Too stressed to work

Scientists must provide lab animals with decent living conditions or accept that their results could be useless, say **Ann Baldwin** and **Marc Bekoff**

MEDICAL and biological research relies heavily on studies of lab animals such as mice and rats. These are often inbred genetic strains, and are kept in "standard" cages so that different groups can be compared – animals missing a particular gene are compared with those that don't, for example, or animals given a drug with those that aren't.

But there is one confounding factor where researchers appear to have a blind spot – stress. Scientists seem to think that as long as animals are kept in roughly comparable conditions, experiments on them will produce meaningful results. In fact evidence is mounting that the standard lab conditions are stressful enough to affect the animals' physiology, and enough so to swamp the effects of an experimental perturbation or drug.

Comparing results where stress isn't taken into account is therefore meaningless. What's more, even if all animals were kept under equally stressful conditions, the results of experiments may still bear little or no relation to those that would be obtained with healthy animals.

Anyone who has had pet mice and rats knows how much they love to climb, burrow and run around in wheels. Yet lab rodents, unless they are being used in behavioural studies, are usually housed in small empty cages, with bedding if they are lucky. Studies show that rodents housed in standard cages in busy facilities show signs of emotional stress, such as excessive grooming, aggression and stereotypic behaviours such as jumping repeatedly or gnawing at their bars (*Trends in Neurosciences*, vol 24, p 207).

Males in particular will spend much of their time fighting if kept in these conditions. However, if they are given a couple of simple diversions, such as a perspex tube and a shelf, the fighting disappears. If you ask investigators about their rodents' behaviour they will usually answer, "Oh no, my rats don't fight." But most tests are done during the day, when these nocturnal animals are fast asleep, so researchers are unlikely to find them fighting.

The problem is more than behavioural. We know that the animals' physiology is affected; rats housed in such conditions show an inflammatory response in their intestines accompanied by leaky blood vessels (*Microcirculation*, vol 5, p 299 and vol 6, p 189). As a result, the gut's defence barrier breaks down, leading to chronic inflammatory conditions such as "leaky gut". This inflammation adds uncontrolled variables to experiments on these animals, confounding the data. Moreover, we now know that mice display empathy (*Science*, vol 312, p 1967), so stress experienced by one animal can affect others too.

We are also starting to realise that noise is a major source of stress for lab animals. Animal facilities can be incredibly loud places, with sound levels often reaching between 90 and 100 decibels (*Physiology and Behaviour*, vol 53, p 1067). To put this into context, 95 dB is comparable to a subway train, and a jackhammer is about 110 dB. Labs are much quieter at weekends, suggesting that much of the noise is caused by researchers as they work.

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Recent studies show that noise affects the animals' physiology. For example, noise levels of 90 dB increase rodent heart rate and blood pressure (*Journal of Applied Animal Welfare Science*, vol 9, p 179), cause leaky gut and damage small blood vessels (*Journal of the American Association for Laboratory Animal Science*, vol 45, p 74 and vol 46, p 58). Yet many scientists involved in animal research are unaware that loud noise might affect their results (*JAALAS*, vol 46, p 38).

For anyone still not convinced, we believe another recent study clinches the argument. It involves one of the most clear-cut types of animal study, comparing healthy animals with those that have a genetic mutation. In this case, mice missing the gene for a protein called fibulin-4 were found to have defects in their aortas. Yet when the mice were housed in relatively large cages with a shelf, tunnel and wheel, rather than in small, empty cages, those defects almost disappeared (*PLoS ONE*, vol 2, e229). It shows that lab animals' environmental conditions can completely change the results of a genetic study. This too seems to have fallen on deaf ears since it was published in February.

More work is needed, of course, and you could argue that in some cases studies on animals with different levels of stress might be necessary to tease out the subtle effects of particular mutations. Even so, the overall message is clear: stress is significantly affecting the physiology of lab animals and the results we obtain from them.

There are already animal welfare grounds for reducing the stress that lab animals experience, but now there is also a strong scientific argument that researchers need to change their mindset. If we are going to use rodents as models to test drugs or provide us with reliable scientific data, we must give the emotional state of these animals serious consideration. ●

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