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Comfortable Mice Make Better Science

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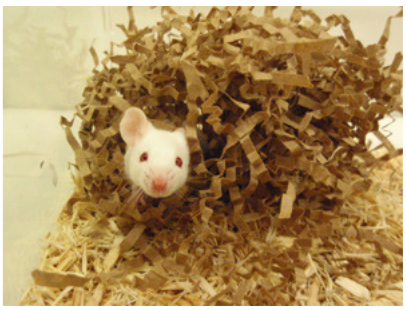
Nine out of 10 drugs successfully tested in mice and other animal models ultimately fail to work in people, and one reason may be traced back to a common fact of life for laboratory mice: they're cold, according to a researcher at the Stanford Univ. School of Medicine.



Joseph Garner and his collaborators found that giving lab mice nesting materials helps them naturally regulate their body temperatures at comfortable levels. *Courtesy of Brianna Gaskill*

Laboratory mice, who account for the vast majority of animal research subjects, are routinely housed in chilly conditions, which may affect their well-being as well as the outcome of research studies, said Joseph Garner, associate professor of comparative medicine.

"If you want to design a drug that will help a patient in the hospital, you cannot reasonably do that in animals that are cold-stressed and are compensating with an elevated metabolic rate," Garner says. "This will change all aspects of their physiology such as how fast the liver breaks down a drug — which can't help but increase the chance that a drug will behave differently in mice and in humans."

In a new study, Garner and his colleagues report finding an easy solution to the problem: Simply provide the animals with the proper materials, and they'll build a cozy nest that allows them to naturally regulate their temperatures to a comfortable level. These thermally content mice would be more physiologically comparable to humans and thus might serve as more meaningful research subjects, Garner said.

"Why not let them do what they do in the wild, which is build nests? Mice can happily infest a meat freezer, with temperatures far below zero, but they survive and breed because they build these wonderful nests," he says.

The study, part of nearly seven years of work with mouse nesting behavior, is the first to "ask" mice to rate the value of nesting material in terms of temperature savings, which is an important first step in setting standards for nesting material, said Garner, whose work has focused on the well-being of the mouse. He is the senior author of the study, which was published online in *PLoS ONE*.

Mice, which Garner calls “one of the most fantastic animals on Earth,” have evolved in the same environment as humans for thousands of years, making them remarkably adaptable, able to live virtually anywhere. For that reason, they make excellent research subjects, with hundreds of millions of them populating laboratories around the world.

Given the option, mice gravitate to temperatures of between 30 and 32° Celsius (the equivalent of about 86 and 90° Fahrenheit). But based on federal regulations, U.S. research laboratories are routinely kept on the cold side — between 20 to 24°C. There can be advantages to these cold temperatures. For instance, mice have aggressive tendencies that are suppressed in cooler climes. Female mice also lactate better in cooler temperatures, though their pups don’t do as well in the cold.

When kept in temperatures toward the low end of this scale — between about 18 and 20°C (64-68°F) — the mice begin to show changes in immune function and their growth may be retarded. “So we’re housing them right at that threshold,” Garner says. “That means the mice may be compromised physiologically, potentially affecting research results.”

Simply raising the temperature in the lab isn’t an option, not least because the mice would then become unmanageably aggressive, he said. Rather, Garner and his colleagues looked to other options in their study, which involved 36 male and 36 female mice of three common strains. The researchers created sets of two cages linked by a small tube so the mice could move between them. One cage in each set was maintained at a chilly 20°C (68°F) and was equipped with varying quantities of shredded paper, which the animals could use to construct nests for shelter and warmth. The other cage was kept at one of six temperatures: 20, 23, 26, 29, 32 or 35°C (68, 73, 79, 84, 90 or 95°F), but without nesting material.

The mice then had the choice of staying put and tolerating the cold, choosing a balmier cage, eating more to add fat and elevate metabolic rate, or building a nest.

Each strain and sex had slightly different preferences, the researchers found. None was content to simply sit out the cold, either moving to a toastier location, if available, or building elaborate, dome-like nests to warm themselves. The more nest-building material they had, the more they were willing to settle for a cooler clime, as the nests served to temper the chill, the researchers found.

In fact, the nest-building drive was so strong that the mice often would spend hours collecting strands of paper, bit by bit, from the chilliest cage and then transporting it to a more comfortable spot in another cage to build a sturdy little home.

Garner said these mice decided they wanted to have it all, choosing a warm spot and building a nest as well. “Naughty little rascals” is how he described them. “They would go on holiday somewhere warm AND take their nest with them,” he says. “Some people like to take a pillow on holiday and some don’t. These mice were packing their own pillow.”

The fact that some mice moved nesting material to the warmer cage means that the nests serve a function beyond warmth, argued Garner, perhaps providing physical comfort, or a form of protection that decreases the animals’ anxiety and stress levels.

The nest-building mice tended to eat less, as they didn’t need the extra calories to satisfy their higher metabolic demands, the researchers found. In general, the females preferred warmer temperatures than the males -- by about 5 degrees: they are smaller and have less fat to generate heat.

The researchers concluded that the mice could manage with 6 grams of nesting material but sometimes could use as much as 10 grams, suggesting the larger amount be supplied routinely in research labs.

Another benefit of the nests is that they facilitate researchers’ work with the mice — it’s easier to pick them up as well as observe them. “The shape of the nest tells an experienced person whether the animals are too hot or too cold, whether they are sick or whether they are about to give birth,” Garner says. “Once you learn how to ‘speak mouse nest,’ the nest is a wonderful tool that anyone can use to assess the general state of the mouse.”

The study’s first author is Brianna Gaskill, at the Charles River Laboratories. Garner and Gaskill collaborated with colleagues at the Univ. of Calgary, Purdue Univ. and the Environmental Protection Agency.

Source: Stanford Univ., Ruthann Richter