What it is like to use animals in neurobiological research in the UK?

Why we need rats

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I'm a big fan of rodents. As a kid, I had two pet mice (called Pip and Marty). As a teenager, I had four Russian dwarf hamsters (Sex, Drugs, Rock and Roll) and, as a student, I had a couple of piebald rats (Chicken and Noodle). Now, as a neuroscientist at a UK university, I have a colony of rats with numbers instead of names. It's a dilemma that many researchers face: how to reconcile their empathy with animals with their desire to develop safe and effective therapies for diseases or injuries. It is ethically challenging: for 7 years, I was simultaneously a vegetarian and vivisector.

For some people, the use of animals in medical research is never justifiable. For others, the use of animals in medical research requires a pragmatic balance of costs and benefits. There is already an enormous body of thoughtful opinion on these positions, and rather than rehash these now, I recommend to you the excellent *The Animal Ethics Reader*, particularly section V on Animal Experimentation[1]. This outstanding book excerpts a wide spectrum of views, from anti-vivisectionists, through Rabbis, secular philosophers and to researchers using animals. Here, I will simply describe what it is like for me to use animals in stroke research in the UK.

What is a stroke?

The brain and spinal cord control every part of us, from breathing and moving, to thinking and feeling. This nervous system consumes an enormous amount of energy and oxygen, normally provided by an uninterrupted supply of blood. A 'stroke' occurs if this flow is interrupted – for example, by a blockage or a rupture within the brain. If this happens, then large numbers of cells begin to die within minutes, and disabilities can follow rapidly. For example, the ability to speak or move can be lost permanently, because dead neurons are not replaced.

Prevention is undoubtedly the best cure: risk factors for stroke include smoking, drinking, a high-fat diet and too little exercise. Although strokes largely affect older people, young people can have strokes also: a good friend of mine had a stroke while still a student. Adopting a healthy lifestyle is important because we don't have a cure for stroke: once you've had a stroke, rehabilitation may help, but in many cases you won't make a full recovery. In the UK and USA, stroke is the third greatest killer and the leading cause of disability, leaving millions disabled worldwide. My research aims to discover a method for reversing disability after stroke.

Working with animals

We don't fully understand what happens to the brain and spinal cord after a stroke happens: it's therefore not possible to simulate this completely on a computer or in a Petri dish. Here's one type of experiment that I do to understand strokes better. We buy rats that are 17 months old: based on their lifespan, we think they are similar in 'rat years' to a 70-year-old (stroke-prone) human. We temporarily put the rats to sleep using the same general anaesthetic that many veterinarians use. While they are unconscious, we use a tiny needle to inject a minute amount of drug into the brain which causes a small stroke in one area that controls precise forelimb movements. In a typical experiment, after stroke, we give each rat either an experimental therapy or a control therapy. This whole procedure takes about an hour. We then place the rat in an intensive care incubator, and give it pain relief medication. When the rats wake up, we put them back with their cagemates with free access to food and water.

You may be surprised to know that these 'focal' strokes are so small that you would not be able to distinguish rats with strokes from normal rats: the rats still move around apparently normally, and it requires a trained observer to detect the disability using special behavioural tests (e.g. watching how the rat grasps a banana-flavoured pellet or runs across a walkway). Our ultimate goal is to see whether we can find a therapy which reverses these disabilities in rats, and then (one day) to see whether we can reverse disabilities in humans after stroke. After several months of behavioural testing, we also need to examine the rat nervous system *post mortem*. To do this, I put the rat to sleep permanently using the same drugs as a veterinarian would. We do all our measurements and analyses blind (so that we do not know which rat received which treatment): at the end of the experiment, we break the code and determine whether the rats receiving the experimental therapy improve significantly relative to those

A white Wistar laboratory rat

receiving the control therapy. I'm happy to say we have some very promising results, but much more work remains to be done.

Who checks how I use animals?

In the UK, use of animals in medical research is heavily regulated by legislation and is continuously monitored by the Home Office. There are many levels of monitoring. First of all, scientists have to work at an approved institution: this ensures that facilities for animal housing and surgery meet required standards. Secondly, a leading experienced scientist must apply to the Home Office for a Project Licence that describes the work to be carried out, and justifies the impact on animals in terms of the possible benefits to society. These applications are also assessed at our university by an ethical review board. Third, each scientist has to apply to the Home Office for a Personal Licence to work with animals. The Licence states in advance what procedures they intend to carry out, and a sponsor agrees to ensure that the applicant receives sufficient training to be proficient at these procedures. Furthermore, there are a number of people who advise scientists on matters of animal welfare. We have specialist animal technicians who independently check the welfare of the animals on a daily basis. We also have a vet and a Named Animal Care and Welfare Officer (NACWO) who monitor our animal work and help us optimize the welfare of the animals that we use.

How can we improve how we use animals?

When designing and carrying out experiments, scientists are guided by the 'three Rs': Replacement, Refinement, and Reduction. These principles are so important that there is now a National Centre for the Replacement, Refinement and Reduction of animals in research[2]. I'll give some examples from my work as to how these principles can be implemented.

Replacement

We try *not* to use animals wherever possible. Indeed, it is often expensive and time consuming to use animals in research: scientists usually have to win their own funding in order to pay their staff, rent their laboratories, maintain their equipment and buy reagents. Funding institutions like the Medical Research Council ask scientists to provide written justification of any proposed work involving animals. For example, I'm currently applying for a grant from the Wellcome Trust and they require me to explain: "Why is animal use necessary: are there any other possible approaches?". Accordingly, scientists use alternatives to animals wherever feasible (e.g. we use Petri dishes of self-renewing human cells during development of some of our potential therapies).

Refinement

My group is always looking for ways to improve the standards of care for our rats by refining our procedures. We chose early on to induce small focal strokes in rats rather than large strokes that cause substantial disability and we always give anaesthetics during surgery and pain relief (analgesics) after surgery. Recently we have begun housing most of our rats in small colonies in 'environmentally-enriched' housing rather than as pairs: we provide larger cages, ramps, levels and wheels. We are also going to improve our facilities to allow monitoring of additional physiological parameters (e.g. pulse rate and blood oxygen) during surgery.

Reduction

In my current application to the Wellcome Trust for a grant, I have to explain the design of my proposed experiments, including "the case for the number of animals required". They remind me that "any research that might be carried out that leads to a reduction in the number of animals used is encouraged..." One way that I reduce the numbers of rats that I use is by using each rat for multiple purposes. For example, I can assess recovery of function in each rat using five different behavioural tests, rather than using five different rats for each test. I can also measure each rat longitudinally (e.g. weekly) after stroke and use special statistical methods to reveal the changes over time in the pattern of recovery: a good understanding of statistics helps researchers use fewer animals and get better results. I also examine the brain and spinal cord of each rat at post mortem. These and other measures allow me to reduce the number of animals that I use: a recent successful therapy-testing experiment lasting 6 months used only 15 rats per group, with three groups in total.

Summary

Careful use of animals has already helped us discover treatments for various diseases and injuries. Researchers continue to explore ways to improve the ways in which they use animals for medical research, using the three Rs as guidance. In this way, we hope to develop new, safe and effective therapies for various diseases and injuries. ■

References

1. Armstrong, S.J. and Botzler, R.G. (eds.) (2003) The Animal Ethics Reader, Routledge, London
2. www.nc3rs.org.uk