Changing Length of Days Reverses How Estrogen Affects Aggressiveness in Mice

October 18 2006

New research shows how simply varying the length of daylight to which mice are exposed to can change how aggressively they react to other mice. The study found that in the short days of winter, the class of hormones called estrogens acts to increase aggression in males of a particular type of mouse called the Oldfield Mouse (Peromyscus polionotus).

However, in the long days of summer, estrogen decreases aggression among male Oldfield mice, a species commonly found in the southeastern United States.

“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.”

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,” said Randy Nelson, co-author and professor of psychology and neuroscience at Ohio State. “There are now several studies showing that in some species estrogen plays a key role in aggressiveness as well."

While this research has just begun, the findings could have broad implications in humans, for issues such as aggression and the role of estrogen in promoting cancer, Trainor said.

Nelson and Trainer presented their results Oct. 18 in Atlanta at the annual meeting of the Society for Neuroscience.

A major finding of this study was that the length of exposure to daylight affected how estrogen interacted – or didn't interact – with genes in the brains of mice that regulated aggression.

"Typically, when scientists talk about a gene-environment interaction, they are talking about a very complicated environment," Nelson said.

"But here we have a very simple environmental factor, the hours of light in day, that causes a dramatic change in how genes influence behavior."

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

In mice housed in short days (limited daylight as in winter), the drug halting estrogen production made the normally aggressive mice less aggressive. In mice kept in long day length conditions (as in summer), the normally docile mice were more aggressive. This showed that estrogen was indeed controlling levels of aggression in these mice.

But the researchers 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 takes place 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.

One hypothesis had been that one type of receptor was important in winter-like short days, and the other receptor in summer-like long days – which could help begin to explain why estrogen could make mice more aggressive in winter, and less aggressive in summer.

To investigate whether this theory was true, Nelson and Trainor conducted an experiment in which they injected mice with an estrogen-like drug which attaches almost exclusively to estrogen receptor alpha, to see how it would affect aggression.

The results showed that the alpha receptor played a key role in 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.

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

The researchers generated another hypothesis by using microarrays, small chips that examine thousands of genes at a 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 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 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 on this.”

These findings have many implications for humans, according to the researchers. For one, it suggests 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.”

Source: Ohio State University