New insights into the effects of glucagon-like peptide-1 on heart rate and sinoatrial node function

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Glucagon-like peptide-1 (GLP-1) is an incretin hormone produced in endocrine cells in the small and large intestines with known effects on insulin secretion.\textsuperscript{1,2} GLP-1 elicits its effects via a G-protein coupled receptor denoted GLP-1R.\textsuperscript{2} Multiple GLP-1 related compounds have now been approved for the treatment of type 2 diabetes mellitus (T2DM) and for body mass management.\textsuperscript{2} Patients with T2DM are at increased risk of cardiovascular diseases, which substantially increase morbidity and mortality in these individuals.\textsuperscript{2} Importantly, a number of trials in patients with T2DM have shown that treatment with GLP-1R agonists effectively reduces major adverse cardiovascular events and cardiovascular mortality.\textsuperscript{3,4} As a result, there remains substantial interest in the use of GLP-1R agonists for the treatment or prevention of cardiovascular disease in T2DM and potentially in other conditions as well.

While the beneficial effects of GLP-1R agonists in clinical trials have generated enthusiasm for these compounds, there is much that is still unknown about their effects on the heart and cardiac function. This is due in part to an incomplete understanding of which cell types in the heart express GLP-1R and a need for studies assessing the cellular and molecular mechanisms for GLP-1 (and related analogues) effects on the heart.

It is well documented in clinical and pre-clinical/animal studies that GLP-1R agonists elicit a positive chronotropic effect\textsuperscript{1,2}; however, the basis for this increase in heart rate is poorly understood. Previous studies have provided evidence for both direct and indirect effects of GLP-1/GLP-1R agonists on the heart to explain increases in heart rate.\textsuperscript{5,6} Understanding the basis for the effects of GLP-1 on heart rate is important because an increase in heart rate is associated with worse outcomes in some heart disease patients.\textsuperscript{7}

Heart rate is determined by the intrinsic spontaneous activity of the sinoatrial node (SAN).\textsuperscript{8,9} The specialized pacemaker myocytes of the SAN generate spontaneous action potentials, characterized by a phase 4 diastolic depolarization, due to the coordinated activity of a number of ionic mechanisms.\textsuperscript{8,9} More specifically, the hyperpolarization-activated current ($I_{\text{f}}$), carried by hyperpolarization-activated cyclic nucleotide gated (HCN) channels, contributes to
the generation of the diastolic depolarization. In addition, the rhythmic release of Ca$^{2+}$ from the sarcoplasmic reticulum leads to the generation of a Na$^+$-Ca$^{2+}$ exchanger mediated current ($I_{NCX}$) during diastolic depolarization. Each of these ionic mechanisms (as well as a number of other ion channels in the plasma membrane) affect the slope of the diastolic depolarization and hence the frequency of spontaneous action potential firing and heart rate. SAN function (and heart rate) are modulated by the autonomic nervous system, which affects the ionic mechanisms noted above via downstream signaling pathways in SAN myocytes.

In their recent study, Lubberding et al have conducted an elegant series of experiments to further assess the effects of GLP-1 on heart rate and SAN function. Their studies were conducted in a highly relevant porcine model using both intact anesthetized pigs as well as isolated pig hearts and isolated SAN tissues. The authors used single nucleus RNA sequencing to demonstrate that the GLP-1R is located in a population of cells from the SAN that also express HCN4 indicating that GLP-1R is present in pig SAN myocytes. Functional studies demonstrate several key outcomes including (1) that GLP-1 increases heart rate in the pig, (2) the positive chronotropic effects of GLP-1 in the pig are maintained in the presence of autonomic nervous system blockade, α- and β-adrenergic receptor blockers, as well as in the presence of ivabradine (used to block $I_f$), (3) the effects of GLP-1 on heart rate in the pig are prevented by exendin 9-39 (a GLP-1R antagonist), and (4) GLP-1 increases spontaneous action potential firing and diastolic depolarization slope in isolated pig SAN preparations. Phosphoproteomic analysis identified potential effects of GLP-1 on Ca$^{2+}$ signaling and cAMP signaling among other pathways. Based on these experiments the authors conclude that GLP-1 increases heart rate in the pig via direct effects on the SAN and suggest that these effects may involve, at least in part, effects on Ca$^{2+}$ signaling in the SAN.

The results of this study are important and provide critical new insight into the potential mechanisms through which GLP-1 (and possibly other GLP-1R agonists) can increase heart rate. Nevertheless, some questions remain unanswered. While the data demonstrating that the
GLP-1R agonist liraglutide increases heart rate in the pig via direct effects on the SAN are convincing, a prior study in mice concluded that GLP-1 increases heart via effects on the autonomic nervous system. A separate study identified direct effects of liraglutide on heart rate and SAN function in rabbits and mice but, in contrast to the present study, concluded that these effects involved HCN channels and Iᵢ. Whether these differing results are related to species differences or other factors requires further investigation. Related to this, the exact cell types in the heart that express the GLP-1R remains an ongoing issue.

The phosphoproteomic work is insightful and leads to intriguing hypotheses on the mechanisms through which GLP-1 could affect spontaneous action potential firing in SAN myocytes. The authors have suggested effects on Ca²⁺ signaling and cAMP regulation; however, direct assessment of ion channels and sarcoplasmic reticulum Ca²⁺ handling, and their regulation by GLP-1/cAMP signaling, are still needed to validate these hypotheses. The phosphoproteomics results also identified a number of other alterations that could be involved in the effects of GLP-1 in the SAN, which warrant further study. Future studies should also assess the effects of GLP-1 on SAN function in models of T2DM, or other models of heart disease, as there could be effects that are unique in different disease conditions. Whether cardiac GLP-1R expression patterns are altered in different disease states requires further study. Finally, recent studies have demonstrated that chronic GLP-1 treatment in type 2 diabetic mice has effects on atrial ion channel function and fibrosis; therefore, studies on the effects of chronic GLP-1 treatment on SAN structure and function are needed.

In summary, Lubberding et al have generated a very important data set that provides much needed new insight into the effects of GLP-1 on heart rate and SAN function. The study adds to a growing body of literature aimed at addressing this important issue. Continued efforts to investigate the mechanistic effects of GLP-1R agonists on the heart, including the SAN, are critical in order to understand the implications of heart rate effects in patients being treated with GLP-1R agonists.
References

Figure: Schematic representation of the effects of glucagon-like peptide-1 (GLP-1) on heart rate and sinoatrial node function in a porcine model. GLP-1 increased heart rate in anesthetized pigs \textit{in vivo} and in isolated pig hearts. In isolated SAN preparations from the pig heart GLP-1 increased spontaneous action potential firing frequency by increasing the slope of the diastolic depolarization. These data demonstrate that GLP-1 can increase heart rate via direct effects on the SAN in the pig. Figure created with BioRender.com.