# Scientists unravel clue in cortisol production

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When a person's under stress or injured, the adrenal gland releases cortisol to help restore the body's functions to normal. But the hormone's effects are many and varied, lowering the activity of the immune system, helping create memories with short-term exposure, while impairing learning if there's too much for too long. Given the variety of its effects,understanding how cortisol is made is essential to producing medications that can alter its production.

Scientists at the Georgia Institute of Technology have discovered an important step in cortisol production, finding that although the output of the hormone is continuous, the molecular production is cyclic in nature – involving a rhythmic binding and unbinding of a protein essential to its production. The research, which increases understanding of how the brain and the endocrine system work together to regulate health, appears in the February issue of the journal *Molecular Endocrinology*.

Turning cholesterol into the stress hormone cortisol involves many reactions and begins when the hypothalamus sends a signal to the adrenal glands. Proteins then flood into the nucleus to bind to the DNA, creating the gene CYP 17. What happens next is well understood; CYP 17, along with a battery of other enzymes, transforms cholesterol into cortisol. But what isn't understood is how this protein binding creates CYP 17, or which proteins are important. So, graduate students Eric Dammer and Adam Leon, along with Marion Sewer, assistant professor in Georgia Tech's School of Biology, decided to model the events that occur after the adrenal gland receives the signal.

One of the things the signal does is cause adrenal cells to increase their production of cyclic AMP (cAMP), a chemical that encourages proteins to interact. So they began by causing the cells to make more cAMP. Then as the proteins assembled on the DNA, they tested the cells at different intervals in order to get a snapshot of which proteins were interacting, both with each other and the DNA and in which order this occurred. Then they mutated the proteins to stop them from fulfilling their roles.

"One of the best ways to try and figure out the function of a protein or a gene is to get rid of it or mutate it so that it's not acting normally. Then you compare it with one that is acting normally," said Sewer.

In this study, they focused on a protein known as steriodogenic factor 1 (SF-1), which is essential for making all steroid hormones. Researchers were interested in discovering what events have to occur in order for SF-1 to bind to DNA.

The first thing they found was that because DNA is so tightly packed in the nucleus, SF-1 can't bind to it until it's unpacked by a group of proteins. Once that happens, SF-1 binds to the genes, beginning the process that makes CYP 17 and ultimately cortisol. But it's not a continuous process, they found.

"Once SF-1 binds, it leaves. A few minutes later other proteins come in and condense the DNA," said Sewer. "After that SF-1 binds again, then leaves, and the proteins cause the DNA to contract again."

This cycle goes on as long as the adrenal gland is receiving the signal.

"Even though you get a sustained production of cortisol, the actual molecular events that happen in the nucleus are dynamic," said Sewer. "It's an extremely complex series of events that starts within minutes of

the adrenal gland receiving the signal. Without all these transient binding events, the adrenal gland fails to produce optimal levels of cortisol."

Next the team will investigate how small molecules – ligands – regulate cortisol production by binding to SF-1 and controlling the receptor's ability to bind to DNA.

Source: Georgia Institute of Technology