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Study shows antidepressant could do double duty as diabetes drug

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University of Texas Medical Branch at Galveston researchers have discovered that the commonly used antidepressant drug paroxetine could also become a therapy for the vascular complications of diabetes.

The scientists made their discovery after screening 6,766 clinically used drugs and pharmacologically active substances.

"We developed this assay and used it to test literally every single existing drug and a good selection of other biologically active compounds," said UTMB professor Csaba Szabo, senior author of a paper on the research published online by *Diabetes*. "We were quite surprised when paroxetine came out as an active compound —a result, we later determined, of what seems to be a completely new effect unrelated to its antidepressant actions and not shared by any other known antidepressant drug."

The initial screening process tested the ability of different compounds to protect the cells that make up the inner linings of blood vessels from the destructive effects of the high sugar levels produced by diabetes, known as hyperglycemia. In people with diabetes, hyperglycemia causes these endothelial cells to generate toxic molecules known as reactive oxygen species (ROS), which ravage blood-vessel linings and lead to diabetic endothelial dysfunction, the key factor in such destructive diabetic complications as heart attacks, strokes, retinopathy, nephropathy and neuropathy.

In subsequent test-tube studies, researchers found that

paroxetine—which is sold as an antidepressant under the trade name "Paxil"—prevents hyperglycemia-initiated ROS damage to endothelial cells in two ways. First, it directly reduces concentrations of superoxide, a powerful ROS. Second, it suppresses superoxide production by mitochondria, tiny structures whose real job is making the energy-transfer molecules needed for most cellular processes. In a hyperglycemic environment, mitochondria are cells' biggest source of superoxide. According to the researchers' findings, paroxetine inhibits this activity without interfering with the mitochondria's vital normal function.

Further experiments yielded still more evidence that paroxetine protects endothelial cells under hyperglycemic conditions. Reactive oxygen species cause significant damage to DNA, RNA and proteins, but cell-culture experiments showed that paroxetine significantly reduced this effect. The drug had similarly beneficial results when tested on rat "aortic rings"—small pieces of blood vessel kept alive with tissue-culture techniques. When treated with the vasodilator acetylcholine, these rings dilated just as if they were still part of a functioning circulatory system; endothelial dysfunction caused by diabetic hyperglycemia normally interferes with this function, but paroxetine restored it.

Finally, the researchers tested paroxetine in rats that had been injected with streptozotocin, a chemical that induces diabetes. The animals given paroxetine developed hypoglycemia, but like the aortic rings, their arteries retained the ability to dilate—an indication that the drug had prevented damage to their epitheliums.

"The future potential of this study is that we may be able to 're-purpose' paroxetine for the experimental therapy of diabetic cardiac complications," Szabo said. "We'll need to carefully characterize its safety profile in diabetic patients, but I think there's definite potential here."

Provided by University of Texas Medical Branch at Galveston