Old antidepressant offers promise in treating heart failure

January 7 2010

A team of Johns Hopkins and other researchers have found in animal experiments that an antidepressant developed over 40 years ago can blunt and even reverse the muscle enlargement and weakened pumping function associated with heart failure.

In a report to be published in the Jan. 8 edition of the journal Circulation Research, the international team of U.S. and Italian heart experts describes in a dozen key laboratory experiments in rodents how the antidepressant clorgyline, which is no longer in use in humans, blocks the action of enzyme monoamine oxidase-A (MAO-A) and stops its breakdown of a key neurohormone. Norepinephrine, as it is called, controls the pace of blood pumping and makes the heart pump harder and faster in response to stress.

The latest study results, they say, are believed to be the first evidence showing how elevated MAO-A activity biochemically drives heart failure and that its dangerous downstream effects can be stalled by drug therapy.

"Our study helps describe heart failure as a vicious chemical circle of stimulant norepinephrine overload and breakdown, and it offers a disease blueprint with monoamine oxidase-A as the target for drugs similar to clorgyline to rein in the disease," says senior study investigator and cardiologist Nazareno Paolocci, M.D.

"When norepinephrine is not properly stored and released from the

nerves directed to the heart, monoamine oxidase-A breaks it down, generating dangerous chemical species in the nerves and the heart muscle.

"These toxic free radicals produce the same deleterious effects on heart muscle size and pumping function long observed in heart failure," says Paolocci, an assistant professor at the Johns Hopkins University School of Medicine and its Heart and Vascular Institute, and at the University of Perugia in Italy.

Paolocci cautions that their studies with clorgyline are initial proof of an important principle, but far from any current use of the drug to treat heart disease in humans. He says newer drugs in the same class, such as moclobemide (sold as Aurorix or Manerix, and already approved by the U.S. Food and Drug Administration), will have to be tested first, citing numerous and potentially lethal drug effects with clorgyline that prevent it from being prescribed.

Notable side effects from clorgyline, Paolocci says, include insomnia and agitation, or high blood pressure after ingestion of foods containing the amino acid tyramine, a protein building block that stimulates a surge of stored stimulatory hormones, specifically, norepinephrine. Patients who have taken clorgyline, whose chemical binding to MAO-A is irreversible, had to carefully avoid such tyramine-rich foods as red wine, chocolate, certain beans, meat and especially aged cheeses. The phenomenon was sometimes dubbed the cheese effect.

It was previous observations of this norepinephrine surge and accelerated breakdown that led logically, the team reports, to see if inhibitor drugs - preferably those already on the shelf - could stop or reverse the damage.

Among the study's first findings was that after six weeks, mice with failing hearts responded to concurrent low-dose clorgyline treatment,

with restoration of normal heart function and only half the harmful changes seen in untreated mice over the same time period.

Heart muscle cell death rates were normal in clorgyline-treated mice, but three and a half times higher in untreated mice. Heart muscle chamber expansion also slowed in the clorgyline-treated group, returning to an average chamber dimension of 1.2 millimeters, when the heart was contracting. Hearts in the untreated group expanded to an average of 3 millimeters. In addition, depleted stores of the hormone norepinephrine were replenished in treated mice, but not at all in untreated mice.

The team believes that when norepinephrine is not properly stored in the nerves, it overflows into the heart, accelerating the hormone's breakdown by MAO-A. This in turn leads to the buildup inside the heart of harmful reactive oxygen species, such as hydrogen peroxide, that strain normal muscle cell contraction.

"Now that we know clorgyline works, we can focus future drug testing on newer, safer MAO-A inhibitors, such as moclobemide, whose chemical bindings are reversible, unlike those of clorgyline," says Paolocci.

Lead study investigator Nina Kaludercic, Ph.D., a postdoctoral fellow at Johns Hopkins and the University of Padova in Italy, says that researchers had long known that the buildup of hydrogen peroxide was dangerous, but no one knew that MAO-A was a major source due to the elevated breakdown of norepinephrine and how MAO-A's action spurred heart failure.

In other experiments in live heart cells taken from mice and rats, Kaludercic and her colleagues clarified MAO-A's connection to the muscle-enlarging effects of catecholamines, of which norepinephrine is one. They found that incubating the cells with norepinephrine for a day

triggered increased MAO-A enzyme activity, generating hydrogen peroxide and muscle cell expansion, much like what happens in humans with failing hearts. Again, subsequent clorgyline treatment, at a single low dose of 2 micromoles per liter, reversed the damage.

Another key finding was that the overflow of norepinephrine did not just lead to raised activity of the muscle's alpha and beta receptors, which trigger the heart to beat harder and faster, but also led to upped activity of MAO-A.

Kaludercic says these experiments "deepen our understanding" of the close ties between the brain and the heart, and how problems with nerve-muscle interaction can influence key organ failure.

Researchers next plan to analyze medical records from people who have already taken MAO-A inhibitors to determine if their drug therapy offered any protection or lower risk of developing heart failure or other kinds of cardiovascular disease. They also plan experiments in animals to assess if clorgyline therapy can reverse heart failure at later stages of the disease, and at which dose. In addition, the team has proposed studies to evaluate other MAO-A inhibitors, including moclobemide, and what effects, if any, they have on failing hearts.

Some 5.7 million American men and women suffer from chronic heart failure, which caused an estimated 290,000 deaths in 2005. A majority of sufferers have high blood pressure, the leading risk factor for the disease.

Provided by Johns Hopkins Medical Institutions