How does day length affect aggression in mice? It's in the genes

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Imagine if a naturally occurring chemical in your body could help make you feel more calm and relaxed – but it would only work during the long days of summer. The same chemical would, instead, make you aggressive and nasty when you were exposed to less daylight during the winter.

That's exactly what occurs for a specific species of mouse, according to a new study at Ohio State University, published online this week in the *Proceedings of the National Academy of Sciences*.

Researchers found that the class of hormones called estrogens acts to increase aggression in the Oldfield Mouse (Peromyscus polionotus) during the short days of winter. However, when daylight increases in the summer, estrogen decreases aggression among male Oldfield mice, a species commonly found in the southeastern United States.

The finding is significant because it is one of the first studies to show how a very simple environmental factor – in this case, the length of daylight – can have a powerful effect on how genes influence behavior, at least in some species.

"We found that estrogen has totally opposite effects on behavior in these mice depending only on how much light they got each day," said Brian Trainor, co-author of the study and postdoctoral fellow in psychology and neuroscience at Ohio State University.

"It is quite a surprising finding."

While other studies have examined how environment interacts with genes to influence behavior, most of these studies have examined very complex environmental conditions, said Randy Nelson, co-author and professor of psychology and neuroscience at Ohio State.

"We're looking at a very simple environmental factor influencing a complex behavior," Nelson said. "In these mice, day length controls the gene expression that influences aggression."

In one study, male mice were castrated to stop production of testosterone. They then were fitted with implants that controlled their testosterone levels. The males were then treated with a drug which halts the production of estrogen. The same type of drug is commonly used to treat estrogen-dependent breast cancer.

In mice facing short days (limited daylight as in winter), the drug's halting of estrogen production made the normally aggressive mice less aggressive.

In mice kept in long-day conditions (as in summer), the normally docile mice were more aggressive. This showed the researchers that estrogen was indeed controlling levels of aggression in these mice.

But the studies went further and identified the mechanisms that may underlie how the length of daylight affects the way estrogen works to either increase or decrease aggression.

"It is well known that genes interact with the environment, but scientists often don't understand how this works on the molecular level," Trainor said. "We wanted to find out more about how this interaction happens in mice."

In one study, they looked at how day length interacted with two types of receptors in parts of the brain that affect aggression – estrogen receptor alpha and estrogen receptor beta. These receptors are like docking stations that send signals from the estrogen molecules into the cells.

A previous study suggested that one type of receptor was important in short days, and the another receptor in long days. If true, it could help explain why estrogen could make mice more aggressive in winter, and less aggressive in summer.

To test this theory, Nelson and Trainor treated one group of mice with an estrogen-like drug which attaches primarily to estrogen receptor alpha and treated another group of mice with a different estrogen-like drug that attaches primarily to estrogen receptor beta.

The results showed that the alpha receptor played a key role in increasing aggression in short days and decreasing aggression in long days. Surprisingly, the beta receptor had identical effects on behavior, increasing aggression in short days and decreasing aggression in long days.

"So the differences in how estrogen affected behavior in long days compared to short days could not be explained by the hormone using different receptors in different times of year," Trainor said. "That was really important."

So how did estrogen have opposite behavioral effects depending on seasonal light conditions"

The researchers had another idea that would use microarrays -- small computer chips that examine thousands of genes at the same time to see which ones are active. They compared genes from mice living in winter-like short days with those living under longer day lengths. The results

showed that certain genes associated with estrogen were more active in the long-day mice than in the short-day mice.

That suggested that estrogen works in mice living in long days through these specific genes, creating a genomic pathway leading to less aggressive behaviors, Trainor said.

The flip side of this finding is that estrogen increases aggression in short-day mice through different cellular mechanisms not involving genomic pathways.

While it would be difficult to test that hypothesis directly, neuroscientists know that when hormones work through genomic pathways, behavioral effects can take hours, days or even weeks to occur. But neuroscientists believe that when hormones send messages to cells outside of this gene-controlled network, behavior can change in mere minutes.

So in another study, the researchers injected short-day and long-day mice with estradiol, a type of estrogen. The findings showed that the injection increased aggression in mice in winter-like short days almost immediately. It had no noticeable immediate behavioral effect on the mice living in longer day lengths.

Overall, then, these studies showed estrogen increases aggression in short-day mice by working through non-genomic pathways in the brain, but the hormone decreases aggression in long-day mice through genomic pathways.

"In the vast majority of cases, hormones seem to affect behavior by working through genomic pathways, so it is always interesting when you find something different," Nelson said.

"This seems to be one of those instances where estrogen is working in a different way in long-day mice. But there is a lot more work to be done to understand this."

These findings have many implications for humans, according to the researchers. For one, they suggest more work needs to be done to determine the role estrogen plays in aggression in humans. In general, estrogen works to inhibit aggression in humans, but this study suggests research needs to look more at the role of estrogen receptors in some parts of the brain, Nelson said.

Also, scientists are very interested in understanding how estrogen works at the molecular level in humans, especially its role in promoting cancer.

"A lot of the research looks at how genes and hormones work in a controlled environment outside the body. But this study shows that the environment can play a very significant role in how estrogen reacts in mice," Trainor said.

"If something as simple as the length of day can affect how estrogen is used in the body, at least in some species, how are other environmental factors such as diet affecting estrogen in humans" It is something we don't know enough about."

The study is also important because it is one of the few that has shown how hormones other than testosterone can affect aggression in mammals.

"This goes against the common belief that testosterone is the hormone that regulates aggression," Nelson said. "There are now several studies showing that in some species estrogen plays a key role in aggressiveness as well."

Source: Ohio State University