Erectile dysfunction drugs allowed more chemotherapy to reach brain tumors in laboratory study

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In a study using laboratory animals, researchers found that medications commonly prescribed for erectile dysfunction opened a mechanism called the blood-brain tumor barrier and increased delivery of cancer-fighting drugs to malignant brain tumors.

The experiments were conducted at Cedars-Sinai Medical Center's Maxine Dunitz Neurosurgical Institute and published in *Brain Research*.

Viagra (sildenafil) and Levitra (vardenafil) are known as PDE5 inhibitors because they block an enzyme, phosphodiesterase5, which interrupts a series of biochemical events that cause the decreased blood flow of erectile dysfunction. This laboratory rat study, published online ahead of print in the journal, found that similar biochemical interactions in the small vessels of the brain play a major role in the blood-brain tumor barrier, which impedes delivery of anti-tumor drugs into brain tumors. PDE5 inhibitors were found to open the barrier and increase drug transport in this early animal study.

Although the normal blood-brain barrier, which regulates access to the brain from the bloodstream, shares many characteristics with the blood-brain tumor barrier, the signaling mechanism blocked by PDE5 inhibitors is unique to the blood-brain tumor barrier. This allows the PDE5 inhibitors to selectively increase drug transport to malignant brain tumors without affecting normal brain tissue.

According to the researchers, these findings may have significant implications in improving drug delivery to brain tumors in patients.

"This is the first study to show that oral administration of PDE5 inhibitors increases the rate of transport of compounds across the blood-brain tumor barrier and improves the effectiveness of the anti-tumor drug adriamycin in the treatment of brain tumors in a rat model. We chose adriamycin for this study because it is one of the most effective drugs against brain tumor cell lines in the laboratory but it has very little effect in animals and humans because it is unable to cross the blood-brain tumor barrier. The combination of vardenafil and adriamycin resulted in longer survival and smaller tumor size," said neurosurgeon Keith L. Black, M.D., chairman of the Department of Neurosurgery at Cedars-Sinai Medical Center and director of the Maxine Dunitz Neurosurgical Institute.

Black, the article's first and corresponding author, has been recognized for his earlier groundbreaking work to break through the blood-brain tumor barrier with natural and synthetic bradykinin, a peptide that temporarily opens the barrier and increases anti-cancer drug delivery into certain tumors by more than 1,000 percent. In 2000, he received the Javits Neuroscience Investigator Award from the National Institute of Neurological Disorders and Stroke, part of the National Institutes of Health, for his blood-brain barrier research.

In the current studies, the blood-brain tumor barrier-opening effects of PDE5 lasted considerably longer than those of bradykinin and allowed greater transport across the barrier into tumor tissues. Because vardenafil was found to be more effective than sildenafil in increasing blood-brain tumor barrier permeability and transport, vardenafil was used in a survival study of 29 tumor-bearing rats. Those treated with saline (control) survived 32 days on average while those treated with vardenafil alone survived about 35 days and those treated with adriamycin alone

survived about 42 days. When vardenafil was combined with adriamycin, rats survived an average 53 days.

Although the researchers exposed the laboratory animals to doses of sildenafil and vardenafil that are comparable to the dose range approved for erectile dysfunction in humans, there were no detectable side effects in the rats, and neither drug increased transport of tracers into normal brain tissue.

Source: Cedars-Sinai Medical Center