VIEWPOINT

Observations on the Discovery of Glucagon-Like Peptide-1 Action

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As the benefits of glucagon-like peptide-1 (GLP-1) medications expand beyond diabetes and obesity,[1] there is great interest in the scientific events and roles of key individuals contributing to the discovery of the biological action of GLP-1. During the period of time described in a 2024 Viewpoint,[2] we were postdoctoral fellows in Dr Joel Habener's laboratory at Massachusetts General Hospital (MGH; 1984-1988) in Boston, where the initial work was conducted. We write to contribute our observations on the events and roles of individuals.

The ambiance and friendship were excellent among all researchers in the Habener group, where we worked closely with Dr Svetlana Mojsov and others, including Dr Daniel Drucker. Prior to the work on proglucagon processing, the Habener laboratory had already studied and published several papers on the biosynthesis and post-translational processing of prohormones, such as parathyroid hormone, calcitonin, several glycoprotein hormones, and somatostatin. Hence, discussion of how and where prohormones, including proglucagon, might be cleaved to yield smaller bioactive proteins was a regular feature of laboratory discourse and in our meetings, where data were freely shared.

Following cloning of the glucagon complementary DNA (cDNA) and genes from anglerfish and rat, the putative sequences encoding GLP-1 and GLP-2 were identified. The identification of a GLP-1 sequence as a putative peptide within proglucagon focused the Habener laboratory on identifying the biological action of the various GLP-1 forms. Mojsov, working in the Endocrine Unit as director of the Peptide Chemistry Core Facility, collaborated with Habener and Dr Lelio Orci to develop antibodies and radioimmunoassays to study proglucagon-derived peptides. Mojsov then used these reagents to study the post-translational processing of proglucagon in the rat pancreas and intestine, identifying multiple forms of GLP-1, including both GLP-1(1-37) and GLP-1(7-37) in extracts from the pancreas and intestine.[3]

From his studies of proglucagon cleavage in 3 different cell lines, fibroblasts, pituitary cells, and islet cells transfected with the proglucagon cDNA, carried out in collaboration with Mojsov, Drucker identified that proglucagon processing yielded multiple molecular forms of GLP-1, including GLP-1(7-37) in the pituitary and islet endocrine cell lines.[4] Notably, a longer 37-amino acid form of GLP-1, GLP-1(1-37), had been reported to exhibit activity in studies of adenylate cyclase activation in rat hypothalamic and pituitary cell membranes as well as in analyses of insulin secretion[5]; however, this form of GLP-1 subsequently turned out to be inactive.

Drucker, working in the Habener laboratory, was responsible for identifying the potential actions of GLP-1 as well as the cell determinants and identity of key peptides liberated from proglucagon processing. Drucker was the first person to our knowledge to conduct studies on GLP-1 action at MGH. Noting the presence of both GLP-1(1-37) and GLP-1(7-37) generated in the studies of proglucagon processing, Drucker tested the various isoforms of GLP-1 in the same 3 cell lines (fibroblasts, pituitary cells, and an insulin-secreting islet cell line) to study the direct actions of GLP-1. Drucker showed that GLP-1(7-37) but not GLP-1(1-37) was able to powerfully stimulate insulin secretion and cAMP (cyclic adenosine monophosphate) levels and, in collaboration with Dr Jacques Philippe, showed that it also increased insulin gene expression in the insulin-secreting islet cell line. Notably, these experiments were carried out at several different glucose concentrations (25 mM vs 5.5 mM), representing the first demonstration that the actions of GLP-1 on insulin-producing islet cells were glucose-dependent. These exciting experimental results were regularly discussed as part of our laboratory meetings that periodically included Mojsov and others working on projects related to hormone processing and action.

Drucker's experiments describing the discovery of GLP-1 action on insulin-producing islet cells were reported in a manuscript from the Habener laboratory describing GLP-1 action,[6] with Mojsov as a coauthor, reflecting her contribution of peptides used in the experiments.

The relative timing and priority of the key experiments, specifically those conducted by Drucker using the islet cells, vs the subsequent collaborative studies by Mojsov, Habener, and Dr Gordon Weir carried out at the Joslin Diabetes Center, were noted in the Discussion section of the 1986 post-translational processing publication from Mojsov,[2] where it is stated, "We and others have observed an insulinotropic effect of GLP-1 on islet cells in vitro" and the footnoted reference to support this statement references "D. J. Drucker, J. Philippe, S. Mojsov, W. L. Chick, and J. F. Habener, manuscript in preparation."

Critically, after Drucker's findings on the biological effects of GLP-1 to stimulate glucose-dependent insulin secretion were known in the laboratory, a collaboration was arranged by Habener and Mojsov with Weir working at the Joslin Diabetes Center to test GLP-1 in the perfused rat pancreas, with the positive results published as a rapid communication.[7] This publication also mentioned Drucker's results in the Discussion section as "manuscript in preparation." As frequently happens, the original referenced Drucker et al islet cell line manuscript underwent several rounds of revision at *PNAS* (*Proceedings of the National Academy of Sciences of the United States of America*) before ultimately being accepted for publication.[6]

The pioneering set of experiments of Drucker, who started the work on the biology and actions of GLP-1, merits acknowledgment. Drucker's discovery that GLP-1 acted directly on islet β-cells to stimulate insulin biosynthesis and secretion in a glucose-dependent manner was fundamental to identifying a truncated form of GLP-1 as biologically active and set in motion the subsequent work in Boston and elsewhere. In this Viewpoint, we seek to provide a more complete

chronology of roles and events surrounding the GLP-1 discovery in Boston. The story of the GLP-1 discovery is a timely reminder of the therapeutic implications of supporting basic science research. New medicines based on GLP-1's actions are providing compelling new therapeutic options for diabetes, obesity, and a range of cardiometabolic and neurological disorders.

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