Are cold feet plaguing your relationship? Physiologists identified biological mechanism that could be responsible

July 31 2012

Cold feet -- those chilly appendages that plague many people in the winter and an unlucky few all year round -- can be the bane of existence for singles and couples alike. In a new study, scientists led by Selvi C. Jeyaraj of the Research Institute at Nationwide Children's Hospital have identified a biological mechanism that may be responsible for icy extremities: an interaction between a series of molecules and receptors on smooth muscle cells that line the skin's tiny blood vessels.

The new research, along with an accompanying editorial by Martin C. Michel of Johannes Gutenberg University in Mainz, Germany, and Paul A. Insel of the University of California at San Diego, suggest new contributors to this near-universal problem and potential targets to treat more serious problems that affect blood vessels in the cold, such as in Raynaud's disease.

The article, entitled "Cyclic AMP-Rap1A Signaling Activates RhoA to Induce a2C-Adrenoceptor Translocation to the Cell Surface of Microvascular Smooth Muscle Cells" (http://bit.ly/N8ZzKh), appears in the Articles in PresS section of the American Journal of Physiology – *Cell Physiology* (http://ajpcell.physiology.org/) published by the American Physiological Society. The accompanying editorial, "Can You Blame Cold Feet on Epac (and Rap1A)? Focus on "Cyclic AMP-Rap1A Signaling Activates RhoA to Induce α2C-adrenoceptor Translocation to the Cell Surface of Microvascular Smooth Muscle Cells," is also online

(http://bit.ly/LYDXFd).

Methodology

Jeyaraj and her colleagues studied smooth muscle cells derived from tiny blood vessels harvested from human skin biopsies and similar cells from mouse tail arteries. These cells contain receptors known as a2C-AR, which cause constriction in their associated blood vessels and shut off blood flow under chilly conditions to conserve heat. The scientists also worked with different cells, called HEK cells, that do not normally express a2C-AR but that can be modified to do so. Also studied were cells taken from tail arteries of mice genetically altered to no longer express a protein called Rap1A, which the authors hypothesized would interact with a2C-AR.

Results

The researchers found that when they dosed cells that expressed a2C-AR with chemicals that activate Rap1A, either directly or through means that involve another protein called Epac, the cells drew from pools of a2C-AR near the cell's nucleus and moved these receptors to the cell surface. The series of events involved rearrangment of the cell's internal "skeleton," fibers that determine its shape and can transport items from one area of a cell to another.

Importance of the Findings and What Part of Cell Physiology Gets 'The Rap'

Authors of the study and the accompanying editorial suggest that the series of events and biological interactions they identified could be responsible for the mechanism the body uses to limit blood supply to the skin in cold temperatures, which conserves more blood flow—and

hence, warmth—for the body's internal organs. The findings may provide clues to where dysfunction occurs in disorders in which blood flow is erroneously cut off, such as Raynaud's disease. In this condition, sufferers lose circulation to the fingers, toes, and occasionally other areas when the body overreacts to cold temperatures. Raynaud's can sometimes be serious, leading to atrophy of skin and muscle, ulceration and rarely to ischemic gangrene. On a lighter note, the results also provide a possible explanation for the age-old problem of cold feet.

"Thus, if your partner complains again about your cold feet," the editorial authors write, "you have some new excuses: 'It's Epac's fault!' or 'Rap1A should get the rap!'"

Study Team

In addition to Selvi C. Jeyaraj, the study team also includes Nicholas T. Unger and N. Paul El-Dahdah of The Research Institute at Nationwide Children's Hospital, Ali H. Eid of Qatar University, Srabani Mitra of Ohio State University, Lawrence A. Quilliam of Indiana University School of Medicine, Nicholas A. Flavahan of Johns Hopkins University, and Maqsood A. Chotani of The Research Institute at Nationwide Children's Hospital and Ohio State University.

Provided by American Physiological Society