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論文題目	Noninvasive quantitative evaluation of viable islet grafts using ¹¹¹ In-exendin-4 SPECT/CT (¹¹¹ Inインジウム標識exendin-4 SPECT/CTを用いた、生存移植膵島量の非侵襲的評価)		
(論文内容の要旨)			
<p>Islet transplantation (IT) is an effective β-cell replacement therapy for patients with type 1 diabetes mellitus. However, due to the lack of methods to detect islet grafts and evaluate their β-cell mass (BCM), further optimization of IT protocols remain challenging. Therefore, the development of noninvasive β-cell imaging is required. Recently, exendin-based glucagon-like peptide-1 receptor (GLP-1R)-targeted imaging has been developed as a promising noninvasive β-cell imaging technique. But most studies involving such imaging have focused on insulinoma or the pancreas alone, whereas only a limited number of studies have examined the possibility of islet graft evaluation for IT. This study aimed to investigate the utility of the ¹¹¹Indium-labeled exendin-4 probe {[Lys12(¹¹¹In-BnDTPA-Ahx)] exendin-4} (¹¹¹In exendin-4) single-photon emission computed tomography/computed tomography (SPECT/CT) to evaluate islet graft BCM after intraportal IT.</p> <p>Different numbers of pancreatic islets from C57BL/6J mice were incubated with 0.37 MBq of ¹¹¹In-exendin-4 for 30 minutes, and the correlation between the radioactive isotope (RI) uptake and islet numbers was examined. Streptozotocin-induced diabetic mice were intraportally transplanted with 150 or 400 syngeneic islets via ileocecal vein. Nonfasting blood glucose and body weight were measured every day for the first week after transplantation and once a week after that. After a six-week observation following IT, the <i>ex-vivo</i> liver graft uptake of ¹¹¹In exendin-4 was compared with liver insulin content level. Furthermore, the <i>in-vivo</i> liver graft uptake of ¹¹¹In exendin-4 using SPECT/CT was compared with liver graft BCM as measured by a histological method. In addition, in order to demonstrate the colocalization of radioactive signals with fluorescence signals of islet grafts in the liver autoradiography (ARG) experiment was performed.</p> <p>During intraperitoneal glucose tolerance test (IPGTT) six-week following IT 150 IT group had significantly higher plasma glucose levels than the control and 400 IT groups at all-time points ($p < 0.05$), with no significant difference between the control and 400 IT groups.</p> <p>The <i>ex-vivo</i> ¹¹¹In-exendin-4 liver graft uptake showed the highest level at 400 IT compared to 150 IT and control groups ($p < 0.01$ and $p < 0.001$, respectively). At the same time, <i>ex-vivo</i> ¹¹¹In-exendin-4 pancreas graft uptake was highest in the control group (control vs 400 IT, $p < 0.0001$; control vs 150 IT, $p < 0.0001$). Liver graft insulin content in the 400 IT group was significantly higher than 150 IT groups (400 IT vs 150 IT, $p < 0.001$), while insulin was not detected in the liver of the control group (400 IT vs control, $p < 0.001$). Furthermore, the <i>in-vivo</i> liver graft uptake of ¹¹¹In exendin-4 using SPECT/CT was compared with that of liver graft BCM measured by a histological method. As a result, probe accumulation was significantly correlated with islet numbers. In addition, ARG showed the colocalization of the radioactive signals with fluorescence signals of islet grafts in the liver.</p>			

In summary, *in-vivo* SPECT/CT could visualize liver islet grafts in the liver noninvasively following intraportal IT. ¹¹¹In-exendin-4 uptake in the liver was corroborated with glycemic outcome and liver insulin content. Furthermore, ¹¹¹In-exendin-4 uptake in the liver correlated with histologically analyzed liver graft BCM. The results suggest that ¹¹¹In-exendin-4 SPECT/CT can provide quantitative information for the islet graft BCM.

(論文審査の結果の要旨)

膵島移植は1型糖尿病の有用な治療法である。しかし、移植後生存膵島量の維持・保護に関しては課題が多く、インスリン治療からの離脱の維持など長期成績の更なる向上には、移植後生存膵島量の非侵襲的評価法の確立が重要である。本研究では、生体の膵臓における β 細胞量評価法である¹¹¹In-exendin-4 SPECT/CTを用い、移植後生存膵島量の非侵襲的評価を試みた。

同系統マウスの膵島を経門脈的に移植したストレプトゾトシン誘発糖尿病マウスでは、その凍結肝切片オートラジオグラフィにおける放射能シグナル像はインスリン免疫染色による蛍光シグナル像と一致した。また、切除肝臓全体における¹¹¹In-exendin-4プローブ集積値は移植した膵島数が多いほど高値であり、肝内インスリン含有量の結果とも一致した。また、¹¹¹In-exendin-4 SPECT/CTでは肝内移植膵島を描出可能であった。さらに、SPECT/CT画像上の¹¹¹In-exendin-4プローブ肝集積値は移植した膵島数が多いほど高値であり、組織学的手法により算出された肝内膵 β 細胞量と正の相関を示した。これらのことから、¹¹¹In-exendin-4 SPECT/CTを用いて移植後生存膵島量の推定が可能であった。以上の研究は、1型糖尿病に対する移植後生存膵島量の非侵襲的評価法の確立に貢献し、糖尿病学の発展に寄与するところが多い。

したがって、本論文は博士(医学)の学位論文として価値あるものと認める。なお、本学位授与申請者は、令和5年8月3日実施の論文内容とそれに関連した試問を受け、合格と認められたものである。