**Cocaine** is a strong central nervous system stimulant that increases levels of dopamine, a brain chemical associated with pleasure and movement, in the brain's reward circuit. Certain brain cells, or neurons, use dopamine to communicate. Normally, dopamine is released by a neuron in response to a pleasurable signal (e.g., the smell of good food), and then recycled back into the cell that released it, shutting off the signal between neurons. Cocaine acts by preventing the dopamine from being recycled, causing excessive amounts of dopamine to build up, amplifying the message, and ultimately disrupting normal communication. It is this excess of dopamine that is responsible for cocaine's euphoric effects.

With repeated use, cocaine can cause long-term changes in the brain's reward system and in other brain systems as well, which may eventually lead to addiction. With repeated use, tolerance to the cocaine high also often develops. Many cocaine abusers report that they seek but fail to achieve as much pleasure as they did from their first exposure. Some users will increase their dose in an attempt to intensify and prolong the euphoria, but this can also increase the risk of adverse psychological or physiological effects.

**Cigerettes** Oct. 27, 2004 -- Just like [heroin](http://www.webmd.com/mental-health/substance-abuse) and [morphine](http://www.webmd.com/drugs/drug-327-Morphine+Oral.aspx?drugid=327&drugname=Morphine+Oral), [smoking](http://www.webmd.com/smoking-cessation/default.htm) cigarettes triggers the release of addictive "feel-good" brain chemicals, new research shows.

The finding helps researchers understand why smokers have such a tough time quitting despite all the health dangers. They presented their report at the annual meeting of the Society for Neuroscience, held this week in San Diego.

It's the first human study to show that smoking cigarettes stimulates the brain's production of chemicals called **[opioids](http://www.webmd.com/mental-health/narcotic-abuse)**. The opioids are known to play a role in soothing pain, increasing positive emotions, and creating a sense of reward. Both morphine and heroin trigger this same chemical flow.

The new study also confirms previous findings -- from animal studies -- that smoking cigarettes affects the flow of another feel-good brain chemical called **dopamine**. Researchers are now investigating the interaction between the two chemicals in the brains of smokers and nonsmokers.

"It appears that **smokers have an altered opioid flow all the time**, when compared with non-smokers, and that smoking a cigarette further alters that flow by 20 to 30 percent in **regions of the brain important to emotions and craving,"** says lead researcher David J. Scott, a graduate student in neuroscience at the University of Michigan in Ann Arbor, in a news release.

**Hormones, stress and aggression--a vicious cycle**

**Rat research shows a feedback loop between stress hormones and the brain's attack center.**

By RACHEL ADELSON

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New research may help explain why, under stress, we are quick to lash out and slow to cool down.

A team of behavioral neuroscientists led by Menno Kruk, PhD, of the Leiden/Amsterdam Center for Drug Research, has found in rats a fast positive feedback loop between a hormonal stress response and their brains' aggression systems. Given how similar human neurophysiology is to that of the rat (and indeed many other mammals, plus birds and lizards), the finding may ultimately help to explain the self-perpetuating nature of violence. The results, reported in the October issue of Behavioral Neuroscience (Vol. 118, No. 5), point to possible ways for people--given future research and development--to prevent pathological violence.

The researchers conducted five experiments on 53 male rats, electrically stimulating their brains' aggression-control centers to see if this raised blood levels of a stress hormone. They also investigated whether higher levels of the same hormone were associated with the aggressive behavior elicited by that center. The results: Raising (or lowering) one variable raised (or lowered) the other. Thus, stress and aggression worked in a fast positive feedback loop.

If a similar mechanism is found in humans, it could help explain not only why the stress of traffic jams leads to road rage, but also why aggressive behavior triggers an ongoing stress reaction that is hard to stop. Says Michael Potegal, PhD, a researcher at the University of Minnesota Hospital who studies anger and aggression, the result is "consistent with, and advances, earlier work. We recently found a brief and modest rise in salivary **cortisol** following tantrums in 3-year-old children."

**Opponent-free aggression**

The study also found evidence that the rats' brain-attack center works not by controlling motor responses, but rather by changing their social perceptions. Once "threatened" (even falsely, as happened in the experiment), they'll attack.

In the study, Kruk, lab technician Wout Meelis, and József Halász, PhD, and József Haller, PhD, the latter pair from the Institute of Experimental Medicine in Budapest, electrically stimulated the rats' hypothalamic "attack center," a major brain area from which attack behavior can be reliably triggered. Upon stimulation, the rats suddenly released the **stress hormone corticosterone**, very like the **cortisol humans** release under stress.

Hormone levels went up even without another rat present. This is significant because rats don't usually fight unless they have a motivator, a social cue and an opponent.

"We showed that fighting is not necessary to get the adrenocortical response," says Kruk. "The activation of the aggressive system, not the physical exercise of fighting, causes the stress response."

**Both sides now**

To study the hypothesized feedback loop from the other direction, the scientists first removed rats' adrenal glands to prevent any natural release of corticosterone. Then they injected the rats with corticosterone. Within minutes, the hormone facilitated the exact same type of attack behavior fostered by hypothalamic stimulation. (Kruk notes that hormones don't actually cause aggression, but rather--at the genetic level--make stimulatory and inhibitory neurons more or less sensitive to specific stimuli from other neurons. When hormones affect stimulatory neurons, they make it easier for a stimulus to elicit a behavior. (Because of the speed of attack, the researchers in this case do not rule out nongenomic effects.)

Thus, stimulating an "aggression controller" in the brain led to higher stress hormones, and injecting stress hormones facilitated aggression. "Such a mutual facilitation may contribute to the precipitation and escalation of violent behavior under stressful conditions," the authors conclude.

What's more, activating the aggression system turns on the adrenocortical stress response without actual fighting--or even someone to fight. A hypothetical picture emerges: First, as has long been known**, a signal from the nervous system (via pituitary hormone ACTH) signals the adrenals to produce a corticosteroid** response that prepares the body for an emergency response, popularly called **"fight or flight**." Second, in this new finding, the same corticosteroid signal also feeds back to the brain, which lowers attack thresholds and facilitates fighting. Fighting, itself a stressor, then further activates the stress response. And so it goes.

**The speed of stress**

The researchers were impressed with the swiftness of both responses. "Taken together, the speed of both processes allows for mutual positive feedback within a single fighting episode, which typically for these rats lasts from 10 to 30 minutes in a natural setting," says Kruk.

This is much faster than under normal circumstances: In rats, the behavioral effects of adrenocortical stress hormones usually take at least 30 to 40 minutes to appear and only slowly fade.

"Apparently, the emergency of social conflict cannot wait so long. Responses must work much faster to be useful and adaptive," says Kruk.

The hypothesized escalation may help rats to successfully finish fights because stopping halfway is dangerous. Kruk and his colleagues speculate that the peripheral feedback loop may be useful because it tells the nervous system that emergency mechanisms are properly activated.

However, this survival mechanism might also, out of context, spiral out of control. The researchers note how their findings **"would explain why aggressive behavior escalates so easily and is so difficult to stop once it has started**, especially because **corticosteroids rapidly pass through the blood-brain barrier**."

**Thresholds of violence**

The findings suggest that even when stress hormones spike for reasons not related to fighting, the side effect of lowering attack thresholds **may still precipitate violent behavior**.

The findings may ultimately also shed light on why normally pacific people turn violent in settings previously associated--for them--with aggression: Their stress hormones rise, facilitating the onset of aggression and making them more likely to become violent in seemingly benign settings.

These adrenocortical (stress) and hypothalamic (aggression) responses are ancient, inbred and found across many mammalian species including rats, cats and monkeys. As a result, the authors suggest that the stress-aggression feedback loop could well operate in the real world, not just the lab, as well as in humans.

However, research into human aggression tends to be more complex and far harder to pursue. Potegal points out that, "It is possible that the rats [in this study] might have gotten similar behavior and hormone effects if the researchers were looking at **hypothalamically** elicited flight rather than fight. Also, one must be careful about equating cortisol release with generic 'stress'--you can experience chronic stress without having higher cortisol, or have higher cortisol but not show outward signs of stress.

"Nonetheless, **the authors are quite correct that the hormone could 'supercharge' the aggression**, and there are analogous findings with other forms of physiological activation in humans," he adds.

Says Kruk, "**We have strong indications that repeated or exaggerated reliance on this functional emergency mechanism--the mutual positive feedback--may cause long-term changes in the aggressive system that change the propensity for aggression."**

The authors comment that their findings could explain why, in a conflict, the glandular release of stress hormones may effectively cancel out the effect of therapies meant to curb bad behavior. Regulating the stress response could offer a new way to understand and control human violence. The scientists speculate that medications, including as-yet undeveloped anxiety-reducers that regulate the stress response, might reduce acute stress-precipitated violence.

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