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Establishment of Animal Models of Post-Traumatic Stress Disorder in Cynomolgus Monkeys and Behavioral and Neurophysiological Studies

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Abstract

Abstract: To establish an evaluation method for PTSD animal models of cynomolgus monkeys, and to explore the differences in neurophysiological indexes of PTSD cynomolgus monkeys such as cortisol, dopamine, brain-derived neurotrophic factor and serotonin in cynomolgus monkey PTSD.

Methods: Sixty adult female cynomolgus monkeys were selected and divided into control group (n=30) and experimental group (n=30) according to the random number table method. In the experimental group, the cynomolgus monkey PTSD experimental animal model was designed by claustrophobia + electrical stimulation. The two groups were detained in cage for 100 days, single cage feeding and cohabitation. Regularly observe and record the behavioral indicators of the two groups of animals, and pay attention to whether there is any trauma or disease. Venous blood was collected before, half, one, and three months of detention, and two groups of neurophysiological indicators were detected. All observations were tested for normal distribution before statistical analysis. If they were normal distribution, use independent sample t test or multi-sample ANOVA for statistical analysis. If the data is non-normally distributed, use nonparametric Wilcoxon rank sum test. Statistical analysis was performed with a significance level of $\alpha=0.05$. Result: Compared with the control group, the activity, curiosity and fear behavior time of the experimental group were significantly different, and the duration and frequency of stress behavior were different ($P<0.05$). The content of BDNF and 5-HT in the experimental group was decreased and the content was increased ($P<0.05$). In the experimental group, the BDNF content decreased gradually and the TNF-α content increased gradually with the prolongation of detention time (P<O. 05).

Results: Compared with the control group, the activity, curiosity and fear behavior, duration of stress behavior and frequency of cynomolgus monkeys in the experimental group were significantly different, $P<0.05$. The levels of corticosteroids and cortisol in the plasma of the experimental group were compared with the control group. The difference was significant ($P<0.05$ or $P<0.01$). The levels of BDNF and 5-HT in the experimental group were significantly lower than those in the control group, $P<0.05$. The TNF-α content in the experimental group gradually increased, which was also significantly different from the control group (P<O. 05).

Conclusion: Experimental cynomolgus monkeys are prone to psychological stress, resulting in persistent PTSD-like physiological and behavioral abnormalities, which are related to "traumatic" exposure and lack of social support; adrenal cortex hormones, cortisol and BDNF, 5-HT, NF-α levels The changes are related to the stress effects of the Hypothalamic-Pituitary-Adrenal (HPA) axis.

Keywords: Animal Model; Cynomolgus Monkey; Neurobiology; Post-Traumatic Stress Disorder

Introduction

For mental illness, animal models are critical for studying disease mechanisms and developing new treatments, especially given the limited availability of basic experiments in the human brain. These models must contain behaviors similar to human conditions, predictably responding to available clinical treatments, based on known (or strongly hypothetical) etiological factors, and molecularly consistent with human disease markers. Different types of models are generated to help understand the changing effects of persistence and traumatic exposure [1]. Increasing the predictability of Post-Traumatic Stress Disorder (PTSD) animal models requires active collaboration among scientists [2]. Modeling the modeling of post-traumatic stress disorder is challenging because it is a heterogeneous disorder with more than 20 symptoms [3]. Clinical research is increasingly using objective biological measures (such as imaging, peripheral biomarkers) or experimental reports of nonverbal or physiological responses. A more objective measurable phenotype to this transformation complements the existing PTSD animal model and supports the introduction of homologous measures between species by PTSD [4]. Most models reliably produce long-lasting, widespread anxiety-like or depression-like behavior, as well as fear of over activity. These paradigms lead to increased anxiety, exaggerated scares, cognitive impairment, increased fear conditioning, reduced social interactions, and changes in hormones associated with post-traumatic stress disorder [5]. There are still many animal models of post-traumatic stress disorder that have mimicked the limited aspects and effects of human conditions, which are produced in a very short time [6]. In addition, some models provide evidence of "wound" memory without demonstrating changes in anxiety levels [7], Excessive excitement and physiological symptoms are comparable to those observed in post-traumatic stress disorder [8]. What is unique about psychosocial predators? An animal model of post-traumatic stress disorder produces a series of physiological and behavioral changes similar to PTSD, in addition to memory "traumatic" exposure [9]. In addition, according to the current findings, at least some of the effects of our model persisted after 2 months of intense onset [10]. Therefore, our PTSD animal model can be used to study the mechanisms of multiple aspects of post-traumatic stress disorder [11].

PTSD investigators are increasingly using homologous biological measures to assess risk, response, and treatment markers in preclinical and clinical settings to bridge the gap between human and animal post-traumatic stress disorder studies and create A framework for biomarkers in animal models of post-traumatic stress disorder was found. Based on the above research status, an experimental animal model of PTSD functional stress non-human primate (cynomolgus monkey) was established in Hainan, and the corresponding animal behavior, physiological and biochemical, gene expression and other indicators were analyzed and studied, which was PTSD. This provides ideal experimental materials and theoretical basis for the study of the occurrence and development mechanism, diagnosis and treatment strategies of PTSD.

Materials and Methods

Animals and Grouping

From October 2016 to December 2017, Hainan Xinzhengyuan Biotechnology Co., Ltd. provided [numbered SCXK (Joan) 2011-0002] 60 adult cynomolgus monkeys (for ordinary animals, CV), male, there were 30 females with an average age of 48.63±3.46 and an average body weight of 5.04±2.36/kg. According to the random number table method, they were divided into 30 experimental groups (15 males and 15 females) with a monthly age of 49.25±2.26. The body weight was 4.85±3.24/kg; the control group was 30 (15 males and 15 female), the age was 50.08±1.04, and the average body weight was 5.09±2.04/kg. The cynomolgus monkeys were independently fed in stainless steel cages. The length of the stainless steel cage was 110×width 60×height 90/cm. The experimental group and the control group cohabited one room. The environmental conditions were the same, the standard feeding, drinking water at any time, and the surrounding companions kept visual and auditory. contact. The ambient temperature is maintained between 24-26°C and the humidity is between 45.45-50.60%. The experimental site was in the experimental building of Hainan Xinzhengyuan Biotechnology Co., Ltd. The care and use of the animals in this study was in line with the international and domestic animal experiment ethical principles and norms, and the experiment was approved by the Ethics Committee of Hainan Provincial People's Hospital.

Model Preparation

Preparation and behavioral observation of PTSD animal model: In order to overcome the shortcomings of the existing behavioral research methods on the "secondary interference stress response" of animals, the PTSD experimental animal model was made with reference to claustrophobia + electrical stimulation, using modern biosensing, high-tech electronic equipment, cameras, computers and other technologies. In the laboratory of sound, photoelectric shielding and strict environmental control, the animal's feeding behavior, conflict behavior, alert behavior, rest behavior, exercise behavior, etc. are monitored for a long time without interference. The whole record and preliminary statistical process are completely automated by computer. Control is complete. In the laboratory of sound, photoelectric shielding and strict environmental control, the animal's feeding behavior, conflict behavior, alert behavior, rest behavior, exercise behavior, etc. are monitored for a long time without interference. The whole

record and preliminary statistical process are completely automated by computer. In the preparation of cynomolgus monkey PTSD claustrophic + shock model, regulated DC power supply (0~30 V), manufacturer: LODESTAR, specification model: LP3005D. Special attention should be paid to the magnitude of the electric shock. After repeated experiments, the author chose 15 mA as the stimulation current, which is more difficult than the general stimulation current, which can cause the pain of the experimental cynomolgus monkey, but it does not reach the extent of harming the body of the experimental animal. And construct the behavioral spectrum of cynomolgus monkeys under the condition of electric stimulation: the symptoms of intrusion: mainly manifested as panic, blinking, aggressive, plucking, jumping, self-destructive behavior, and hip-hopping; avoidance symptoms: mainly manifested as Body cringe, eye depression, solitude, licking, scratching head, etc.; high alert symptoms: mainly manifested as nervousness, active attack, large activity, irritability, blinking, fear of people. Behavioral observation and recording: The average of each observation day is divided into four time periods of 30 minutes as a time interval. According to the pre-arranged observation plan, the observer observes the behavior of the individual individuals in each of the four observation periods on each observation day [12]. In order to obtain an average duration of various behaviors per time period and the activity pattern of caged cynomolgus monkeys in each observation period. The observations in behavioral observations mainly include social communication, eating, rest, anxiety and emotional attachment. On this basis, the changes in motor behavior of experimental animals were observed to determine whether the model was similar to the clinical manifestations of PTSD. The PTSD model of cynomolgus monkey was established and behavioral evaluation was performed. Venous blood was collected before detention, half-month, one month, and three months during detention. Cortisol, tumor necrosis factor, dopamine, brain-derived neurotrophic factor, serotonin was performed by Guangzhou Yongnuo Biotechnology Co., Ltd. And other biological indicators test and brain-derived neurotrophic factor gene dynamic analysis.

Data Processing and Analysis

All observations were tested for normal distribution before statistical analysis. If the data is normally distributed, use independent sample t test or multi-sample analysis of variance. If the displayed data is non-normal, use a nonparametric Wilcoxon rank sum test. Statistical analysis was performed with a significance level of α=0.05. Data analysis was performed using SPSS 22.0 software.

Results

The Decomposition of Abnormal Behavioral Factors in Cynomolgus Monkeys

Traumatic memory is a basic feature of post-traumatic and is a clinically basic manifestation of stress disorder (PTSD). The memory of traumatic events, as well as the sensory and emotional factors that occur during activities, such as invasive thinking, physiological over-excitement. The behavioral behavior of the PTSD animal model is stress state. The cynomolgus monkeys mainly show symptoms such as increased alertness, invasive re-experience and numbness (behavioral, morphological, and physiological) [13].Usually manifested as a number of abnormal behaviors, including back and forth pacing, swinging, plucking, jumping, body flipping, saluting, licking, scratching, self-holding, shaking, grinding, blowing; self-destructive behavior, including self-Bite (strongly biting your body parts, mainly legs, feet, inner thighs, fingers, genitals, tails, etc.), self-mutilation (the behavior of causing trauma with a head impacting a cage). In the PTSD symptom family, it is: short-distance movement: observe the individual's short-distance movement to avoid danger; alert jump-off: observe the individual to avoid danger, alertly jump to other safer positions; observe the companion: observe the individual Observing peers; alert calls: Observing individual alert calls, often when the breeder or veterinarian enters the cage; other barking: when the group is at rest, no one enters or leaves the cage, observing the individual involuntarily calling a few; : Observing an individual shaking a cage to demonstrate; Expelling: Observing an individual to drive away other individuals, common in the right to compete for food or mating; Attack: Observing an aggression between an individual and an individual, often in the fight for food and social anger; Escape: Observing an individual Escape from the competition for the environment, often fleeing with the weak; ears stand backwards: observing the individual's ears to stand backwards, often in preparation for an attack, is a demonstration; threat: observe individuals demonstrating to other individuals, including roaring, toothy or Open your mouth; be threatened: observe that an individual is threatened by other individuals; be attacked: observe that the individual is being Body attack; walking in parallel: walking parallel to other individuals; biting: observing the individual biting other individuals. Finally, the behavior of cynomolgus monkeys is classified as the symptoms of intrusion (number of times): blindness, blinking, aggressiveness, plucking, jumping, self-destructive behavior, hip-hopping, etc.; avoidance symptoms (number of times): body shrinking, eye depression,

solitude Highly alert symptoms (number of times): eye tension, active attack, large activity, incitement, blinking, fear of people, etc. There was a significant difference in the abnormal behavior of single-cage monkeys in the two groups ($P<0.05$). See Table 1 and Figure 1.

Group	Numbering	Intrusion symptoms (number of times)	Avoiding symptoms (number of times)	Highly alert symptoms (number of times)	Total
test group	1	8	4	11	23
	2	5	9	5	19
	3	3	12	8	23
	4	7	2	5	14
	5	6	2	10	18
	6	2	4	4	10
	7	4	8	5	17
	8	7	4	5	16
	9	2	2	6	10
	10	5	4	7	16
	11	7	3	2	12
	12	7	3	3	13
	13	6	5	7	18
	14	4	4	3	11
	15	7	3	2	12
	16	6	3	9	18
	17	5	5	8	18
	18	7	4	6	17
	19	8	6	5	19
	20	5	3	9	17
	21	9	4	7	20
	22	4	5	5	14
	23	5	7	7	19
	24	8	10	7	25
	25	9	4	7	20
	26	11	5	5	20
	27	6	4	4	14
	28	8	6	7	21
	29	9	3	8	20
	30	6	2	9	17

Control group	1	9	1	5	15
	2	5	6	3	14
	3	2	3	4	9
	4	4	3	3	10
	5	4	1	7	12
	6	2	5	9	16
	7	1	2	2	5
	8	3	3	4	10
	9	1	4	2	7
	10	2	2	5	9
	11	5	4	2	11
	12	4	2	5	11
	13	5	5	3	13
	14	4	2	6	12
	15	2	3	5	10
	16	3	5	3	11
	17	2	4	3	9
	18	4	4	2	10
	19	3	6	4	13
	20	1	2	3	6
	21	5	2	2	9
	22	4	3	2	9
	23	3	5	1	9
	24	5	3	5	13
	25	6	2	4	12
	26	3	2	3	10
	27	5	3	4	12
	28	2	4	6	12
	29	1	2	3	6
	30	1	3	5	9

Table 1: Abnormal behavior records of single-cage captivity in two groups of cynomolgus monkeys.

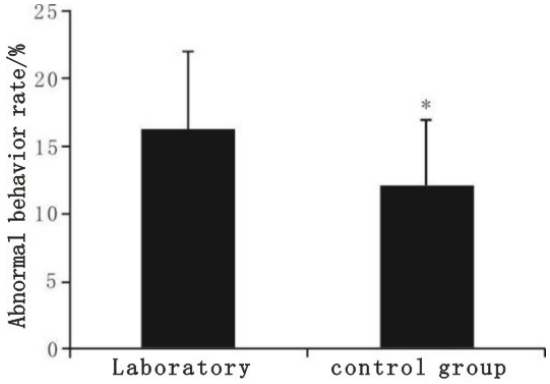

Figure 1: The effect of abnormal behavior of two groups of cynomolgus monkeys, compared with the control group, *p<0.05.

Comparison of Adrenal Cortex Hormone and Cortisol Levels in Venous Blood of Cynomolgus Monkeys and Comparison of BDNF, TNF-α and 5-HT levels

The cynomolgus monkeys were stimulated by claustrophobia and electrical stimulation, and the levels of plasma adrenocortical hormone and cortisol increased, and the difference was significant (P<0.05 or P<0.01). The results are shown in Table 2.

Numbering	time	Adrenal cortex hormone (pmol/L)	Cortisol (nmol/L)
test group (n=30)	Before detention	13.02±2.41	227.04±5.94
	Half a month	36.05±2.46	369.35±65.43
	1 month	36.59±6.33	489.50±90.58
	3 month	38.75±4.24	589.36±103.32
Control group (n=30)	Before detention	12.53±7.39	219.56±59.59
	Half a month	27.03±6.47**	267.32±57.36ΔΔ
	1 month	29.24±6.24**	274.48±74.37ΔΔ
	3 month	31.37±8.69**	277.61±46.97ΔΔ
Note: Compared with the experimental group, * indicates P < 0.05, ** indicates P < 0.01, compared with the experimental group, Δ indicates P < 0.05, and ΔΔ indicates P < 0.01.			

Table 2: Changes in plasma levels of adrenocortical hormone and cortisol in cynomolgus monkeys at different time points (n=60).

The levels of BDNF and 5-HT were decreased, and the level of TNF-α was increased. In the experimental group, the BDNF and 5-HT levels gradually decreased and the TNF-α content gradually increased with the prolongation of detention time. There were significant differences in TNF-α, BDNF and 5-HT (P<0.05 or P<0.01). The results are shown in Table 3.

Numbering	BDNF(μg/ml)					
	Before detention	**Half a month**	**1 month**	**3 month**	***F value***	***P value***
test group (n=30)	69.84±19.29	53.94±14.24*	42.01±12.53*	39.95±11.4*	26.258	0.000
Control group (n=30)	70.01±22.35	67.32±20.35*	68.32±21.57*	69.26±22.54*	0.086	0.967
Numbering	**TNF-α(μg/ml)**					
	Before detention	**Half a month**	**1 month**	**3 month**	***F value***	***P value***
test group (n=30)	98.37±28.86	124.3±32.35*	262.7±53.26*	265.3±51.48*	128.403	0.000
Control group (n=30)	102.38±30.25	104.44±31.62*	104.16±31.23*	103.62±1.34*	0.035	0.991
Numbering	**5-HT(ng/L^{-1})**					
	Before detention	**Half a month**	**1 month**	**3 month**	***F value***	***P value***
test group (n=30)	1674.54±432.35	1471.25±371.53*	1354.43±340.64*	1062.49±281.46*	15.078	0.000
Control group (n=30)	1646.24±404.03	1612.36±392.47*	1597.76±373.14*	1610.35±481.05*	0.075	0.973
* indicates that the experimental group and the control group were compared in the same period: P<0.05.						

Table 3: Comparison of BDNF, TNF-α and 5-HT levels in the two groups of cynomolgus monkeys (, n=60).

Analysis of BDNF, PKBI, GSK-3B, PRKCG Gene Polymorphisms in The Main Conduction Pathway of BDNF in Cynomolgus Monkeys

For BDNF in cynomolgus monkeys, specimen collection and preservation: 5 to 10 ml of blood was taken from the head vein of all the crabs in all studies., and EDTA was anticoagulated and sent to the Central Laboratory of Hainan Provincial People's Hospital, frozen at -20°C. Primer design: Primer Premier 5.0 primer design software was used to design BDNF gene primers; PCR amplification reaction: primer synthesis, PCR kit purchased from Shanghai Jierui Bioengineering Co., Ltd.; DNA sequencing: all rs6265, rs712444, rs2494746, rs6782799, The rs3745406 site PCR product was sent to Guangzhou Yongnuo Biotechnology Co., Ltd. for sequencing, using Hardy. The weinberg balance rule is used to test the genetic balance. The SPSSl7.O statistical software package was used for statistical analysis of unit points. The results showed no significant difference between the experimental group and the control group ($P>0.05$), which was consistent with the results of Guo Juncheng et al. [14].

Discussion

The non-human primate monkey is an ideal model animal with 98% homology with the human genome. It is highly similar to humans in terms of tissue structure, immunity, physiology and metabolism. Non-human primate monkeys can be the best. PTSD animal model [15]. The establishment of experimental animal models of PTSD functional stress non-human primate (cynomolgus monkey) and the evaluation of corresponding indicators provide ideal experimental materials and theoretical basis for the study of the mechanism and diagnosis of PTSD, diagnosis and treatment strategies [16]. A variety of PTSD animal devices have been established, and cynomolgus monkey PTSD can completely simulate the symptoms and pathological processes of clinical PTSD [17]. The device used in the test can be selected according to the purpose of the study to prepare a device for the cynomolgus monkey PTSD animal model. The cynomolgus monkey is placed in a closed iron cage surrounded by a conductive stainless steel fence. The cynomolgus monkey cannot escape the continuous current stimulation of the foot. The cynomolgus monkeys were restless in a small, confined, opaque small carton, and given random electrical stimulation. The cynomolgus monkeys showed behavioral behaviors such as biting and barking [18]. Repeatedly performing the above stress stimulation, a cynomolgus monkey PTSD experimental animal model with a significant change in behavior compared with the normal control group can be prepared in a relatively short period of time. In addition, the randomization of the stimulation interval can make the experimental animals unable to prepare psychologically for the next injury stimulus, which can increase the degree of panic in the experimental animals, which is similar to the clinical occurrence of PTSD. Psychological changes further affect physiological functions, causing a series of physiological and biochemical changes centered on the sympathetic adrenal system [19]. Brain-Derived Neurotrophic Factor (BDNF) is a neurotrophic protein. BDNF is distributed in a wide range of areas such as the central nervous system, peripheral nervous system, endocrine system, bone and cartilage tissue. During the development of the central nervous system, it plays an important role in the survival, differentiation and growth of neurons. Many scholars have shown that BDNF has a wide range of neurotrophic effects, which are related to the pathophysiology of phobia and anxiety. Brain-Derived Neurotrophic Factor (BDNF) is known to regulate neuronal survival, growth differentiation and synapse formation, and is associated with depression and Post-Traumatic Stress Disorder (PTSD) [20]. Experimental results BDNF and 5-HT levels are reduced, as a biomarker for the potential risk of post-traumatic stress disorder, BDNF is associated with its susceptibility to the onset of post-traumatic stress disorder. At the same time, our view suggests that 5-HT regulates BDNF expression in an acute psychologically stressed cynomolgus monkey model. Tumor necrosis factor TNF-α has a wide range of biological functions, and plays an important role in the regulation of immune-inflammatory coordination signaling networks as an important pro-inflammatory factor. TNF-α plays an important role in neuronal death [21]. Aggressive behavior is one of the most challenging symptoms in psychiatry, and aggressive biomarkers lack large sample validation. The results of this study showed an increase in TNF-α levels, suggesting an increase in stress levels in cynomolgus monkeys. Serotonin (5-HT) is an attack biomarker [22] Changes in fear perception and TNF-α levels in cynomolgus monkeys may be one of the mechanisms by which the central limbic system rewards loops to alleviate depressive symptoms [23]. Studies of the relationship between corticosteroids and cortisol and stress suggest that long-term elevated cortisol levels and dysregulated hypothalamic-pituitary-adrenal (HPA) axes appear to have an effect on static load and mental illness [24]. Studies have shown that elevated plasma levels of corticosteroids and cortisol affect the potential integrated neurobiological indications of cynomolgus monkey PTSD [25]. It is shown that when animals are exposed to stressors, their metabolic rate, energy expenditure and utilization are mainly increased by activating the Hypothalamic-Pituitary-Adrenal (HPA) axis [26]. Understanding the neurobiological mechanisms of Post-Traumatic Stress Disorder (PTSD) is critical for the development of biomarkers and more effective drugs for the treatment of this disease. Two-way transformation studies for all aspects of post-traumatic stress disorder need to be designed. Animal models of post-traumatic stress disorder need to capture not only the complexity of post-traumatic stress disorder behavior, but also the effects of various factors that may determine an individual's traumatic vulnerability or resilience, such as genetic susceptibility, Early life experiences and social support. The current review covers recent transformation methods to bridge

the gap between human and animal post-traumatic stress disorder research and to create a framework for discovering biomarkers and new therapies. The development, establishment and application of the experimental model affect the establishment and level of PTSD results to a certain extent. We will further explore the experiment. I believe that with the development of science and technology and the improvement of experimental conditions, the experimental animal model will be more ideal and reach the quantification criteria.

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