Title	Brain uptake of halogenated products of D-glucal
Sub Title	
Author	本間, 義夫(Honma, Yoshio) 村瀬, 裕子(Murase, Yuko) 石井, 通子(Ishii, Michiko)
Publisher	共立薬科大学
Publication year	1981
Jtitle	共立薬科大学研究年報 (The annual report of the Kyoritsu College of Pharmacy). No.26 (1981.) ,p.95- 96
JaLC DOI	
Abstract	
Notes	抄録
Genre	Technical Report
URL	https://koara.lib.keio.ac.jp/xoonips/modules/xoonips/detail.php?koara_id=AN00062898-00000026-0095

BRAIN UPTAKE OF HALOGENATED PRODUCTS OF D-GLUCAL

Yoshio Homma, Yuko Murase, Michiko Ishii

本間義夫，村瀬裕子，石井通子

Since a class of unsaturated sugar derivatives, the glycals, were discovered in 1913, these compounds have attracted considerable interest. Their unusual reactivity and the ease of transformation make them particularly important compounds in carbohydrate chemistry. D-Glucal, a kind of the glycals derived from D-glucose, contains a double bond which lies between carbon atoms 1 and 2, therefore, it adds two atoms of halogen or hydrogen *etc.*

In the course of a study concerning the relative permeability of blood-brain barrier (BBB) to a number of sugars including D-glucose and 2-deoxy-D-glucose, we sought to discover a D-glucose analog that retains specificity and can readily converted to their radiolabeled derivatives that would be reasonably stable *in vivo*, and we found that the dihalogen addition products of D-glucal have reasonably greater brain uptakes than 2-deoxy-D-glucose and D-glucose.

In this study we have investigated a process to synthesize the D-glucal dihalides from D-glucose and have measured and compared the brain uptake of the D-glucal dihalides with those of 2-deoxy-D-glucose and D-glucose according to the procedure of Oldendorf.

Male Donryu rats, 250—300 g, on routine laboratory diet were anesthetized with intraperitoneal pentobarbital. The left common carotid artery was surgically exposed and cannulated using a sharp 27-gauge needle and 0.2 ml of the buffered Ringer solution containing the radioactive mixture described above was injected within approximately 0.2 sec. The needle did not impede the free carotid flow past the puncture site, therefore, it was left in the artery after injection to avoid excessive bleeding. The temp. of the injected solution is 20—22°C. The rat was decapitated 15 sec after the injection. During this 15 sec interval the labeled test substance not taken up by brain on a single passage through brain microcirculation, is carried out of the brain blood compartment. The midbrain and the cortex were homogenized in 10 ml of Insta-gel Emulsifier (Packard Instr. Co.) in a homogenizer for 10—15 min., respectively.

Brain uptake was measured relative to tritiated water (^{3}HOH) injected simultaneously as a highly diffusible internal standard, because simultaneous counting of ^{3}H and the radionuclides used in this work is easy and rapid passage through BBB of tritiated water is established.

The ^{82}Br-, ^{36}Cl- and ^{14}C- to -^{3}H ratios in the tissue are divided by the same ratios in the injected mixture, respectively, and the results are multiplied by 100 to provide the brain

* 本報告は *J. Radioanal. Chem.* **56** (1982) (in press) に発表。

uptake of the test substances as a percentage of the water under these circumstances of injection. The brain uptake index (BUI) is thus calculate:

$$\text{BUI} = \frac{^{82}\text{Br, } ^{36}\text{Cl and } ^{14}\text{C in brain tissue}/^{3}\text{H in brain tissue}}{^{82}\text{Br, } ^{36}\text{Cl and } ^{14}\text{C in mixture}/^{3}\text{H in mixture}} \times 100\%$$

The BUI of [^{82}Br]D-glucal dibromides was 59.4±2.4% for the midbrain and 60.1±2.4% for the cortex. The BUI of [^{36}Cl]D-glucal dichlorides resulted in the following data: 55.2±2.2% for the midbrain and 59.5±2.4% for the cortex. The concentration of these injected D-glucal dihalides was 0.23 mM. Since this concentration is much lower than the physiological concentration level of the corresponding hexoses in rat (5 mM), it is unnecessary to take into account the reduction of the BUI which is observed at elevated injected concentrations.

The average BUI of 2-deoxy-D-[1-^{14}C]glucose was 49.4±2.0% for the midbrain and 49.2±2.0% for the cortex. Those of D-[6-^{14}C]glucose was 32.9±1.3% for the midbrain, 33.6±1.3% for the cortex.

Since the brain uptake of the labeled compounds and tritiated water takes place during the first 1—2 sec after injection, the possibility of chemical alteration of the injected compounds prior to the BBB penetration may be excluded, and the remaining fraction not taken up by brain during the single passage is carried on out of the brain blood compartment before decapitation takes place at 15 sec after injection. Consequently, the radioactive substances actually found in the brain tissue are the injected substances which penetrate the BBB and metabolic products of them.

^{18}F-2-Deoxy-2-fluoro-D-glucose (^{18}FDG) has been used as a useful glucose analog in the study of various aspects of glucose metabolism. In favor of the proposed method over ^{18}FDG and another glucose analog, *i.e.*, ^{18}F-3-deoxy-3-fluoro-D-glucose (3^{18}FDG) are the following:

1) D-Glucose dihalides has higher brain uptake than D-glucose and 2-deoxy-D-glucose.

2) The reported synthetic procedures of ^{18}FDG and 3^{18}FDG require 1.5—2 h, whereas direct addition of halogens to D-glucal is completed whithin a few minutes and the overall sample preparation time for animal studies is about 10 minutes. It may be noted that this method is especially advantageous for production of radiopharmaceuticals labeled with short half-lived radionuclides such as ^{18}F.

3) ^{18}FDG and 3^{18}FDG include only one ^{18}F atom in each molecule, whereas D-glucal dihalides is capable of including two radiohalogens. Consequently, usable activity from the proposed compound is twice as much as those from equal moles of ^{18}FDG and 3^{18}FDG.

4) D-Glucal, the precursor of the proposed compound, is synthesized from D-glucose by way of several nonradioactive steps and can be readily available for months without any detectable chemical alteration provided the compound is kept in a refrigerator at −20°C.