Small study shows dramatic results in lowering heart disease risk

Obese men can significantly reduce heart disease on a three-week low-fat, high-fiber diet and daily exercise – even though they may lose only a few pounds, according to research published in the Oct. 21 issue of *Circulation: Journal of the American Heart Association.*

Obese men who consumed a diet high in grains, vegetables and fruit and took brisk daily walks reduced their high blood pressure, a hallmark risk factor for congestive heart failure, kidney disease, coronary artery disease and stroke.

"This is the first study to show that this type of diet and exercise can reduce oxidative stress, lower blood pressure, and improve risk factors for other chronic diseases in a very short time," said R. James Barnard, senior author of the study and professor of physiological science at the University of California, Los Angeles.

Barnard and colleagues studied 11 obese (body mass index of 30 or greater) men aged 38 to 72, who voluntarily enrolled in the Pritikin Longevity Center 21-day residential diet and exercise program. Seven of them had hypertension defined as a reading of over 140 mm Hg systolic (the top number) and 90 mm Hg diastolic (the lower number).

The meals consisted of less than 10 percent of calories from fat, 15 to 20 percent from protein and 70-75 percent from unrefined carbohydrates. Carbohydrates were derived from five servings of high-fiber whole grains, four servings of vegetables and three servings of fruit daily. Grains, vegetable and fruit were served all-you-want buffet style. The men had one serving of chicken or fish for dinner. The exercise program consisted of brisk walking on a treadmill for 45 to 60 minutes a day.

Blood samples were drawn for cholesterol, glucose and insulin measurements (all associated with heart disease) at the start and end of the program. The researchers also measured blood pressure, nitric oxide availability and oxidative stress. *Nitric oxide helps prevent heart disease in several ways,* including helping to relax blood vessels, thus reducing blood pressure. It also prevents cells in the walls of blood vessels from proliferating and clogging the arteries, a process that contributes to atherosclerosis. Oxidative stress refers to the presence of oxygen free radicals that can attack cells and tissues and contributes to cardiovascular disease and other health problems.

By the end of the program, none of the seven hypertensive men had high blood pressure. Systolic blood pressure was reduced by 14 percent, diastolic blood pressure by 10 percent and oxidative stress by 28 percent, while nitric oxide availability improved by 28 percent. Total cholesterol decreased by 19 percent, insulin levels by 46 percent and blood glucose by 7 percent.

Although body weight and body mass index decreased slightly (about 4 percent each), the men were all still obese at the end of the three-week program.

The risk reduction occurs quickly, even if a person is still obese, Barnard noted.

"You can lose weight over time, but fortunately, we can ease high blood pressure and the risk of atherosclerosis and heart disease while, or even before, you shed excess pounds," he said.

Similar positive changes have been seen in non-obese people at risk for heart disease in other studies, Barnard added.

"Within three weeks, we showed normalization of blood pressure and mitigation of other atherosclerotic risk factors, all of which will reduce the risk of chronic disease if kept up as part of a lifestyle change," said Christian Roberts, another of the study's authors.

"But if you return to an inappropriate diet and stop exercising, you will no longer benefit, and in fact you will regress," he cautioned.

Cocaine harms brain's 'pleasure center'

New research results strongly suggest that cocaine bites the hand that feeds it by harming or even killing the very brain cells that trigger the "high" that cocaine users feel.

This most comprehensive description yet of cocaine-induced damage to key cells in the human brain's dopamine "pleasure center" may help explain many aspects of cocaine addiction, and perhaps aid the development of anti-addiction drugs. It also could help scientists understand other disorders involving the same brain cells, including depression.

The results are the latest from research involving post-mortem brain tissue samples from cocaine abusers and control subjects, performed at the University of Michigan Health System and the VA Ann Arbor Healthcare System. The paper will appear in the January issue of the *American Journal of Psychiatry.*

"This is the clearest evidence to date that the specific neurons cocaine interacts with don't like it and are disturbed by the drug's effects," says Dr. Kurley Little, associate professor of psychiatry at the U-M Medical School and chief of the VAHS Affective Neuropharmacology Laboratory. "The questions we now face are: Are the cells dormant or damaged, is the effect reversible or permanent, and is it preventable?"

BRAIN SAMPLES

Little and his colleagues report results from 35 known cocaine abusers and 35 non-drug users of about the same age, sex, race and causes of death. Using brain samples normally removed during autopsy, the researchers measured several indicators of the health of the subjects' dopamine brain cells, which release a pleasure-signaling chemical called dopamine. The cells interact directly with cocaine.

The team looked at levels of a protein called VMAT2, as well as VMAT2's binding to a selective radiotracer molecule, and overall dopamine level.

In all three, cocaine users' levels were significantly lower than control subjects. Levels tended to be lowest in cocaine users with depression.

The paper gives the most conclusive evidence yet that dopamine neurons are harmed by cocaine use, because it uses three molecular measures that provide a trustworthy assessment of dopamine neuron health.

Dopamine, Little explains, triggers the actions required to repeat previous pleasures. It's not only involved in drug users' "high" – it helps drive us to eat, work, feel emotions, and reproduce. Normally, when something pleasurable happens, dopamine neurons pump the *chemical into the gaps between* themselves and related brain cells. Dopamine finds its way to receptors on neighboring cells, triggering signals that help set off pathways to different feelings or sensations.

Then, the dopamine is normally brought back into its home cell, entering through a gateway in the membrane called a transporter. While our brain waits for another pleasurable stimulus – a good meal, a smile from a friend, a kiss – dopamine lies waiting inside the neuron, sequestered in tiny packets called vesicles. VMAT2 acts as a pump to pull returning dopamine into vesicles.

When it comes time for another dopamine release, the vesicles merge with the cell membrane, dumping their contents into the gap, or synapse, and the pleasure signaling process begins again.

DOPAMINE DEATH

Dopamine neurons in the brain's pleasure center die off at a steady rate over a person's lifetime. Severe damage is a hallmark of Parkinson's disease, causing its loss of movement control.

"As the words themselves suggest, there's an intimate connection between motion and emotion," says Little. "Emotion puts you in motion – they're pre-activity preparations. It's not surprising that the basal ganglia, where these dopamine neurons are, is very active in 'emotional states.'"

When first taken, cocaine has a disruptive effect on the brain's dopamine system: It blocks the transporters that return dopamine to its home cell once its signaling job is done. With nowhere to go, dopamine builds up in the synapse and keeps binding with other cells' receptors, sending pleasure signals over and over again. This helps cause the intense "high" cocaine users feel.

Since the dopamine system helps us recognize pleasurable experiences and seek to repeat them, cocaine's long-term *dopamine effects likely con*tribute to the craving addicts feel, and the decreased motivation, stunted emotion and uncomfortable withdrawal they face.

In recent years, many researchers have come to suspect that chronic cocaine use causes the brain to adapt to the drug's presence by altering the molecules involved in dopamine release and reuptake, and in the genetic instructions needed to make those molecules. Little and his colleagues are studying the effects of long-term cocaine use on the brain at a molecular level, in an attempt to explain the effects seen in cocaine users and addicts.

In several studies, including the current one, they've used postmortem samples of brain tissue from known cocaine users who were using the drug at the time of their deaths, and from well-matched control subjects. They focused in on the striatum, an area of the brain with the highest concentration of dopamine neurons.

With approval from the U-M Institutional Review Board and appropriate consent, they interviewed relatives and friends of the subjects, and asked about the subjects' alcohol use, mental illness and other characteristics.