INPLASY PROTOCOL

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None declared.

The validity of chronic restraint stress for modeling depression in rodents: a Systematic Review and Meta-analysis

Mao, Y[1]; Xu, Y[2]; Yuan, X[3].

Review question / Objective: **The aim of the present study was to evaluate the depression-like behavior in rodents induced by CRS model by performing a meta-analysis of studies based on the results of the sucrose preference test.**
Eligibility criteria: **Enrolled studies in the meta-analysis satisfied the following criteria: (1) published in English; (2) reported as an original research; (3) reported the implementation of CRS protocols in rodents (mice or rats) lasting at least 1 week; (4) tested depressive-like behaviors including a sucrose preference test (calculated according to the following formula: % sucrose preference = [sucrose intake/total fluid intake] × 100); (5) provided the outcomes of SPT (%) in the text, figures or graphs; (6) used normal experimental animals that were wild-type and housed in a suitable environment. Studies were excluded from the meta-analysis if not meeting the above criteria at the same time.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 November 2021 and was last updated on 07 November 2021 (registration number INPLASY2021110024).

INTRODUCTION

Review question / Objective: **The aim of the present study was to evaluate the depression-like behavior in rodents induced by CRS model by performing a meta-analysis of studies based on the results of the sucrose preference test.**

Condition being studied: **Depression is currently ranking the top five leading causes of the global burden of disease, affecting 20% of the population worldwide.**

According to the World Health Organization, over 300 million people are suffering from major depressive disorder (MDD) worldwide . Depression is a mood disorder characterized by depressed mood, social isolation, anhedonia and feeling of worthlessness, badly influencing overall life quality and even endangering their lives through recurrent thoughts of suicide . Depression represents a chronic and recurrent psychiatric condition with varying symptoms among patients. Patients with chronic diseases have a higher risk of depression, which in turn discounts the recovery of chronic diseases and treatment compliance. Depression imposes not only a huge healthcare and economic challenge on the society, but also presents considerable social impacts. MDD is now the main risk factor of suicide-related deaths and is also the second leading cause of disability worldwide . Unfortunately, 30-50% patients suffering from depression are resistant to current antidepressant treatments . Stress, or psychological stress, is a reaction mode. When the human body is stimulated by external adverse factors, it will trigger stress reactions (anxiety, depression, fear and other adverse emotions). Chronic stress, also called long term stress, means that the stress process and the event that causes stress lasts longer . It has been recognized that the physiological response to chronic stress exposure works as a potent modulator of immune, endocrine and metabolic pathways . Chronic stress is a significant risk factor for the development of depression, leading to synaptic changes and depressive-like behaviors in rodents. Currently, chronic stress models is the most widely used animal model of depression. It is difficult to determine what the underlying mechanism might be in human studies. Instead, animal studies allow experimental induction of depression-relevant behaviors and permit deep investigation of molecular pathways. During the last 50 years, the great progress in elucidating the pathophysiology of depression has been attributable to the implementation of numerous animal models of depression . Most of the current knowledge about the mechanism underlying depression has come from animal models though none animal models can be entirely congruent with the human condition. Modeling depression in animals is vital for uncovering the mechanisms underlying depression. Chronic psychosocial stressors are well-known risk factor in humans for the development of depression. Systematic reviews and meta-analyses, as standard practices in clinical research, have been increasingly performed to validate preclinical studies of etiology, diagnosis and prognosis. In terms of animal experiments, it was estimated that approximately 50% of published results are not reproducible, named as “replication crisis” 2. However, fewer pooled analyses were conducted to evaluate the reliability and efficiency of results within basic life science research. Herein, the aim of the present study was to evaluate the depression-like behavior in rodents induced by CRS model by performing a meta-analysis of studies based on the results of the sucrose preference test.

METHODS

Participant or population: Enrolled studies in the meta-analysis satisfied the following criteria: (1) published in English; (2) reported as an original research; (3) reported the implementation of CRS protocols in rodents (mice or rats) lasting at least 1 week; (4) tested depressive-like behaviors including a sucrose preference test (calculated according to the following formula: % sucrose preference = [sucrose intake/total fluid intake] × 100); (5) provided the outcomes of SPT (%) in the text, figures or graphs; (6) used normal experimental animals that were wild-type and housed in a suitable environment. Studies were excluded from the meta-analysis if not meeting the above criteria at the same time.

Intervention: Chronic restraint stress for modeling depression.

Comparator: CUMS and CSDS model.

Study designs to be included: RCT.

Eligibility criteria: Enrolled studies in the meta-analysis satisfied the following criteria: (1) published in English; (2) reported as an original research; (3) reported the implementation of CRS protocols in rodents (mice or rats) lasting at least 1 week; (4) tested depressive-like behaviors including a sucrose preference test (calculated according to the following formula: % sucrose preference = [sucrose intake/total fluid intake] × 100); (5) provided the outcomes of SPT (%) in the text, figures or graphs; (6) used normal experimental animals that were wild-type and housed in a suitable environment. Studies were excluded from the meta-analysis if not meeting the above criteria at the same time.

Information sources: We comprehensively searched for potentially eligible studies published in PubMed, Embase, Medline and the Web of Science databases.

Main outcome(s): Fifty-seven studies in the enrolled 34 articles were involved in the pooled analysis including 7 species of rodents. Our pooled analysis demonstrated that there was a decreased sucrose preference in the stress group compared with the controls and that the duration of CRS differentially affected the depression validity of the animal model. Interstrain variability was identified, for instance the rats exhibit greater susceptibility to restraint stress compared to mouse strains.

Quality assessment / Risk of bias analysis: The Higgins I2 statistic was used to estimate the heterogeneity among the enrolled studies. This statistic represents the percentage of variation between studies ranging from 0% to 100%. P value ≤ 0.1 or I2 ≥ 50% indicates substantial statistical heterogeneity between studies. The publication bias was assessed using a funnel plot (a visual aid for detecting bias). The effect measure (log|SMD|) versus its precision (SE of log|SMD|) is plotted in the funnel plot. In the case of publication bias absence, the data of most studies are expected to be distributed in a funnel-shaped area in the plot.

Strategy of data synthesis: We evaluated the efficacy and stability of the CRS protocol to model depressive-like behavior based on sucrose preference test in model animals. Standardized mean difference (SMD) with 95% confidence interval was defined as the effect indicator, and a meta-analysis was performed by pooling mean sucrose preference (%), SD/SEM/SE of the mean and sample size 2 using Stata software version 11.1 (STATA Corporation, College Station, TX). The SMD is a measure of effect size, reflecting the degree of the outcomes of the stressed group differing from that of the controls (calculated according to the following formula: SMD = (M1 – M2) /SD, where M1-M2 is difference in means of the two groups, and SD is the pooled and weighted standard deviation) 2. A fixed-effect model was adopted in the pooled analysis. The results of the meta-analysis were displayed as forest plots.

Subgroup analysis: CRS model based on the sucrose preference test in C57BL/6J mice, Sprague-Dawley rats, Kunming mice, ICR mice, athymic nude mice, BALB/c mice was analysised.

Sensitivity analysis: We evaluated the efficacy and stability of the CRS protocol to model depressive-like behavior based on sucrose preference test in model animals. Standardized mean difference (SMD) with 95% confidence interval was defined as the effect indicator, and a meta-analysis was performed by pooling mean sucrose preference (%), SD/SEM/SE of the mean and sample size 2 using Stata software version 11.1 (STATA Corporation, College Station, TX). The SMD is a measure of effect size, reflecting the degree of the outcomes of the stressed group differing from that of the controls (calculated according to the following formula: SMD = (M1 – M2) /SD, where M1-M2 is difference in means of the two groups, and SD is the pooled and weighted standard deviation) 2. A fixed-effect model was adopted in the pooled analysis. The results of the meta-analysis were displayed as forest plots.

Country(ies) involved: China.

Keywords: depression; chronic restraint stress; sucrose preference; anhedonia; validity; meta-analysis.

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