JGP Journal of General Physiology

RESEARCH NEWS

Probing insulin secretion with a new tool

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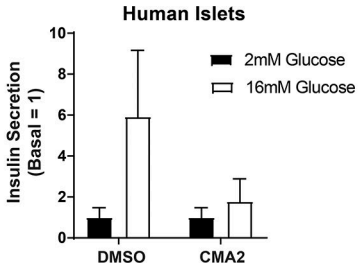
JGP study explains how chromomycin A_2 affects insulin secretion.

Glucose is a primary source for cellular energy, but chronic exposure to elevated glucose is toxic for cells. Pancreatic β cells respond to spikes in blood glucose levels by secreting insulin, a hormone that instructs other body cells to take up and metabolize the sugar. Impaired insulin secretion or loss of β cells can cause diabetes, a disease that in 2017 affected almost 10% of US adults (1). The pathways regulating insulin secretion have been intensively studied but are still not fully understood. In their new *JGP* paper, Kalwat et al. present their insights on how the compound chromomycin A_2 (CMA2) affects β-cell insulin secretion—findings that could lead to better understanding of this important process (2).

β-cell insulin secretion is regulated through two major pathways, both stimulated by the products of glucose metabolism. In the triggering pathway, which is fairly well studied, glucose metabolism generates ATP that ultimately spurs opening of plasma membrane calcium channels, thereby prompting the release (via exocytosis) of insulin-containing vesicles. The other pathway driving insulin secretion, the amplifying pathway, is more mysterious (3).

"The amplifying pathway generates a host of metabolic intermediates that increase the amount of insulin a β cell secretes in response to a calcium signal," explains Michael Kalwat, an instructor at the University of Texas Southwestern. "This can account for almost half of the insulin that's secreted."

Seeking new tools to study this process, Kalwat conducted a high-throughput screen to identify compounds that affect β-cell insulin secretion (4). One of the strongest hits from the screen was CMA2, a member of the aureolic acid family produced by the marine bacterium *Streptomyces anulatus*. CMA2 potently inhibits insulin secretion, so it would not be therapeutically useful in treating diabetic disease that results from impaired insulin secretion. "But," notes Kalwat, "whatever you find about how that inhibitor works could point you toward discovering a novel positive regulatory pathway."



Studies by Michael Kalwat (left) and colleagues (not shown) on how the natural product chromomycin A_2 inhibits insulin secretion by pancreatic β cells (see graph) may help identify new positive regulatory pathways involved in this process. Photo courtesy of the author.

Kalwat et al. found that although short-term exposure (1–2 h) to CMA2 did not impact insulin secretion, prolonged treatment (24 h) blocked insulin secretion from both isolated β cells and intact human islets. But CMA2 did not prevent insulin production, nor did it affect glucose-stimulated calcium influx, even after 24 h. Instead, 24 h exposure to CMA2 altered the expression of several β-cell genes, suggesting that a large part of CMA2's effect on insulin secretion might be attributable to its impacts on gene expression. Surprisingly, the closely related compound mithramycin, which can also alter gene expression in cells, was ∼50 times less effective in blocking insulin secretion compared with CMA2.

CMA2 affects a long list of genes, so to help focus their inquiries, Kalwat et al. used the Fusion database, which links natural products like CMA2 with the genes whose expression they modulate, and clusters those genes into functional groups (5). Consistent with prior studies (6), the analysis suggested CMA2 might affect expression of genes in the β-catenin/Wnt signaling pathway, which is known to be important for insulin secretion. Experiments conducted by Kalwat et al. confirmed that CMA2 indeed disrupts signaling by the β-catenin/Wnt signaling pathway.

The authors' results suggest that CMA2 may affect the expression of genes involved in both the triggering and amplifying insulin secretion pathways. This may include targets associated with mitogen-activated protein kinase signaling, S6 phosphorylation, β-catenin/Wnt, and possibly even exocytosis, although the data do not rule out potential interactions with protein targets. Currently, Kalwat is pursuing RNA sequencing analysis to identify which genes are uniquely affected by CMA2 compared with mithramycin. He says, "I anticipate that this data will lead to new knowledge about β-cell function."

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4. Kalwat, M.A., et al. 2016. *ACS Sens.* 1:1208–1212.
5. Potts, M.B., et al. 2013. *Sci. Signal.* 6:ra90.
6. Toume, K., et al. 2014. *Mar. Drugs.* 12:3466–3476.

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