Clinical Trials Study

Potential application of neogalactosylalbumin in positron emission tomography evaluation of liver function

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Manuscript source: Unsolicited manuscript

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Received: August 27, 2016
Peer-review started: August 28, 2016
First decision: February 27, 2017
Revised: March 12, 2017
Accepted: April 12, 2017
Article in press: April 12, 2017
Published online: June 21, 2017

Abstract

AIM
To investigate the evaluation of neogalactosylalbumin (NGA) for liver function assessment based on positron emission tomography technology.

METHODS
Female Kunming mice were assigned randomly to two groups: fibrosis group and normal control group. A murine hepatic fibrosis model was generated by intraperitoneal injection of 10% carbon tetrachloride...
Asialoglycoprotein receptor (ASGPR) is expressed abundantly on the surfaces of mammalian hepatic parenchymal cells but rarely on extra-hepatic cells[1-3]. It is believed that the amount of ASGPR represents the number and density of functional hepatocytes in the liver[4,5]. Studies revealed that expression of ASGPR on hepatic cell surface decreases in both cirrhosis and obstructive jaundice patients, with more significant reduction in cirrhosis patients. Sawamura et al[6] found that cell surface expression of ASGPR is very low on hepatocyte carcinoma cells. No ASGPR expression has been found in any metastatic cancer in liver. Tomiguchi et al[7] noted that among patients with chronic active hepatitis, the decrease of ASGPR level is highly correlated with liver fibrosis and necrosis. Therefore, quantitative assessment of the ASGPR expression in liver could directly reflect liver function with a desired accuracy[8].

Technetium-99m-labeled neogalactosylalbumin (99mTc-NGA), a ligand with high affinity to ASGPR, was developed[9,10] and is being applied for differential diagnosis of focal nodular hyperplasia and hepatic cancer with single photon emission computed tomography (SPECT)[11,12]. However, it is the analogue of NGA, technetium-labeled galactosyl human serum albumin (99mTc-GSA), that became widely used in many studies due to the non-specific binding between 99mTc and NGA. 99mTc-GSA became the first approved receptor binding reagent for scintigraphy in Japan[12]. However, the sensitivity, spatial resolution, and quantitative capacity of SPECT limited its application, whereas positron emission tomography (PET) exhibited significant advantages over SPECT[13-15]. Currently, there is no study using NGA PET scan for liver function evaluation.

18F is the most popular positron-emitting isotope for PET imaging. It has a low positron energy and proper physical half-life (110 min), which makes it suitable for in vivo study. 18F-labeled deoxyglucose (FDG) has been applied widely in clinical diagnosis and evaluation of neoplasms. In this study, we successfully synthesized 18F-labeled NGA, and performed a preliminary investigation on a liver fibrosis mouse model for quantitative liver function analysis.

MATERIALS AND METHODS

Establishment of murine liver fibrosis model
All animal experiment protocols were approved by the Institutional Animal Care and Use Committee and carried out in accordance with guidelines of the Laboratory Animal Center of Peking Union Medical College. Female Kunming mice, 6-7 wk and 19-25 g, were obtained from Beijing Weitonglihua Experimental Animal Corporation (Beijing, China). Liver fibrosis was induced by intraperitoneal (ip) injection of 10% carbon tetrachloride oil solution (CCl4) (National Chemical Reagent Group, Beijing, China) at 0.4 mL every 48 h for 42 d[16].

RESULTS
The liver function of the fibrosis model mice was significantly impaired by the use of CCl4. In the fibrosis model mice, hepatic fibrosis was verified by naked eye assessment and pathological analysis. [18F]FNGA was found to predominantly accumulate in liver and kidneys in both control group (n = 21) and fibrosis group (n = 23). The liver uptake ability (LUA), peak time (Ttr), and uptake rate (LUR) of [18F]FNGA between healthy liver (n = 8) and fibrosis liver (n = 10) were significantly different (P < 0.05, < 0.01, and < 0.05, respectively). LUA was significantly correlated with total serum protein level (TP) (P < 0.05). Ttr was significantly correlated with both TP and glucose (Glucose) concentration (P < 0.05 both), and LUR was significantly correlated with both total bile acid and Glucose concentration (P < 0.01 and < 0.05, respectively).

CONCLUSION
[18F]FNGA mainly accumulated in liver and remained for sufficient time. Functionally-impaired liver showed a significant different uptake pattern of [18F]FNGA compared to the controls.

Key words: Neogalactosylalbumin; Positron emission tomography; Liver function; Liver fibrosis; Mouse model

Du SD, Li SH, Jin B, Zhu ZH, Dang YH, Xing HQ, Li F, Wang XB, Lu X, Sang XT, Yang HY, Zhong SX, Mao YL. Potential application of neogalactosylalbumin in positron emission tomography evaluation of liver function. World J Gastroenterol 2017; 23(23): 4278-4284 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i23/4278.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i23.4278

INTRODUCTION
Asialoglycoprotein receptor (ASGPR) is expressed...
Radiolabeling of NGA

18F-labeled neogalactosylalbumin ([18F]FNGA) was synthesized in Beijing Normal University Chemistry College using a protocol published earlier [17]. The radioactive purity was > 99%. The administration dose was 3.7 MBq for each mouse.

Distribution assay of [18F]FNGA

[18F]FNGA (3.7 MBq in 100 μL solution containing about 40 μg NGA) was injected through the tail vein. Blood samples were collected through orbital bleeding at 5, 30 or 60 min after injection, immediately followed by sacrifice of the animal by cervical dislocation and collection of organ samples. Radioactivity of each organ was measured using a radioactive detector (RM-905a; China) and expressed as relative radioactive dosage per gram (%ID/g), with the accumulated radioactivity in the organ divided by the total injected dose per gram of body weight.

Serological examination

Blood samples were collected through orbital bleeding from all animals at different periods after injection of [18F]FNGA. Testing items included total protein (TP), albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bile acid (TBA), lactate dehydrogenase (LD), cholesterol (ChE), urea nitrogen (BUN), blood glucose (Glu), total cholesterol (TC), triglycerides (TG), calcium ions (Ca), adenosine dehydrogenase (ADA), sodium ions (Na), potassium ions (K), prothrombin time (PT), and international normalized ratio (INR).

MicroPET scan

Mice were anaesthetized by chloral hydrate. Immediately after [18F]FNGA injection at 7.4 MBq/kg, a mouse was laid on a microPET scanner (Siemens, Germany) and serial static emission scanning was performed at 120 kV, 100 mA/s and with a 5 mm section cranial thickness. A whole-body PET emission scan was also performed immediately after the injection of [18F]FNGA in a total of 30 min. A second phase scanning was also performed immediately after the 30-min scan at 5 min per scan with 1 min interval for a total of 30 min. Region of interest (ROI) was drawn and the standardized uptake values (SUV) in each ROI was measured.

PET image analysis

The images were semi-quantitatively analyzed by ImageJ software of the microPET for the average SUV within the ROI. Total body radioactivity (Rtotal) was measured by the entire body scan, excluding the injection spot on the tail. Parameters were set up specifically as follows, to reflect the liver capacity for tracer uptake: Liver uptake ability (LUA) was calculated as the peak radioactive value (Rmax) in liver ROI divided by the Rtotal; Peak time (Tpk) was the time when radioactivity in ROI reaches to the Rmax; Clearance index (CI) was the radioactivity in the heart ROI at the time of liver Tpk divided by the radioactivity of the first scanning in the heart ROI; Liver uptake rate (LUR) was defined as LUR = [(Rmax-Rt)/Rtotal]/(Tpk-Tt), where Tt was the point time of the first scan and Rt was the liver radioactivity of the first scan.

Statistical analysis

Statistical analysis was performed with SPSS 13.0 software (IBM, Chicago, IL, United States). Data were expressed as mean ± SD. Shapiro-Wilk test was employed for normal distribution data. Independent t-test was used for comparison between the groups with normal distribution, and Mann-Whitney method was used for those with abnormal distribution. Pearson or Spearman examination was applied for correlation test for normal or non-normal distribution samples, respectively.

RESULTS

Liver function in fibrosis model mice

The number of blood samples was 31 from the fibrosis mice and 29 from the control mice, with the exception of 2 fibrosis mice having failed sampling. As shown in Table 1, liver function of the fibrosis model mice was significantly impaired by the use of CCl4 for 42 d. Laboratory tests for liver function demonstrated significant differences between the fibrosis model mice and the controls in TP, ALB, and Glu with P < 0.05, and in ALP and ChE with P < 0.01. Obvious pinkish fiber cords were observed, even with the naked eye, in the fibrosis model mice. Hepatic fibrosis was also verified by pathological analysis (data not shown) [16].

Biological distribution of [18F]FNGA in mice

Animals were sacrificed after injection of [18F]FNGA according to the following order: 5 min (8 fibrosis and 6 control mice), 30 min (8 fibrosis and 8 control mice), and 60 min (7 fibrosis and 7 control mice). Organs were removed for radioactivity measurement. Figure 1 demonstrates a semi-quantitative analysis of [18F]FNGA in both control mice (Figure 1A) and fibrosis model mice (Figure 1B).
Radioactivity was observed in both organs immediately after $^{18}$FNGA administration. Liver exhibited a continuous accumulation till reaching a peak level, whereas heart showed a quick clearance after $^{18}$FNGA injection.

**Effect of NGA as a PET tracer for evaluation of liver function**

Parameters based on the PET images are shown in Figure 3. The LUA was significantly lower in fibrotic liver than that in the normal liver ($P < 0.05$; Figure 3A). The $T_p$ took significantly longer in fibrotic liver to reach a peak than in the normal liver ($P < 0.01$; Figure 3B). The $^{18}$FNGA accumulating rate (LUR) of fibrotic liver was significantly slower than that of the controls ($P < 0.05$; Figure 3C). No significant differences were found in CI between the two groups.

**Correlation of PET parameters with the lab tests**

Correlation was found between the PET parameters and serological tests including TP, TBA, and Glu (Table 2). LUA was significantly correlated with TP, $T_p$ was significantly correlated with both TP and Glu, and LUR was significantly correlated with both TBA and Glu.

**PET scanning**

Whole body scan was performed on 10 fibrosis and 8 control mice. Clear liver images were acquired without obvious interference from other abdominal organs. Figure 2A exhibits the serial images of a control mouse over a period of 30 min. The liver outline can be clearly observed at 4 min after tracer injection. The liver radioactivity reached the peak level in the control mouse at about 19 min. However, radioactivity in the fibrosis liver reached the peak much later than that in the control group. The tracer remained in the liver at a high level throughout the scanning period. In addition, a clear heart outline was presented in the early phase. In the later phase of the scanning, high tracer accumulation was found in the bladder. Very low radioactivity was detected in the brain, lung, and limbs.

The typical dynamic curves of $^{18}$FNGA in liver and heart of a control mouse are shown in Figure 2B. High radioactivity was observed in both organs immediately after $^{18}$FNGA administration. Liver exhibited a continuous accumulation till reaching a peak level, whereas heart showed a quick clearance after $^{18}$FNGA injection.

$^{18}$FNGA was found to accumulate mainly in liver and kidney over the time of observation in both control and fibrosis model mice, except for the initial high level in blood detected at 5 min after injection.
with \( P < 0.05 \) in the above conditions.

**DISCUSSION**

Multiple methods have been applied in clinical assessment for liver function, including serological tests\(^{18}\). Child-Pugh and model for end-stage liver disease (commonly known as MELD) scoring systems, indocyanine green clearance, and medical imaging modalities like computed tomography, magnetic resonance imaging, and SPECT\(^{19,20}\). The above-mentioned methods provide data on certain types of liver function to meet the clinical purposes for diagnosis and treatment. However, they have prominent limitations for accurate evaluation. PET has become increasingly important as a functional diagnostic tool with various applications, especially in the diagnosis and evaluation of malignant tumors. Recently, effort has been made in using PET for liver function evaluation through sophisticated calculation of \(^{18}F\)FD-Galactose clearance\(^{21}\). It requires extra invasive arterial sampling, the procedure is far from practical, and the result is not visually observational.

To the best of our knowledge, this is the first study applying \(^{18}F\)FNGA in the evaluation of liver function in a fibrotic liver animal model. We demonstrated the significant differences between the fibrotic liver and the normal control liver in their \(^{18}F\)FNGA LUA, PT, and LUR. In addition, the tracer retained in liver for sufficient long time (> 60 min) and generated a clear image of liver, which is a critical tracer for PET scanning.

Several advantages of \(^{18}F\)FNGA were observed for this application to liver function assessment. The rapid clearance from the cardiovascular system, as well as the extended retention in the liver, minimizes the influence to liver imaging and parameter calculation. The tracer was mainly excreted through kidneys, which was an obvious difference from the \(^{99m}\text{Tc}\)-GSA, which is mainly excreted from the gallbladder-gastrointestinal (GGI) tract. Therefore, the imaging result would be less likely to be influenced by obstruction of the GGI tract, which could lead to more accurate liver function evaluation. However, concern has existed about the possible influence of renal function on scanning result. In this study, all animals were normal healthy, except for the induction of liver fibrosis. And, there is no known effect of CCl\(_4\) on renal function. Nevertheless, further study will be needed in animals with kidney defect.

The receptor index (LHL15 and HH15) in the \(^{99m}\text{Tc}\)-GSA study was widely accepted and has been taken as reference because both NGA and GSA bind to the same receptor on hepatocytes\(^{20}\). In this study, therefore, we generated CI and LUA that played similar functional roles as HH15 and LHL15, respectively. In addition, LUR, which evaluated the liver uptake rate for \(^{18}F\)FNGA, also showed significant differences between the control and fibrotic livers, with the fibrotic liver showing a much slower rate. In addition, these parameters were found to be highly correlated with traditional liver function indicators, such as TP and TBA, suggesting that these parameters are appropriate for liver function evaluation.

**Figure 3** Comparison of the \(^{18}F\)FNGA positron emission tomography scan parameters between fibrosis mice (\(n = 10\)) and control mice (\(n = 8\)). A: The LUA was significantly lower in fibrosis liver than that in normal liver; B: The \(T_p\) took significantly longer in fibrosis liver to reach a peak than in the normal liver; C: The LUR of fibrosis liver was significantly slower than that of the controls. \(^\ast P < 0.05\), \(^\ast\ast P < 0.01\) vs fibrosis. \(^{18}F\)FNGA: \(^{18}F\)-labeled neogalactosylalbumin; LUA: Liver uptake capacity; \(T_p\): Peak time; LUR: Liver uptake rate.

**Table 2** Correlation of positron emission tomography scan parameters with serological test results, \(n = 18\)

| Parameter | LUA | TP | LUR |
|-----------|-----|----|-----|
| **LUA**  |     |    |     |
| TP        | 0.559 | 0.038 | -0.632 | 0.015 | 0.286 | 0.321 |
| TBA       | -0.225 | 0.438 | 0.303 | 0.292 | -0.690 | 0.006 |
| Glu       | -0.631 | 0.068 | 0.719 | 0.029 | -0.730 | 0.025 |

\(^1\)P < 0.05. LUA: Liver uptake capacity; TP: Peak time; LUR: Liver uptake rate; TP: Total protein; TBA: Total bile acid; Glu: Glucose.
When liver function was impaired, blood glucose cannot be quickly converted into glycogen, thus leading to an elevated blood glucose level. In fact, some have proposed the use of an oral glucose tolerance test curve to determine the degree of liver dysfunction, tolerance for surgery, and prognosis. We found that both LUR and TR were significantly correlated with blood glucose level, suggesting that the blood glucose level indeed may indicate one of the aspects of the liver function.

This is a preliminary study investigating the use of $^{18}$F-FNGA as a PET tracer, with limitations existing in many regards. First, this study did not demonstrate the correlation of the severity of fibrosis and tracer uptake by the liver. Second, the mechanism of biological metabolism of the $^{18}$F-FNGA needs to be further investigated. Though the animal model employed in this study was well-established, the liver damage in the model could not be quantitatively defined. A progressive liver function loss would be more appropriate to evaluate the role the $^{18}$F-FNGA PET scan images in reflection of the liver function damage.

Functionally-impaired liver showed a significantly different uptake pattern of $^{18}$F-FNGA compared to control liver in PET examination. $^{18}$F-FNGA was mainly accumulated and retained in the liver, and for sufficient time for PET imaging. Excretion from the kidney could be another advantage for $^{18}$F-FNGA to avoid gastrointestinal side effect.

COMMENTS

Background

There are several liver function evaluation methods routinely using in the clinic, such as serological tests, Child-Pugh and model for end-stage liver disease (commonly known as MELD) scoring systems, etc. But, none of these can assess the function of any particular anatomical fraction of the liver. Asialoglycoprotein receptor (ASGPR) is expressed abundantly on the surfaces of mammalian hepatic parenchymal cells. It is believed that the amount of ASGPR represents the number and density of functional hepatocytes in the liver. A ligand with high affinity to ASGPR, neogalactosyl albumin (NGA) was developed. To date, however, there has been no study using NGA positron emission tomography (PET) scan for liver function evaluation.

Research frontiers

This is the first study applying $^{18}$F-labeled neogalactosylalbumin ($^{18}$F-FNGA) in the evaluation of liver function in a fibrotic liver animal model. Functionally-impaired liver showed a significant different uptake pattern of $^{18}$F-FNGA compared to control liver in PET examination.

Innovations and breakthroughs

This is the first study to show $^{18}$F-FNGA mainly accumulated and retained in the liver, and for sufficient time for PET. Our data demonstrated that the parameters from the pharmacokinetics curve of NGA were significantly different between control and fibrosis mice. More importantly, the data was significantly correlated with the major traditional serological tests.

Applications

In the present manuscript, we have reported, for the first time, application of $^{18}$F-FNGA in the evaluation of liver function in a fibrotic and normal liver animal model. Under PET/computed tomography (CT) scan, it could primarily achieve the goals that present the liver function with computerized 3-D imagining techniques. Thus, this can be an intuitive tool to design operations and may predict the risk of hepatectomy. Finally, it can also be used in other medical fields for assessing liver function.

Terminology

Neogalactosylalbumin, positron emission tomography, liver function, liver fibrosis, mouse model.

Peer-review

This is a very interesting application of the PET/CT technique to the analysis of liver pathophysiology. The data are convincing and the specificity of the labeling is adequate.

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P- Reviewer: Aurello P, Boscá L, Mura VL S- Editor: Ma YJ L- Editor: Filipodia E- Editor: Zhang FF
