Modelling post-stroke depression: a systematic review and meta-analysis of animal studies

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Background: Stroke is a global health problem affecting over 13 million people annually. While often overlooked, post-stroke depression is a common complication experienced by around one third of survivors. Post-stroke depression is associated with poorer rehabilitation outcomes, impaired quality of life and increased mortality rates. To better understand the complex pathology of post-stroke depression and develop more effective treatment strategies, robust animal models are required. Stress-based models including a chronic unpredictable mild stress paradigm and social isolation are commonly used to induce depressive-like behaviours in rodents. Several groups have used these models following cerebral ischaemia to specifically model post-stroke depression. However, there appears to be no consensus on which combination of models should be used and the methods for phenotyping depressive-like behaviours. The aim of this systematic review was therefore to explore which models and behavioural tests are most commonly used to study post-stroke depression.

Methods: We conducted a keywords literature search of PubMed and Ovid databases to identify relevant studies. Study characteristics including post-stroke depression model, species and age were extracted from the included studies. We assessed study quality and bias using a 10-point CAMARADES checklist.

Results: A total 46 studies were included in the systematic review. The vast majority used the transient middle cerebral artery occlusion (MCAO) model of stroke (n=30) and the unpredictable chronic mild stress model of depression (n=31). The sucrose preference test (n=41) followed by the forced swim test (n=19) were the most widely used tests for phenotyping depressive-like behaviours. The median score of the CAMARADES checklist was 5/10 (IQR 4-6). In particular, reporting of blinding and sample size calculations was low.

Conclusions: The unpredictable chronic mild stress model of depression and sucrose preference test, used by the majority of studies, have high validity. We recommend that these become standardised methods for modelling post-stroke depression. However, we did identify a need for improved study design and reporting in future research. An outstanding question is whether cerebral ischaemia alone induces a robust depressive-like phenotype. Our ongoing meta-analysis is investigating the effects of the addition of a depression model on depressive-like behaviours and lesion volume in stroke animals.