each year, with an average loss of about 1.6 billion. In 2010, there were 627 people who died in water transportation in China, 1604 people died in railway traffic, and 42 people were killed in civil aviation. Although PTSD is also a common serious psychological disorder among different disaster survivors in China, there are very few studies and practices on this disease, which seriously restricts the development of mental health plans and psychological assistance work. Therefore, from the actual situation in China, it is necessary to carry out systematic research on PTSD.

According to the most widely used DSM-IV PTSD diagnostic criteria, the 17 clinical symptoms involved in the clinical symptom criteria of PTSD are divided into three clinical symptom clusters, including: The first group is hyperarousal: manifested as persistent anxiety, irritability, insomnia, and decreased concentration; the second group surrounds the intrusions experience: although patients

have difficulty recalling stressful events autonomously, there are a lot of intrusive experiences of traumatic images, flashbacks and recurring painful dreams; the third set of symptoms is avoidance: patients avoid things related to traumatic events, alienation from people, no emotional experience (numbing Numbness and reduced interest in activities. The most typical symptoms are flashback, nightmares, and intrusive appearance, sometimes combined to be called re-experience symptoms. These typical symptoms are considered to be direct or indirect effects of abnormal memory processing in patients with PTSD [19], so PTSD is considered to be a pathological memory-causing and persistent disease [20] [21]. Since the publication of DSM-IV in 1994, the three-dimensional clinical symptom heterogeneity model of PTSD in DSM-IV has been extensively studied and supported [22]. At the same time, a large number of studies have shown that PTSD may involve different psychopathological and biological processes in different symptom clusters [23], and play different roles in the development and treatment of PTSD [24]. Therefore, the basic research on different symptom clusters of PTSD is of great significance for further understanding the physiological mechanism and treatment of PTSD. In addition, there are the Emotion Numbing Model of King *et al.* (1998), the 4-dimensional Dysphoria Model of Simms *et al.* (2002), and the five-dimensional painful arousal model (Elhai *et al.*, 2011), but none of the latter three models are extensive and in-depth with DSM-IV, and have corresponding limitations (see **Table 1**).

Typical PTSD symptoms can be considered as direct or indirect effects of ab

Table 1. Detailed table of four models of clinical symptoms of PTSD.

DSM-IV PTSD Symptom	DSM-IV	Emotional numbness model	Mental pain model	Painful arousal model
B1. Intrusive thinking	Instruction and re-experience	Instruction and re-experience	Instruction and re-experience	Instruction and re-experience
B2. Nightmare				
B3. Flashback				
B4. Emotional response				
B5. Physiological response				
C1. Avoiding trauma-telated thoughus, etc.	Active avoidance and emotinal numbness	Active avoidance	Active avoidance	Active avoidance
C2. Avoiding clues that can suggest trauma				
C3. Selective foegetting		Emotinal numbness	Mental pain	Emotinal numbness
C4. Loss of interest				
C5. Emotinal alienation				
C6. Numbness				
C7. Losing confidence in the future				
D1. Sleep problem	High arousal state	High arousal state		Painful arousal
D2. Irritability				
D3. Attention problem				
D4. Excessive alertness			High arousal state	Anxiety

normal memory processing in patients with PTSD [25], so PTSD is considered by some professional researchers to be a persistent disease caused by pathological memory [26] [27]. Recent studies have shown that PTSD is a disease caused by the participation of the neuroendocrine system, the central nervous system, and the immune system. The abnormality of the memory system occupies the most important position in the occurrence and development of PTSD. Many of the current problems are still unclear, such as differences in brain function changes between the acute and chronic phases of PTSD. However, from the above neuroimaging evidence, we can assume that the brain regions of the brain are more or less involved in the process of memory. The coordination work of the whole brain may be a prerequisite for the body to remember well, and PTSD may be caused by damage to one or more memory systems. In the study of neuroimaging to explore the pathology of abnormal memory of PTSD, scholars have found inconsistent and even contradictory results. The possible causes are different durations of PTSD, different severity of disease, sample size differences, differences in types of trauma, comorbidities in other mental illnesses, whether they have undergone treatment [28], and diverse analytical methods. PTSD is not static, but changes and changes over time [29]. For patients with chronic disease, the activity of amygdala and mPFC is negatively correlated, while the acute course is positively correlated.

2. Advantages and Development Trends of Non-Human Primate Models in Disease Research

Animal models commonly used in medical research include monkeys, tree shrews, pigs, dogs, rabbits, rats, mice, fruit flies, nematodes, zebrafish, etc., which have unique effects in various disease research. Depending on the purpose of the study, different types of animal models can be used as disease models to effectively achieve research goals.

Using the disease model of mice can basically understand the pathogenesis of most human diseases, but to truly describe the pathogenesis of human diseases, especially the pathogenesis of major diseases that threaten humans, it must rely on a more evolved model animal. In particular, studies involving human safety and ethics, such as the efficacy and side effects of drugs, require large model animals, preferably non-human primate models. If the disease model of mice is essential in mechanistic studies, disease models of large animals are indispensable before going to clinical applications, especially those genetically engineered non-human primate disease models [30]. Only by minimizing the genetic differences between model animals and humans can we maximize the proximity to human physiological conditions and maximize the safety of research results into clinical treatment. New drugs in China have been proven to fail more than 95% in Phase I, II, and III clinical trials. The main reason is that many animal models of new drugs only stay in rats, mice, or canines. The genetic difference between these animals and humans is an important reason for the failure of clinical trials

of new drugs. Studies have found that macaques have a good genetic approximation (97.5%), dogs are 19%, and rats are only 14% [31] [32] [33], suggesting that animal models with high levels of evolution are more advantageous.

The monkey in non-human primate is an ideal model animal with 98% homology with the human genome and is highly similar to humans in terms of tissue structure, immunity, physiology, metabolism and social activities. Monkeys have a very important role in the study of human diseases, especially infectious diseases. Macaques can infect infectious diseases that are unique to humans, especially infectious diseases that cannot be replicated by other animals. It is very similar to humans in terms of blood lipids, atherosclerosis, the nature and location of various neurological diseases, clinical symptoms, and the therapeutic effects of various drugs. In addition, macaques are also the best animal models for studying diseases such as nervous system diseases, AIDS, cancer, diabetes, mental illness, surgical diseases and cardiovascular diseases.

International research and utilization of primates are highly valued. There are dozens of primate research institutions in the United States, and there are eight national primate research centers supported by the federal government. Almost all of the projects funded by the US NIH, the world's largest biomedical research funding agency, are based on basic research on disease, some directly related to disease, and some may be indirectly related to disease. Statistics of the internationally renowned scientific journal Nature Genetics magazine published in 2010, 81.6% of which are related to the disease. It has also been shown that the impact factors of many journals closely related to disease research are increasing year by year, which fully demonstrates that basic research around diseases has become a major part of biomedical research.

3. PTSD Animal Model

In the research process of PTSD, behavioral methods inevitably play an important role. In 1996, Pynoos RS *et al.* used electric stimulation technology to construct a mouse model of PTSD, and studied its behavioral response and startle response, successfully simulating similar behavioral symptoms in patients with PTSD [34]. In 2006, Li S *et al.* constructed a mouse model of PTSD from male ICR mice, using foot-radiation stimulation, followed by a 3-week conditional suggestion to study the behavioral improvement of sodium valproate and diazepam in this PTSD model [35]. In 2007, Siegmund A and Wotjak CT used a single foot-radiation stimulation to construct a PTSD animal model in C57BL/6N and C57BL/6Jola mice to study the conditional and sensitizing stimuli in the two lines. In 2008, Pibiri F *et al.* used the principle of social isolation to isolate mice for 3 - 4 weeks, successfully constructed a mouse model of PTSD, and studied the related mechanisms [36]. Tamaki K *et al.* used the forced swimming for 3 h to study the expression changes of hippocampus genes and proteins in mice [37]. Among them, the strong stress model can better simulate human PTSD. SPS is an animal model of PTSD that exhibits clinical signs and neuroendocrine

changes in PTSD and is an internationally recognized animal model of PTSD mice [38] [39] [40].

Current classical animal models include: 1) predator stress; 2) social defeat; 3) shock; 4) re-straint and shock; 5) serial prolonged stress, SPS. Different animal strains as well as gene knockout and genetic recombination lines also provide a wide range of resources for research. Although there is no ideal PTSD animal model to date, the existing models can partially mimic the symptoms of human post-traumatic stress disorder. Relying on these models can recognize the mechanisms by which a series of phenomena occur in the nervous system [41] [42].

Most studies suggest that there is a "dose-effect" relationship between stress intensity and the incidence of PTSD, and the higher the stress intensity, the greater the likelihood of illness [43]. At the same time, some scholars believe that PTSD is caused by pathological memory caused by traumatic events, not the event itself [44]. In mammals, including humans, emotions can play a role in regulating learning and memory processing. PTSD [45], as a mood disorder, can also cause damage to memory function.

The PTSD animal model primarily tests changes in animal behavior and physiology by administering severe traumatic stress to the animal, which is stress intensity (dose) dependent and may persist over a longer period of time or gradually increase over time. The research focuses on the fear conditioning of associative learning and the sensitization of non-associative learning. These are two different learning processes. The former is associated with traumatic memory, manifesting as pathological recurrence, avoidance, and high alertness to traumatic cues; The latter is not directly linked to traumatic memory, mainly characterized by high arousal, irritability, increased startle response, emotional numbness and social withdrawal. The two have different neurobiological foundations. PTSD is a clinical entity composed of a series of psychiatric symptoms. In basic research, researchers generally explore the neurobiological mechanisms of a "single" symptom through a single animal behavioral model. The most studied are the conditional fear memory model and the specific brain mechanism of the sensitized model.

4. Summary

An animal model of post-traumatic stress disorder requires not only the recording of the behavioral characteristics of post-traumatic stress disorder complexity, but also the factors that influence the experiment. These factors depend on the vulnerability or resilience of the individual to the injury, such as the effects of genetic susceptibility, early life experiences, and social factors. The study of PTSD is greatly limited due to the lack of suitable animal models. Its neurobiological pathogenesis research and clinical treatment are facing great difficulties. We need to explore further suitable PTSD animal models, and non-primate macaques may be a better choice.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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