L-type calcium channel blockers may contribute to heart failure, study finds

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L-type calcium channel blockers (LCCBs)—the most widely used drugs for treating hypertension—may harm the heart as much as help it, according to a new study.

The research team, led by Penn State, found that in rats and human cells in vitro, LCCBs cause changes in blood vessels—known as vascular remodeling—that reduce blood flow and increase pressure. Examining epidemiological data, the team also found that LCCBs are associated with a greater risk for heart failure. The findings suggest that care should be taken when prescribing these drugs to patients, particularly older adults and those with advanced hypertension.

"In the United States, nearly half of all adults—or just over a hundred million—have hypertension, and its prevalence is increasing; worldwide, the condition is expected to affect 1.56 billion people by 2025," said Mohamed Trebak, professor of cellular and molecular physiology, Penn State. "L-type calcium channel blockers are one of the most widely prescribed drugs to treat hypertension, yet we have found that these drugs may cause the same type of damage they are intended to prevent."

Trebak explained that vascular smooth muscle cells (VSMCs) make up the walls of blood vessels, where they help the vessels to control blood flow by contracting and relaxing. This activity is regulated by the concentration of calcium within the cells. VSMCs contain numerous calcium-permeable channels to control this calcium concentration. Under conditions of hypertension, these channels allow too much calcium to enter VSMCs, which triggers the cells to undergo physiological changes, known as "remodeling," and to divide and proliferate. These remodeled, proliferative cells cause blood vessel walls to thicken and stiffen and blood pressure to rise.

"L-type calcium channel blockers were created to prevent this from happening," said Trebak. "Yet, we found that these drugs also simultaneously cause remodeling and proliferation of VSMCs through another mechanism."

To investigate the specific mechanisms by which LCCBs affect VSMCs, Trebak and his colleagues used optical, electrophysiological and molecular tools to examine smooth muscle cells in vitro and in rats.

The team found that calcium entry into VSMCs is mediated by stromal-interacting molecule (STIM) proteins activating ORAI calcium channels and that chronic exposure to LCCBs causes these STIM proteins to become overactive, which triggers VSMCs to proliferate. Their results appeared on July 8 in *Proceedings of the National Academy of Sciences*.

Additionally, the researchers examined epidemiological data from the Penn State clinical database and found that incidences of heart failure were significantly higher in hypertensive patients treated with LCCBs than in hypertensive patients treated with other types of hypertension

medications.

"Treatment with LCCBs is clinically associated with elevated incidence of heart failure, which prompts a careful examination of the use of LCCBs during chronic hypertension where vascular remodeling is evident," said Trebak. "Extra care should be taken when hypertensive patients present with COVID-19, as LCCBs may exacerbate their vascular damage.

More information: Martin T. Johnson et al, L-type Ca2+ channel blockers promote vascular remodeling through activation of STIM proteins, *Proceedings of the National Academy of Sciences* (2020). DOI: 10.1073/pnas.2007598117

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