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Studies Link Stress and Drug Addiction

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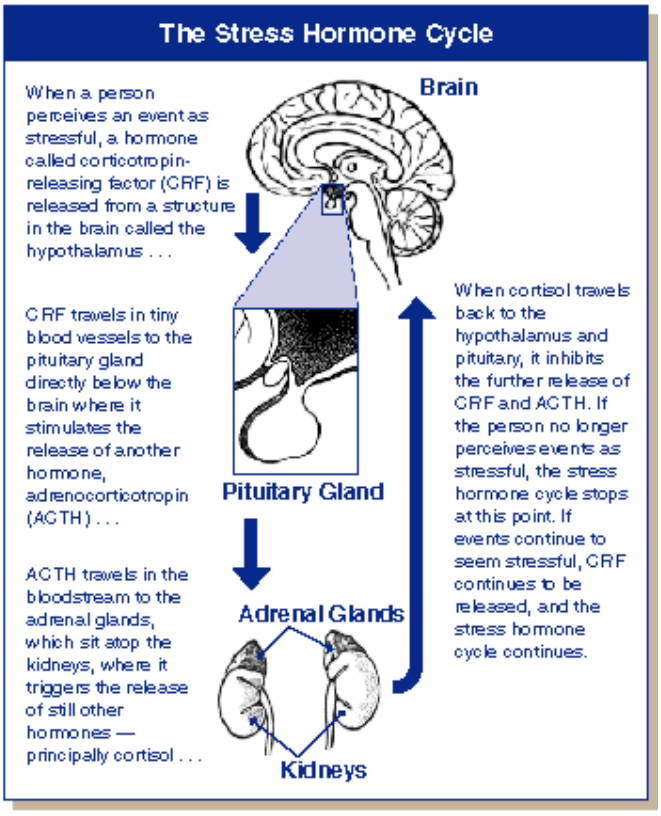
Drug-addicted patients who are trying to remain off drugs can often resist the cravings brought on by seeing reminders of their former drug life, NIDA-funded researcher Dr. Mary Jeanne Kreek of Rockefeller University in New York City has noted. "For 6 months or so, they can walk past the street corner where they used to buy drugs and not succumb to their urges. But then all of a sudden they relapse," she says. "When we ask them why they relapse, almost always they tell us something like, 'Well, things weren't going well at my job,' or 'My wife left me.' Sometimes, the problem is as small as 'My public assistance check was delayed,' or 'The traffic was too heavy.'"

Anecdotes such as these are common in the drug abuse treatment community. These anecdotes plus animal studies on this subject point toward an important role for stress in drug abuse relapse. In addition, the fact that addicts often relapse apparently in response to what most people would consider mild stressors suggests that addicts may be more sensitive than nonaddicts to stress.

This hypersensitivity may exist before drug abusers start taking drugs and may contribute to their initial drug use, or it could result from the effects of chronic drug abuse on the brain, or its existence could be due to a combination of both, Dr. Kreek has proposed. She has demonstrated that the nervous system of an addict is hypersensitive to chemically induced stress, which suggests that the nervous system also may be hypersensitive to emotional stress.



How the Body Copes With Stress

The body reacts to stress by secreting two types of chemical messengers - hormones in the blood and neurotransmitters in the brain. Scientists think that some of the neurotransmitters may be the same or similar chemicals as the hormones but acting in a different capacity.

Some of the hormones travel throughout the body, altering the metabolism of food so that the brain and muscles have sufficient stores of metabolic fuel for activities, such as fighting or fleeing, that help the person cope with the source of the stress. In the brain, the neurotransmitters trigger emotions, such as aggression or anxiety, that prompt the person to

undertake those activities.

Normally, stress hormones are released in small amounts throughout the day, but when the body is under stress the level of these hormones increases dramatically. The release of stress hormones begins in the brain. First, a hormone called corticotropin-releasing factor (CRF) is released from the brain into the blood, which carries the CRF to the pituitary gland, located directly underneath the brain. There, CRF stimulates the release of another hormone, adrenocorticotropin (ACTH), which, in turn, triggers the release of other hormones - principally cortisol - from the adrenal glands. Cortisol travels throughout the body, helping it to cope with stress. If the stressor is mild, when the cortisol reaches the brain and pituitary gland it inhibits the further release of CRF and ACTH, which return to their normal levels. But if the stressor is intense, signals in the brain for more CRF release outweigh the inhibitory signal from cortisol, and the stress hormone cycle continues.

Researchers speculate that CRF and ACTH may be among the chemicals that serve dual purposes as hormones and neurotransmitters. The researchers posit that if, indeed, these chemicals also act as neurotransmitters, they may be involved in producing the emotional responses to stress.

The stress hormone cycle is controlled by a number of stimulatory chemicals in addition to CRF and ACTH and inhibitory chemicals in addition to cortisol both in the brain and in the blood. Among the chemicals that inhibit the cycle are neurotransmitters called opioid peptides, which are chemically similar to opiate drugs such as heroin and morphine. Dr. Kreek has found evidence that opioid peptides also may inhibit the release of CRF and other stress-related neurotransmitters in the brain, thereby inhibiting stressful emotions.

How Addiction Changes the Body's Response to Stress

Heroin and morphine inhibit the stress hormone cycle and presumably the release of stress-related neurotransmitters just as the natural opioid peptides do. Thus, when people take heroin or morphine, the drugs add to the inhibition already being provided by the opioid peptides. This may be a major reason that some people start taking heroin or morphine in the first place, suggests Dr. Kreek. "Every one of us has things in life that really bother us," she says. "Most people are able to cope with these hassles, but some people find it very difficult to do so. In trying opiate drugs for the first time, some people who have difficulty coping with stressful emotions might find that these drugs blunt those emotions, an effect that they might find rewarding. This could be a major factor in their continued use of these drugs."

When the effects of opiate drugs wear off, the addict goes into withdrawal. Research has shown that, during withdrawal, the level of stress hormones rises in the blood and stress-related neurotransmitters are released in the brain. These chemicals trigger emotions that the addict perceives as highly unpleasant, which drive the addict to take more opiate drugs. Because the effects of heroin or morphine last only 4 to 6 hours, opiate addicts often experience withdrawal three or four times a day. This constant switching on and off of the stress systems of the body heightens whatever hypersensitivity these systems may have had before the person started taking drugs, Dr. Kreek says. "The result is that these stress chemicals are on a sort of hair-trigger release. They surge at the slightest provocation," she says.

Studies have suggested that cocaine similarly heightens the body's sensitivity to stress, although in a different way. When a cocaine addict takes cocaine, the stress systems are activated, much like when an opiate addict goes into withdrawal, but the person perceives this as part of the cocaine rush because cocaine is also stimulating the parts of the brain that are involved in feeling pleasure. When cocaine's effects wear off and the addict goes into withdrawal, the stress systems are again activated - again, much like when an opiate addict goes into withdrawal. This time, the cocaine addict perceives the activation as unpleasant because the cocaine is no longer stimulating the pleasure circuits in the brain. Because cocaine switches on the stress systems both when it is active and during withdrawal, these systems rapidly become hypersensitive, Dr. Kreek theorizes.

Evidence for the Link Between Stress and Addiction

This theory about stress and drug addiction is derived in part from studies conducted by Dr. Kreek's group in which addicts were given a test agent called metyrapone. This chemical blocks the production of cortisol in the adrenal glands, which lowers the level of cortisol in the blood. As a result, cortisol is no longer inhibiting the release of CRF from the brain and ACTH from the pituitary. The brain and pituitary then start producing more of these chemicals.

Physicians use metyrapone to test whether a person's stress system is operating normally. When metyrapone is given to nonaddicted people, the ACTH level in the blood increases. However, when Dr. Kreek and her colleagues administered metyrapone to active heroin addicts, the ACTH level hardly rose at all. When the scientists gave metyrapone to heroin addicts who were abstaining from heroin use and who were not taking methadone, the synthetic opioid medication that suppresses cravings for opiate drugs, the ACTH level in the majority of the addicts increased about twice as high as in nonaddicts. Finally, when the scientists gave metyrapone to heroin addicts maintained for at least 3 months on methadone, the ACTH level rose the same as in nonaddicts.

Addicts on heroin underreact because all the excess opioid molecules in the brain greatly inhibit the brain's stress system, Dr. Kreek explains. Addicts who are heroin-free and methadone-free overreact because the constant on-off of daily heroin use has made the stress system hypersensitive, she says, and heroin addicts who are on methadone react normally because methadone stabilizes this stress system. Methadone acts at the same sites in the brain as heroin, but methadone stays active for about 24 hours while the effects of heroin are felt for only 4 to 6 hours. Because methadone is long-acting, the heroin addict is no longer going into withdrawal three or four times a day. Without the constant activation involved in these withdrawals, the brain's stress system normalizes.

Recently, Dr. Kreek's group reported that a majority of cocaine addicts who are abstaining from cocaine use overreact in the metyrapone test, just like the heroin addicts who are abstaining from heroin and not taking methadone. As with heroin addicts, this overreaction in cocaine addicts reflects hypersensitivity of the stress system caused by chronic cocaine abuse.

"We think that addicts may react to emotional stress in the same way that their stress hormone system reacts to the metyrapone test," says Dr. Kreek. At the slightest provocation, CRF and other stress-related neurotransmitters pour out into the brain, producing unpleasant emotions that make the addict want to take drugs again, she suggests. Since life is filled with little provocations, addicts in withdrawal are constantly having their stress system activated, she concludes.

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