

Opportunities for improving animal welfare in rodent models of epilepsy and seizures

Animal models of epilepsy represent an important area for application of the 3Rs; with the potential for refinement of seizure induction, maintenance and monitoring. An expert working group to identify opportunities for refining rodent models of epilepsy and seizures was convened by the NC3Rs. The full report (Lidster et al., 2015) provides background information, practical guidance and recommendations, model-specific refinement opportunities and priorities for further research to facilitate refinement and best practice. Implementation of the recommendations could help to improve the quality of animal studies in epilepsy research and maximise the use of the animals.

The Working Group's recommendations are graded according to the highest levels of evidence: A: Appropriately designed, controlled trials, B: Case control or cohort studies C: Case reports, case series, D: Expert opinion, formal consensus.

A summary of the recommendations are provided below:

Choice of animal model

1. A search of the scientific literature should be carried out to ensure the animal model chosen is scientifically relevant, the least severe model for the scientific purpose, and that any model-specific refinement opportunities are identified (Grade D).
2. Assessment of the harms to animals and potential benefits of the research, should take account of the lifetime experience of the animals and the whole epilepsy syndrome (not just seizures) (Grade D).
3. Variations in the strain, genetic background, source, age and sex of animals can influence seizure susceptibility and mortality and should be taken into consideration when designing, conducting and reporting studies (Grade A/B).
4. Genetic background should be controlled for and appropriate littermate controls with the same genetic background should be used; for example, use age-matched wild-type littermates as controls (Grade A).
5. Consideration should be given to using animals of both sexes. If females are used, the impact of the oestrus cycle on seizure susceptibility needs to be considered (Grade A).

Induction procedures

6. Procedures leading to the induction of seizures and/or epilepsy should be tailored to reach the scientific objectives effectively whilst minimising harms and mortality (Grade D).
7. Research personnel should be adequately trained and competent in the manual skills for appropriate handling and restraint of animals for the administration of substances (Grade A).

In vivo recordings

8. The experimental setup should be maximally effective in delivering the research objectives while prioritising animal welfare and minimising interference with behaviour (Grade D).
9. Wherever possible, radiotelemetry should be used in preference to tethered systems for chronic electrophysiological recordings (Grade D).
10. Radiotelemetry devices should be as light as possible, consistent with the scientific objectives. Consideration should be given to the physiological conformation of the device and its potential impact on posture and natural behaviours (Grade C).
11. Good surgical practice and aseptic technique should be used, with pain management, maintenance of body temperature, replenishment of fluids lost under anaesthesia and effective post-operative care and consideration of antibiotic prophylaxis (Grade D).

Perioperative care

12. Animals should be allowed sufficient time to recover following surgical procedures using anaesthesia, before subsequent recordings/measurements are taken (Grade A).
13. Steps should be taken to identify, assess and alleviate pain following procedures requiring surgery and appropriate pain relief should be provided based on veterinary advice (Grade C).
14. Topical antibiotics should be used for simple surgical procedures and prophylactic antibiotics used for implantation procedures if appropriate based on veterinary advice (Grade D).
15. A modified food source should be provided to encourage eating and prevent weight loss following surgery and/or seizure induction (Grade A). This should be introduced prior to surgery to ensure familiarization and consumption. Food and drink should be accessible from the floor of the cage (Grade D).

Welfare assessment

16. Each animal model of epilepsy should be assessed and an appropriate welfare score sheet validated by both animal care staff and the principal investigator. The score sheet should define when action should be taken to minimise pain, suffering and/or distress by intervention/treatment and application of humane endpoints. Such scoring systems should incorporate both monitoring of actual model induction and monitoring of the resulting epileptic state (Grade D).
17. Animal welfare assessments should be conducted at a frequency appropriate to the state of well-being and health of the individual animal; at least on a daily basis and multiple times per day in the immediate post-operative recovery period or following specific interventions (Grade D).

Humane endpoints

18. A tailored approach should be adopted to assess, define and implement humane endpoints for each experiment in order to minimise harms, whilst allowing achievement of the scientific objectives (Grade C). This should take into consideration the current legal framework, scientific, justifiable and unpredicted endpoints and the results of welfare assessments.

Social housing

19. Mice and rats should be socially housed unless there are compelling scientific or animal health reasons for single housing (Grade A).
20. Animals should be paired or grouped prior to surgery to increase the social bond, thereby reducing the risk of adverse behaviour towards the operated or instrumented animal(s) (Grade D).
21. Socially housed animals should be monitored to identify signs of aggressive behaviour and the consumption of supporting supplementary food intended for the experimental animal (Grade A).

Environmental enrichment

22. Environmental enrichment should be provided to allow animals to express naturalistic behaviours unless there is a justified reason to withhold it (Grade A).
23. Environmental enrichment should be consistent in the home cage to reduce variability (Grade A). Enrichment protocols should be described carefully and detailed in published manuscripts to reduce inter-laboratory variations.

Reporting and data sharing

24. Researchers should report their animal studies in accordance with the ARRIVE guidelines. Journals publishing epilepsy and seizure studies should: a) include the guidelines in their Instruction to Authors; b) require authors to submit an ARRIVE checklist with their manuscripts; and c) encourage editors to review the checklist (Grade D).
25. Common Data Elements (CDE) should be prepared and used to help standardise the collection of data, including those relevant to animal welfare, and facilitate comparison of results (Grade D).
26. Researchers should take advantage of opportunities to make all research studies regardless of their findings openly available to reduce publication bias in epilepsy research (Grade A).
27. The refinement opportunities framework should be developed and used for each project as a tool for predicting, recognising and ameliorating suffering and assessing severity in the particular epilepsy model being used (Grade D).