Common blood pressure drug reduces progressive muscle degeneration in mice

February 2 2007

Scientists supported in part by the National Institutes of Health's National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and National Institute of Neurological Disorders and Stroke (NINDS) have found that that the commonly prescribed blood pressure medication losartan improves muscle regeneration and repair in a mouse model of Duchenne muscular dystrophy (DMD), a devastating disease characterized by rapid progression of muscle degeneration in boys and young men.

The research is based on similarities in the mechanism of DMD and another rare disease — Marfan syndrome — and the discovery that losartan is effective in blocking the key mechanism in animal models of both diseases. Further studies of the drug, scientists emphasize, are needed to assess its value in patients.

Marfan syndrome is a heritable connective tissue disorder affecting many organ systems, resulting in dislocation of the lens of the eye; progressive dilation of the aorta, which puts the aorta at risk of rupture; and small, weak muscles, says Harry C. Dietz, M.D., an author of the study in the February 2007 edition of Nature Medicine. Until recent years, scientists believed that Marfan syndrome was caused by weakness of tissues, says Dr. Dietz, the Victor A. McKusick professor of genetics in the McKusick-Nathans Institute of Genetic Medicine at the Johns Hopkins University School of Medicine and director of the William S. Smilow Center for Marfan Syndrome Research. But research by Dr. Dietz and his colleagues, and funded by the National Heart, Lung, and

Blood Institute, NIAMS and others, has shown that the disease is the result of excessive activity of a growth factor called TGF-beta in the muscles. "We found that muscles were abnormal; they had very small fibers and excess fibrosis — excessive connective tissue, or scarring — between the fibers. What we learned was that high TGF-beta levels were preventing a process called muscle regeneration."

Normally, when a person damages their muscle or when they exercise and send a signal to the muscle to get bigger, the muscle is able to mobilize a population of muscle stem cells that proliferate and then fuse to each other and to damaged muscle fibers to rapidly accomplish muscle repair or muscle growth. In the presence of too much TGF-beta, however, the cells simply do not get the signal to accomplish this regenerative process, says Dr. Dietz. "We learned that simply blocking TGF-beta in a mouse model of Marfan syndrome could rescue muscle regeneration, normal architecture and muscle function."

Previous studies have demonstrated that the muscles of dystrophic mice lose their ability to repair and regenerate efficiently, and as in the human, the muscle tissue is progressively replaced by scar tissue. Knowing that the same phenomenon occurred in Marfan syndrome, Ronald D. Cohn, M.D., assistant professor of pediatrics and neurology at Johns Hopkins' McKusick-Nathans Institute of Genetic Medicine, and Dr. Dietz and their colleagues tried to see if they could extrapolate findings from the Marfan syndrome mouse model to a mouse model of DMD. Their research paid off. They were able to find evidence that excessive TGF-beta had a role in limiting muscle regeneration in response to damage in DMD as well. When the researchers gave the mice losartan to inhibit TGF-beta, they showed that the muscle was able to regenerate and repair much more efficiently. What's more, when they treated the mice with the drug over a period of time, the entire disease was attenuated, says Dr. Cohn. "Here we had two completely different myopathies — muscle diseases — that seemed to show a common

pathway, which inhibits the repair process of skeletal muscle."

Losartan, a frequently prescribed and well-tolerated drug in humans, works to reduce high blood pressure by blocking a molecule called angiotensin II, which has been found not only to regulate blood pressure but also to work against TGF-beta by a number of mechanisms. Now that the drug has proven useful in mouse models of the two diseases, the next step is to test them in people with the diseases. A clinical trial of losartan for Marfan syndrome is scheduled to begin later this month. Researchers are in the process of organizing a clinical trial for DMD; patient recruitment is not yet underway. If the drug proves useful in humans, as it has in mouse models, it will represent a huge advance in the treatment of both diseases.

Current treatment for DMD is steroids. For many people with DMD, steroids seem to bring improvement in muscle function, but that improvement is offset by the drugs' side effects, and the effects are short-lived in some patients. In long-term treatment of mice with losartan, however, the researchers have seen a sustained significant improvement in muscle function. In fact, at about a year of age — which would be equivalent to middle age in a person — the mice with DMD actually had muscle function that was indistinguishable from a normal mouse, says Dr. Dietz. "So I think that it has the strong potential to not only have a more enduring effect, but also to have a more profound effect on maintenance of muscle function" he says. Losartan's safety profile is also more favorable than that of steroids. In 20 years of use in all human age groups, it has shown a "remarkable tolerance profile," he says. The most common side effect of the drug — low blood pressure — can usually be managed by simply lowering the dose of the drug, says Dr. Cohn.

While much prior work in Marfan syndrome and DMD has been focused on trying to replace the product of genes (for Marfan syndrome a deficient protein called fibrillin-1; for DMD, a protein called

dystrophin), Dr. Dietz says this new research is reflective of an emerging shift in attitude: to treat the disease as well as possible with what is available now. "Right now, we don't have the technology to replace the deficient gene product to cure the disease, but we might have the technology to prevent other secondary events that contribute to the disease process," he says. "In essence, we are focusing on the low-hanging fruit that we can currently address and that will have the strong potential to improve the length and quality of life while we are tackling some of the obstacles for a cure at the current time."

NIAMS Director Stephen I. Katz, M.D., Ph.D., is cautiously optimistic about the findings. "This treatment in mice is derived from knowledge of the diseases' mechanisms," he says. "It has been shown to be highly effective in mouse models. But we need to do clinical studies first. If they are successful, this therapy has the potential to help many people with devastating diseases for which there has really been no good treatment."

Pat Furlong, president and CEO of Parent Project Muscular Dystrophy, adds a similar perspective. "The success of losartan in the mouse model of Duchenne muscular dystrophy has been received with great enthusiasm. Researchers and physicians who care for children with DMD recognize the excitement as well as the sense of urgency within the DMD community. Many parents are urging their primary care physicians to agree to add losartan to their son's current regimen. While this approach is understandable, there is concern that extensive off-label use will compromise clinical trials. Unfortunately, the only way to understand if losartan will be effective in DMD boys is clinical trials. Without evidence, we will not understand the interaction of losartan with other compounds, and the use of the drug will be limited to those families who are able to secure and afford the drug. It is generally believed that treatments for DMD will involve combination therapies, and to that extent promising strategies must be methodically evaluated so

that all children might receive benefit."

Source: NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases