MedicalXpress

At last, a reason why stress causes DNA damage

August 21 2011

For years, researchers have published papers that associate chronic stress with chromosomal damage.

Now researchers at Duke University Medical Center have discovered a mechanism that helps to explain the stress response in terms of DNA damage.

"We believe this paper is the first to propose a specific mechanism through which a hallmark of chronic stress, elevated adrenaline, could eventually cause DNA damage that is detectable," said senior author Robert J. Lefkowitz, M.D., James B. Duke Professor of Medicine and Biochemistry and a Howard Hughes Medical Institute (HHMI) investigator at Duke University Medical Center.

The paper was published in the Aug. 21 online issue of *Nature*.

In the study, mice were infused with an adrenaline-like compound that works through a receptor called the beta adrenergic receptor that Lefkowitz has studied for many years. The scientists found that this model of chronic stress triggered certain biological pathways that ultimately resulted in accumulation of DNA damage.

"This could give us a plausible explanation of how chronic stress may lead to a variety of human conditions and disorders, which range from merely cosmetic, like graying hair, to life-threatening disorders like malignancies," Lefkowitz said.

P53 is a tumor suppressor protein and is considered a "guardian of the genome" – one that prevents genomic abnormalities.

"The study showed that chronic stress leads to prolonged lowering of p53 levels," said Makoto Hara, Ph.D., a postdoctoral fellow in the Lefkowitz laboratory. "We hypothesize that this is the reason for the chromosomal irregularities we found in these chronically stressed mice."

Lefkowitz earlier had proved the existence of isolated, and characterized the G-protein-coupled receptors (GPCRs) such as the beta adrenergic receptor. These receptors, which are located on the surface of the membranes that surround cells, are the targets of almost half of the drugs on the market today, including beta blockers for heart disease, antihistamines and ulcer medications.

Now he is continuing studies along another pathway,stemming from the GPCRs, that was discovered in his lab, which is known as the beta-arrestin pathway. At first, the theory was that beta-arrestin proteins turned off or desensitized the G-protein pathways, but evidence is accumulating that these proteins are also responsible for causing certain biochemical activities in their own right.

In the current study, the scientists found a molecular mechanism through which adrenaline-like compounds acted through both G-protein and the beta-arrestin pathways to trigger DNA damage.

The Nature publication showed that the infusion of an adrenaline-like compound for four weeks in the mice caused degradation of p53, which was present in lower levels over time.

The study also showed that the DNA damage was prevented in mice lacking beta-arrestin 1. Loss of beta-arrestin 1 stabilized cellular levels of p53 both in the thymus, an organ that strongly responds to acute or

chronic stress, and in the testes, where paternal stress might affect an offspring's genome.

Future studies planned by the Lefkowitz laboratory include studying mice that are placed under stress (restrained), thus creating their own adrenaline or stress reaction to learn whether the physical reactions of stress, rather than an influx of adrenaline in the lab as was done in the current study, also leads to accumulation of DNA damage.

More information: The first author of the study, "Stress Response Pathway Regulates DNA Damage through β2-Adrenoreceptors and β-Arrestin-1," is Makoto R. Hara of Duke University.

Provided by Duke University Medical Center