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An autoradiographic study of [^{18}F]FDG uptake to islets of Langerhans in NOD mouse☆

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Abstract

To evaluate the potential of in vivo imaging of accumulation of lymphocytes to islets of Langerhans (insulitis), we compared 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) uptake in the pancreas and pancreatic islets of healthy BALB/c mice, phenotypically healthy NOD mice with insulitis and diabetic NOD mice. [^{18}F]FDG was injected i.v. to 14 female BALB/c mice (age 13 ± 3 weeks, plasma glucose 8 ± 2 mmol/l) and 21 age-matched female NOD mice (plasma glucose 8 ± 4 mmol/l, $p = 0.06$). The mice were killed 90-min post injection and distribution of radioactivity was analysed using digital autoradiography. There was no correlation of plasma glucose concentration with the [^{18}F]FDG uptake values. Uptake of radioactivity in NOD mice to the islets affected by insulitis was up to 2.3 times higher ($p = 0.001$) than that to unaffected islets in the same pancreas. Uptake to NOD islets with insulitis was also clearly enhanced (1.0–2.3 times higher) compared to the islets in the BALB/c mice.

In conclusion, NOD mouse islets with insulitis accumulate [^{18}F]FDG markedly more than islets without insulitis or BALB/c islets. However, the relatively small difference in the [^{18}F]FDG intensity between healthy and diseased islets, combined with the limited resolution ability of the positron emission tomography (PET), probably prevent the use of [^{18}F]FDG in PET studies aiming at in vivo documentation of onset and progression of insulitis and prediabetes in mouse and man.

Keywords: Insulitis; NOD mouse; Autoradiography; Imaging; [^{18}F]FDG uptake

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1. Introduction

Because of restricted accessibility of the pancreas, direct analysis of events in the islets of Langerhans that precede the development of auto-immune diabetes has been problematic. Methods of in vivo imaging of insulitis might increase our understanding of the events that are necessary for progression towards overt diabetes and help in defining potential molecular targets for prevention of auto-immunity and type 1 diabetes.

NOD mice spontaneously develop auto-immune insulin-dependent diabetes mellitus, which resembles human auto-immune type 1 diabetes [1]. Development of insulitis, characterized by accumulation of lymphocytes in and around the islets of Langerhans [2,3], is a prerequisite for auto-immune destruction of the beta cells and in man may precede clinical symptoms of insulin deficiency by months or years. Clinical diabetes in man is believed to develop when 80–90% of the insulin producing beta cells have been destroyed [4]. Insulitis in NOD mice begins at the age of 3–5 weeks, its extent then gradually increases until the age of 12–20 weeks [5], and by the age of 30 weeks, the cumulative incidence of diabetes reaches 80% in female NOD mice [6].

2-[^{18}F]Fluoro-2-deoxy-D-glucose ([^{18}F]FDG) is a radiolabeled glucose analog where one hydroxyl group is replaced by fluorine-18 ($T_{1/2}$ = 109.8 min). [^{18}F]FDG is transported into the cells and phosphorylated there like glucose, but it is not further metabolized [7]. The total tissue radioactivity is composed of [^{18}F]FDG and phosphorylated [^{18}F]FDG, which cannot be separated by external radiation measurements. Therefore, tissue radioactivity in this paper is described as [^{18}F]FDG activity.

[^{18}F]FDG is a useful tumor-detecting agent due to the enhanced rate of glucose utilization by neoplastic and inflammatory cells in several tumor types [8]. [^{18}F]FDG is also effectively taken up by most inflammatory cell types and can be used to quantitate cellular glucose uptake ability [9]. In proliferating thymocytes glucose metabolism reaches values, which may be up to 56 times higher than those in resting thymocytes [10,11].

To study whether in vivo administration of [^{18}F]FDG combined with autoradiography of the pancreatic tissue is useful for visualization of accumulation of inflammatory cells to the pancreas, we compared [^{18}F]FDG uptake to the islets in healthy BALB/c mice and in prediabetic and diabetic NOD mice.

2. Materials and methods

2.1. Animals

A total of 25 healthy female BALB/c mice (age 8, 9, 13 or 20 weeks, n = 3–9 in each age group), of which 11 were used in a prestudy and 21 female NOD mice (NOD/Bom; age 8, 12, 14, 15 and 16 weeks, n = 4, 5, 5, 2 and 5 in the age groups, respectively) were purchased from M&B Laboratories (Ry, Denmark). The mice were housed under standard conditions with free access to standard laboratory chow and tap water. Before the experiment the mice fasted for 6 h but had free access to water.

Principles of laboratory animal care were followed and permission for the study was obtained from the Ethics committee for experimental animals at the University of Turku.

2.2. [^{18}F]FDG

[^{18}F]FDG was synthesized with an automatic apparatus by a modified Hamacher method [12]. The specific radioactivity of [^{18}F]FDG at the time of injection was >37 GBq/μmol and the radiochemical purity exceeded 98%.

2.3. Experimental protocol

In a separate prestudy, the optimal time point for the uptake experiments was determined based on the decline in the blood activity curve and increase in [^{18}F]FDG accumulation to the pancreas. [^{18}F]FDG uptakes were measured in BALB/c mice (n = 11, age 20 weeks) at 30, 45, 60 and 90 min post injection. The pancreas-to-blood uptake ratio of [^{18}F]FDG increased steadily for at least 90 min. The ratio at 60 min was 1.5 ± 1.2 and had reached 2.2 ± 0.6 at 90 min (Fig. 1). As the half-life of ^{18}F is 109.8 min, the 90-min time point was chosen for the estimation of [^{18}F]FDG uptake in the pancreas in this study.

In the experimental series, the mice received 3.7 MBq of [^{18}F]FDG in physiological saline through