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From mice to men: the exocrine pancreas does not matter for human GLP-1 receptor imaging

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Non-invasive determination of pancreatic beta cell mass (BCM) in humans is key to understanding the pathophysiology of Type 1 and 2 Diabetes (T1D, T2D). It appears that BCM and beta cell function are not directly linked and beta cell dysfunction (BCD) is a key pathophysiological parameter. The main challenge of pancreatic beta cell imaging is to use a highly specific tracer molecule so that the signal originating from the pancreas reflects actual BCM (*1*).

Khera and co-workers show that reduction of exocrine pancreatic uptake by GLP-1 receptor (GLP-1R) blocking with fluorescent exendin improves *in vivo* imaging of pancreatic beta cells in mice (*2*). We have previously demonstrated that, as opposed to mice, rats do not display exocrine pancreatic uptake, as confirmed by quantitative PCR (*3*) and immunohistochemical GLP-1R staining (*4*). The human pancreas shows an even higher endocrine-exocrine ratio (*3*) and single cell RNA sequencing demonstrates specificity of the GLP-1R for human beta and delta cells (*5*).

Insulin-positive islets are present in pancreata of people with long-standing T1D, indicating that BCD plays an important role in T1D pathophysiology (*6*). Pancreatic exendin uptake in individuals with T1D therefore reflects dysfunctional BCM (representing highly important information about the pathophysiology of T1D) and not uptake in non-beta cells explaining "…the lack of clinical distinction between healthy volunteers and subjects with long-term diabetes..." as claimed by Khera et al. (*2*).

We have recently shown in people with long-standing T1D that exendin uptake in human pancreata can indeed drop to background levels, a strong argument against exocrine pancreas uptake. About half of the tested individuals showed significant pancreatic uptake pointing towards residual BCM (*7*), in line with the concept of beta cell dysfunction in T1D (*6*). Immunohistochemical analysis of human pancreata from individuals with long-standing T1D indeed confirms presence of numerous GLP-1R expressing beta cells and stains delta cells, the latter explaining the low residual uptake after complete loss of beta cells. Data from healthy individuals confirm exclusive staining of beta and delta cells and no staining in exocrine pancreas (*7*). These data are confirmed by *ex vivo* autoradiography of human pancreatic tissue only showing background uptake in the exocrine pancreas (comparable to rats) (*8*).

Finally, in view of the small differences in exocrine pancreatic uptake between wild type and GLP-1R knock-out mice, shown by Khera and co-workers, (Figure 1) (*2*) and the minor uptake reduction after blocking (*2*), the GLP-1R does not play an important role in exocrine pancreas uptake as shown previously (*4*).

Therefore, although the approach Khera and co-workers present (*2*) is highly interesting, the practical value is limited to mouse imaging. In addition, high pharmacological doses of (fluorescent) exendin may lead to receptor saturation phenomena disturbing the linear correlation between tracer uptake and beta cell mass (*1,3*).

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