Fearful memories haunt mouse descendants

Genetic imprint from traumatic experiences carries through at least two generations.

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01 December 2013

Action Press/Rex Features

Mouse pups — and even the offspring's offspring — can inherit a fearful association of a certain smell with pain, even if they have not experienced the pain themselves, and without the need for genetic mutations.

Certain fears can be inherited through the generations, a provocative study of mice reports[1]. The authors suggest that a similar phenomenon could influence anxiety and addiction in humans. But some researchers are sceptical of the findings because a biological mechanism that explains the phenomenon has not been identified.

According to convention, the genetic sequences contained in DNA are the only way to transmit biological information across generations. Random DNA mutations, when beneficial, enable organisms to adapt to changing conditions, but this process typically occurs slowly over many generations.

Yet some studies have hinted that environmental factors can influence biology more rapidly through 'epigenetic' modifications, which alter the expression of genes, but not their actual nucleotide sequence. For instance, children who were conceived during a harsh wartime famine in the Netherlands in the 1940s are at increased risk of diabetes, heart disease and other conditions — possibly because of epigenetic alterations to genes involved in these diseases[2]. Yet although epigenetic modifications are known to be important for processes such as development and the inactivation of one copy of the X-chromsome in females, their role in the inheritance of behaviour is still controversial.

Kerry Ressler, a neurobiologist and psychiatrist at Emory University in Atlanta, Georgia, and a co-author of the latest study, became interested in epigenetic inheritance after working with poor people living in inner cities, where cycles of drug addiction, neuropsychiatric illness and other problems often seem to recur in parents and their children. “There are a lot of anecdotes to suggest that there’s intergenerational transfer of risk, and that it’s hard to break that cycle,” he says.

Heritable traits

Studying the biological basis for those effects in humans would be difficult. So Ressler and his colleague Brian Dias opted to study epigenetic inheritance in laboratory mice trained to fear the smell of acetophenone, a chemical the scent of which has been compared to those of cherries and almonds. He and Dias wafted the scent around a small chamber, while giving small electric shocks to male mice. The animals eventually learned to associate the scent with pain, shuddering in the presence of acetophenone even without a shock.

This reaction was passed on to their pups, Dias and Ressler report today in *Nature Neuroscience*[1]. Despite never having encountered acetophenone in their lives, the offspring exhibited increased sensitivity when introduced to its smell, shuddering more markedly in its presence compared with the descendants of mice that had been conditioned to be startled by a different smell or that had gone

through no such conditioning. A third generation of mice — the 'grandchildren' — also inherited this reaction, as did mice conceived through *in vitro* fertilization with sperm from males sensitized to acetophenone. Similar experiments showed that the response can also be transmitted down from the mother.

These responses were paired with changes to the brain structures that process odours. The mice sensitized to acetophenone, as well as their descendants, had more neurons that produce a receptor protein known to detect the odour compared with control mice and their progeny. Structures that receive signals from the acetophenone-detecting neurons and send smell signals to other parts of the brain (such as those involved in processing fear) were also bigger.

The researchers propose that DNA methylation — a reversible chemical modification to DNA that typically blocks transcription of a gene without altering its sequence — explains the inherited effect. In the fearful mice, the acetophenone-sensing gene of sperm cells had fewer methylation marks, which could have led to greater expression of the odorant-receptor gene during development.

But how the association of smell with pain influences sperm remains a mystery. Ressler notes that sperm cells themselves express odorant receptor proteins, and that some odorants find their way into the bloodstream, offering a potential mechanism, as do small, blood-borne fragments of RNA known as microRNAs, that control gene expression.

Contentious findings

Predictably, the study has divided researchers. “The overwhelming response has been 'Wow! But how the hell is it happening?'" says Dias. David Sweatt, a neurobiologist at the University of Alabama at Birmingham who was not involved in the work, calls it “the most rigorous and convincing set of studies published to date demonstrating acquired transgenerational epigenetic effects in a laboratory model".

However, Timothy Bestor, a molecular biologist at Columbia University in New York who studies epigenetic modifications, is incredulous. DNA methylation is unlikely to influence the production of the protein that detects acetophenone, he says. Most genes known to be controlled by methylation have these modifications in a region called the promoter, which precedes the gene in the DNA sequence. But the acetophenone-detecting gene does not contain nucleotides in this region that can be methylated, Bestor says. "The claims they make are so extreme they kind of violate the principle that extraordinary claims require extraordinary proof,” he adds.

Tracy Bale, a neuroscientist at the University of Pennsylvania in Philadelphia, says that researchers need to “determine the piece that links Dad's experience with specific signals capable of producing changes in epigenetic marks in the germ cell, and how these are maintained”.

“It's pretty unnerving to think that our germ cells could be so plastic and dynamic in response to changes in the environment,” she says.

Humans inherit epigenetic alterations that influence behaviour, too, Ressler suspects. A parent’s anxiety, he speculates, could influence later generations through epigenetic modifications to receptors for stress hormones. But Ressler and Dias are not sure how to prove the case, and they plan to focus on lab animals for the time being.

The researchers now want to determine for how many generations the sensitivity to acetophenone lasts, and whether that response can be eliminated. Scepticism that the inheritance mechanism is real will likely persist, Ressler says, “until someone can really explain it in a molecular way”, says Ressler. “Unfortunately, it’s probably going to be complicated and it’s probably going to take a while.”

Nature | doi:10.1038/nature.2013.14272

References

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2. Heijmans, B. T. *et al. Proc. Natl Acad. Sci. USA* **105**, 17046–17049 (2008).