Proteins that stop a major signaling pathway can also generate new proteins

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The team was able to define the way in which proteins called beta arrestins (for their role in stopping signals) also turn on pathways that ultimately lead to the production of new proteins in virtually all tissues in the body.

Because proteins are the building blocks for all cells, this new pathway for the general control of protein manufacturing has opened a new universe for biological studies.

The beta arrestins were discovered two decades ago as the off switches for G protein-coupled receptors (GPCRs) on the cell surface, which do the job of sending and receiving important signals for cells. This mechanism is the target of about a third of all pharmaceuticals today.

The GPCRs, which were first theorized and discovered at Duke by the study's senior author, Robert J. Lefokowitz, MD, begin a signaling cascade that transmits a message from the cell surface, such as a hormone or neurotransmitter, to the cell's interior and tells it to do something, such as cranking out a particular protein.

These receptors regulate virtually all physiological processes, everything from heart rate to mood. Research on GPCRs has led to numerous successful drugs, including beta blockers which help relieve hypertension, angina and coronary disease, as well as new antihistamines and ulcer drugs. They also formed the basis of Nobel Prize winning work on smell receptors.

"The reason the new work is so exciting to me is that it reminds us, yet again, how the scientific process continuously renews itself, said Lefkowitz, James B. Duke Professor of Medicine and investigator of the Howard Hughes Medical Institute. "We discovered the beta arrestins almost 20 years ago, and now we find out they play signaling roles we never dreamed of back then. We are hopeful that these new ideas may lead to new types of drugs."

The study's findings, published in this month's *Journal of Biological Chemistry*, identified an enzyme called Mnk1 which is activated by beta-arrestin signaling. "What's been discovered here is that beta arrestins initiate important cell signals in their own right, and specifically the control over protein synthesis indicates that they may possess wide control of biological functions," said Scott DeWire PhD, lead author and adjunct assistant professor of medicine at Duke University.

"This added layer of complexity provides us opportunities to study receptors in a whole new way, and possibly identify beta-arrestin-specific signaling," DeWire said. "This is something completely unexpected according to the traditional dogma. Ten years ago, nobody would have imagined that beta-arrestins, with their ability to stop the GPCR signals, could exert global control over protein synthesis."

Source: Duke University