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Novel radiochemical and biological characterization of ^{99m}Tc-histamine as a model for brain imaging

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Abstract

Background: Histamine was successfully labeled with technetium-99 m (^{99m}Tc). The studied reaction parameters included substrate concentration, reducing agent concentration, pH of the reaction mixture, reaction time, in vitro stability of the ^{99m}Tc-histamine, and biodistribution in experimental animals.

Method: Accurately weighed 3 mg histamine was dissolved and transferred to an evacuated penicillin vial. Exactly 50 μg $SnCl_2$ dihydrate was added and the pH of the mixture was adjusted to 4 using 0.1N HCl, then the volume of the mixture was adjusted to one ml by N_2-purged distilled water. One ml of freshly eluted ^{99m}TcO4- (~ 400MBq) was added to the above mixture. The reaction mixture was vigorously shaken and allowed to react at room temperature for sufficient time to complete the reaction

Result: The complex gives a maximum labeling yield of 98.0% ± 0.34%, and maintained stability throughout the working period (6 h). Biodistribution investigation showed that the maximum uptake of the ^{99m}Tc-histamine in the brain was 7.1% ± 0.12% of the injected activity/g tissue organ, at 5 min post-injection. The clearance from the mice appeared to proceed via the circulation mainly through the kidneys and urine (approximately 37.8% of the injected dose at 2 h after injection of the tracer).

Conclusions: Brain uptake of ^{99m}Tc-histamine is higher than that of (^{99m}Tc-ECD and ^{99m}Tc-HMPAO) therefore ^{99m}Tc-histamine could be used for brain single-photon emission computed tomography (SPECT). Furthermore, ^{99m}Tc-histamine could be considered as a novel radiopharmaceutical for brain imaging.

Keywords: Histamine; Hexamethylpropyleneamine oxime and ethyl cysteinate dimer; Technetium-99 m; Labeling; Biodistribution; Brain; Imaging

Background

Several recent reviews describe the use of single-photon emission computed tomography (SPECT) alone or in combination with PET and/or functional magnetic resonance imaging (fMRI) in studies of human cognition, imaging of neuroreceptor systems, aiding diagnosis or assessment of progression or treatment response in various psychiatric and neurologic disorders, neuropharmacologic challenge studies and in the new field of molecular imaging, including imaging of transgene expression (Devous 2002; Catafau 2001; Mazziotta and Toga 2002; Lee and Newberg 2005; Bonte and Devous 2003; Devous Sr 1998; Brooks 2005; Heinz et al. 2000; Dickerson and Sperling 2005; Bammer et al. 2005; Eckert and Eidelberg 2005; Kuzniecky 2005). Brain SPECT is now commonly used in the diagnosis, prognosis assessment, evaluation of response to therapy, risk stratification, detection of benign or malignant viable tissue, and choice of medical or surgical therapy, especially in head injury, malignant brain tumors, cerebrovascular disease, movement disorders, dementia, and epilepsy (Lee and Newberg 2005; Bonte and Devous 2003; Devous Sr 1998; Brooks 2005; Heinz et al. 2000; Dickerson and Sperling 2005; Bammer et al. 2005; and Kuzniecky 2005). The selection of the proper isotope to be used in labeling and in imaging is important because it should have a suitable short half-life to avoid unwarranted harmful exposure to radiation and suitable photon energy

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within the range of gamma camera. The two most proper isotopes that fulfill these two precautions are ^{123}I and ^{99m}Tc. Brain imaging in humans is currently achieved by using ^{99m}Tc-ethyl cysteinate dimer (^{99m}Tc-ECD), ^{99m}Tc-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO), ^{125}I-sibutramine, and ^{125}I-fluoxetine (Ogasawara et al. 2001; Chang et al. 2002; Bonte et al. 2010; and El-Ghany et al. 2007). The major disadvantage of these compounds is their poor brain uptake in experimental animals (4.7% for ^{99m}Tc-ECD and 2.25% for ^{99m}Tc-HMPAO) (Walovitch et al. 1989; Neirinckx et al. 1987). Such low uptake enforces us to try to find novel radiopharmaceuticals that can overcome this limitation and can be used as more efficient brain imaging agents. Histamine [2-(1H-imidazol-4-yl)] ethanamine is an organic nitrogen compound involved in local immune responses as well as regulating physiological function in the gut and acting as a neurotransmitter (Marieb 2001). Histamine increases the permeability of the capillaries to white blood cells and some proteins to allow them to engage pathogens in the infected tissues (Di Giuseppe et al. 2003). Histamine is known to be involved in so many physiological functions because of its chemical properties that allow it to be so versatile in binding (Noszal et al. 2004). In this paper, histamine was labeled with the most widely used imaging radionuclide, ^{99m}Tc. Factors affecting the labeling yield of ^{99m}Tc-histamine complex and biological distribution in Swiss Albino mice (25 to 30 g) were studied in detail (Motaleb and Sanad 2012). The radiochemical yield of the product was determined by paper chromatography, paper electrophoresis, and high-performance liquid chromatography (HPLC).

Methods

Drugs and chemicals

Histamine was purchased from Sigma-Aldrich Chemical Company, St. Louis, MO, USA, and all other chemicals were purchased from Merck (Whitehouse Station, NJ, USA) and they were reactive grade. The water used is purged deoxygenated bidistilled water.

Labeling of histamine

Accurately weighed 3 mg histamine was dissolved and transferred to an evacuated penicillin vial. Exactly 50 μg $SnCl_2$ dihydrate was added and the pH of the mixture was adjusted to 4 using 0.1 N HCl, then the volume of the mixture was adjusted to 1 ml by N_2-purged distilled water. One milliliter of freshly eluted $^{99m}TcO_4^-$ (approximately 400 MBq) was added to the above mixture. The reaction mixture was vigorously shaken and allowed to react at room temperature for sufficient time to complete the reaction (Boyd 1986). The proposed structure of the ^{99m}Tc-histamine via reaction of histamine with $^{99m}TcO_4^-$ in the presence of stannous chloride dihydrate at pH 4 at room temperature is shown in Figure 1b, where the oxidation state of ^{99m}Tc changed from +7 into +5 to form a complex with two molecules of histamine. ^{99m}Tc-histamine complex coordinated as a Tc (V) oxocore, leading to complexes in which a TcO^{3+} core exists (Jurisson et al. 1986; Abrams et al. 1991).

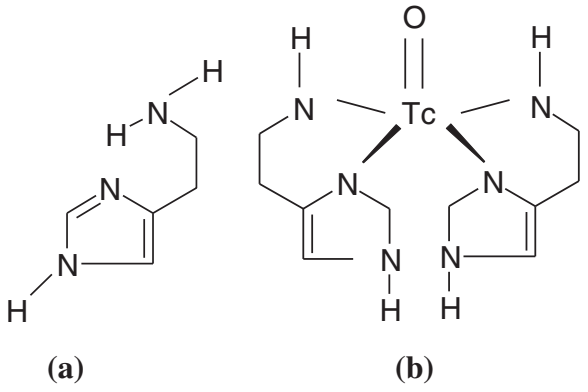

Figure 1 The chemical structure of histamine (a), proposed structure of the ^{99m}Tc-histamine (b).

Factors affecting % labeling yield

This experiment was conducted to study the different factors that affect labeling yield such as tin content as ($SnCl_2 \cdot 2H_2O$), substrate content, pH of the reaction, and reaction time. In the process of labeling, trials and errors were performed for each factor under investigations till obtains the optimum value. The experiment was repeated with all factors kept at optimum changing except the factor under study, till the optimal conditions are achieved (Robbins 1984).

Quality control

Paper chromatography

Radiochemical yield of ^{99m}Tc-histamine was checked by paper chromatography method in which, the reaction product was spotted on ascending paper chromatography strips (10 × 1.5 cm). Free $^{99m}TcO_4^-$ in the preparation was determined using acetone as the mobile phase. Reduced hydrolyzed technetium was determined by using an ethanol/water/ammonium hydroxide mixture (2:5:1) or 5 N NaOH as the mobile phase. After complete development, the strips were dried then cut into 0.5-cm pieces and counted in a well-type γ-scintillation counter.

HPLC analysis

An HPLC analysis of histamine solution was done by an injection of 10 μl from the reaction mixture into the column (RP-18-250 × 4.6 mm^2, 5 μm, Lischrosorb) built in an HPLC Shimadzu model (Kyoto, Japan) which consists of pumps LC-9A, Rheohydron injector and UV spectrophotometer detector (SPD-6A) adjusted to the 256-nm wavelength. The column was eluted with mobile phase methanol/H_2O (50:50) and the flow rate was adjusted to 1 ml/min. Then fractions of 1 ml were collected separately using a fraction collector up to 20 ml and counted in a well-type γ-scintillation counter.

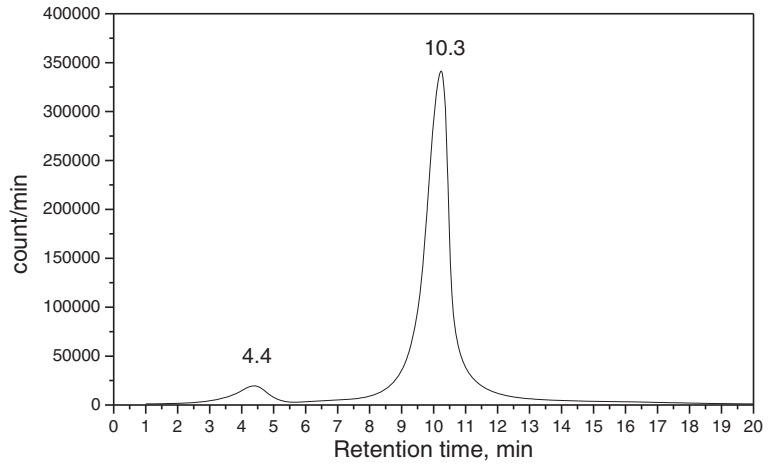

Figure 2 HPLC radiochromatogram of ^{99m}Tc-histamine complex.

Stability of ^{99m}Tc-histamine in human serum

The stability of ^{99m}Tc-histamine was studied in vitro by mixing 1.8 ml of normal human serum and 0.2 ml of ^{99m}Tc-histamine and incubated at 37°C for (24 h). Exactly 0.2 ml aliquots were withdrawn during the incubation at different time intervals up to 6 h and subjected to paper chromatography for determination of the percent of ^{99m}Tc-histamine, reduced hydrolyzed technetium and free pertechnetate

Animal studies

The study was approved by the animal ethics committee, Labeled Compound Department, and was in accordance with the guidelines set out by the Egyptian Atomic Energy Authority. Swiss Albino mice (25 to 30 g) were intravenously injected with 100 μl (100 to 150 MBq) of sterile ^{99m}Tc-histamine adjusted to physiological pH via the tail vein and kept alive in metabolic cage for different intervals of time under normal conditions. For quantitative determination of organ distribution, five mice were used for each experiment and the mice were sacrificed at different times post-injection. Samples of fresh blood, bone, and muscle were collected in pre-weighed vials and counted. The different organs were removed, counted, and compared to a standard solution of the labeled histamine. The average percent values of the administrated dose/organ were calculated. Blood, bone, and muscles were assumed to be 7%, 10%, and 40%, respectively, of the total body weight (Motaleb 2001). Corrections were made for background radiation and physical decay during experiment. Differences in the data were evaluated with the Student's *t* test. Results for *P* using the two-tailed test are reported and all the results are given as mean ± SEM. The level of significance was set at $P < 0.05$.

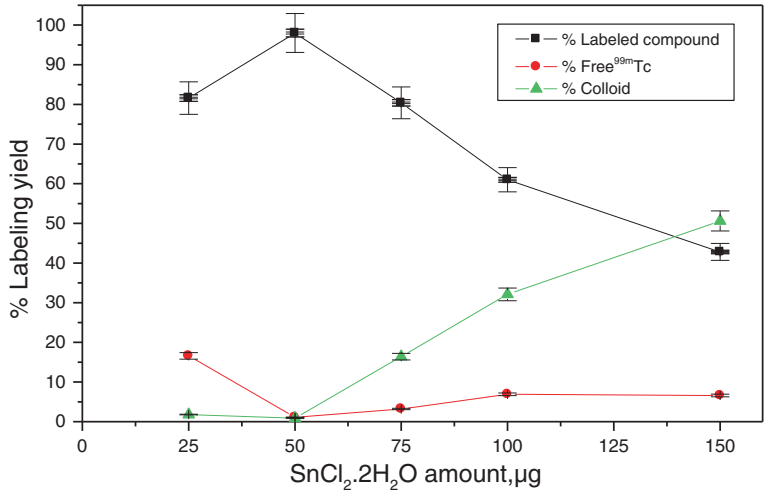

Figure 3 Effect of Sn (II) amount on the labeling yield of ^{99m}Tc-histamine, complex. Conditions: 3 mg histamine, 25-150 μg Sn (II), pH 4 and 30 min. reaction time, n=3.

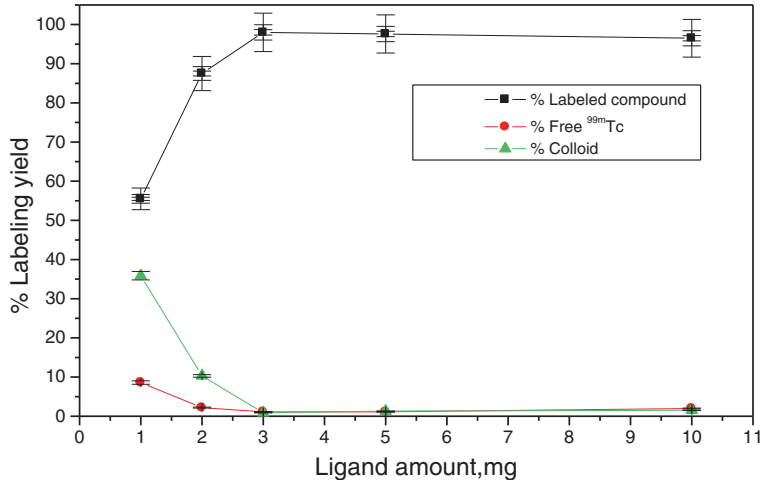

Figure 4 Effect of histamine amount on the labeling yield of ^{99m}Tc-histamine complex. Conditions: 1-10 mg of histamine, 50 μg Sn (II), pH 4 and 30 min. reaction time, n=3.

Determination of the partition coefficient of ^{99m}Tc-histamine

The partition coefficient was determined by mixing ^{99m}Tc-histamine with equal volumes of 1-octanol and phosphate buffer (0.025 M at pH 7.4) in a centrifuge tube.

The mixture was vortexed at room temperature for 1 min and then centrifuged at 5,000 rpm for 5 min. Subsequently, 100 μl samples from the 1-octanol and aqueous layers were pipetted into other test tubes and counted in a gamma counter. The measurement was repeated five times. The partition coefficient value was expressed as log *p* (Motaleb et al. 2011).

$$\mathrm{P} = \frac{\text{Counts per min in octanole} - \text{Counts per min back ground}}{\text{Counts per min in buffer} - \text{Counts per min back ground}}$$

Results and discussion

Separation of ^{99m}Tc-histamine complex

In the case of the ascending paper chromatographic method, acetone was used as the developing solvent; free $^{99m}TcO_4^-$ moved with the solvent front ($R_f = 1$), while ^{99m}Tc-histamine and reduced hydrolyzed technetium remained at the point of spotting. In the case of the ascending paper chromatographic method, mixture was used as the developing solvent; reduced hydrolyzed technetium remains at the origin ($R_f = 0$), while other species migrate with the solvent front ($R_f = 1$). The radiochemical purity was determined by subtracting the sum of the percent of reduced hydrolyzed technetium and free pertechnetate from 100%. The radiochemical yield is the mean value of five experiments.

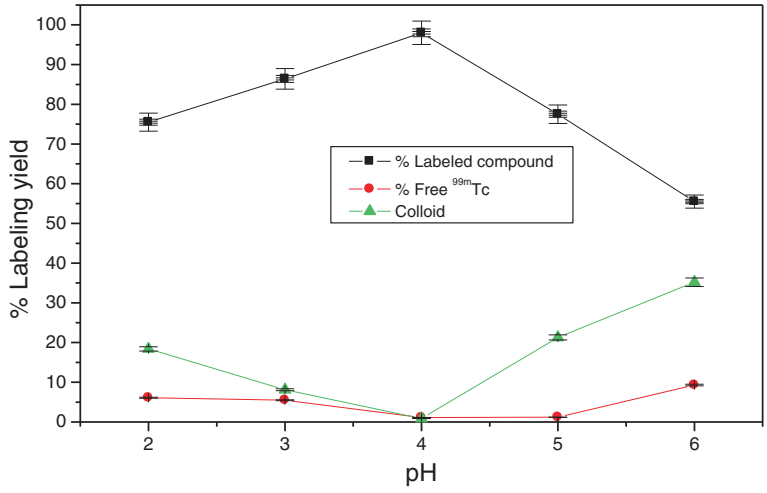

Figure 5 Effect of pH of the reaction mixture of ^{99m}Tc-histamine complex. Conditions: 3 mg histamine, 50 μg Sn (II), pH 2-6 and 30 min. reaction time, n=3.

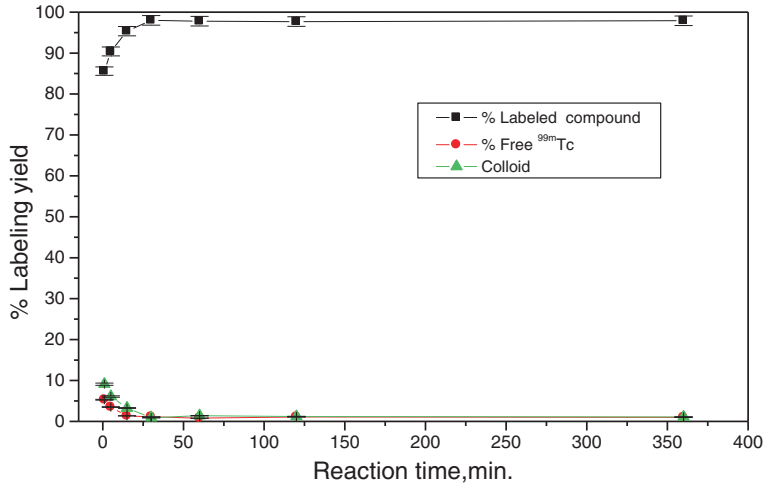

Figure 6 Effect of reaction time on the labeling yield of ^{99m}Tc-histamine complex. Conditions: 1-360 min. at optimum conditions, reaction time, n=3.

HPLC chromatogram was presented in Figure 2 and shows two peaks, one at fraction No. 4.4, which corresponds to $^{99m}TcO_4^-$, while the second peak was collected at fraction No. 10.3 for ^{99m}Tc-histamine, which was found to coincide with the UV signal.

Factors affecting labeling yield

Effect of $SnCl_2 \cdot 2H_2O$ amount

As shown in Figure 3, the radiochemical yield was dependent on the amount of $SnCl_2 \cdot 2H_2O$ present in the reaction mixture. At 25 μg $SnCl_2 \cdot 2H_2O$, the labeling yield of ^{99m}Tc-histamine was 81.6% due to the fact that $SnCl_2 \cdot 2H_2O$ amount was insufficient to reduce all pertechnetate so the percentage of $^{99m}TcO_4^-$ was relatively high (16.6%). The labeling yield significantly increased by increasing the amount of $SnCl_2 \cdot 2H_2O$ from 25 to 50 μg (optimum amount), at which a maximum labeling yield of 98% was obtained. By increasing the amount of $SnCl_2 \cdot 2H_2O$ above the optimum concentration value, the labeling yield decreased again because the excess $SnCl_2 \cdot 2H_2O$ was converted to colloid (50.6% at 150 μg $SnCl_2 \cdot 2H_2O$) (Liu et al. 2004).

Effect of histamine amount

The labeling yield of ^{99m}Tc-histamine complex was 55.5% at 1 mg histamine and increased with increasing the

Table 1 Biodistribution of ^{99m}Tc-histamine in normal mice

Organs and body fluid	% I.D./organ and body fluid at different post-injection times				
	5 min	15 min	30 min	120 min	240 min
Liver	8.11 ± 0.3	6.2 ± 0.1	5.2 ± 0.2	3.2 ± 0.1	1.3 ± 0.02
Urine	5.10 ± 0.2	8.60 ± 0.11	18.1 ± 1.1	23.0 ± 2.3	31.5 ± 2.3
Kidneys	10.5 ± 0.1	12.25 ± 0.3	16.8 ± 1.2	15.2 ± 0.3	6.30 ± 22
Blood	28.4 ± 0.5	24.8 ± 0.9	6.1 ± 0.12	3.50 ± 0.1	1.2 ± 0.05
Heart	1.3 ± 0.01	1.40 ± 0.02	1.6 ± 0.01	0.9 ± 0.03	0.70 ± 0.02
Lung	30.5 ± 0.2	12.8 ± 0.3	11.30 ± 0.2	5.40 ± 0.10	3.25 ± 0.6
Intestine	3.50 ± 0.1	2.80 ± 0.2	1.4 ± 0.02	1.2 ± 0.03	0.9 ± 0.02
Stomach	1.6 ± 0.06	1.20 ± 0.02	2.2 ± 0.05	3.3 ± 0.13	3.70 ± 0.2
Spleen	1.6 ± 0.03	4.52 ± 0.21	6.20 ± 0.2	5.3 ± 0.32	3.80 ± 0.16
Bone	1.90 ± 0.1	1.6 ± 0.3	2.0 ± 0.11	1.80 ± 0.30	1.70 ± 0.13
Muscle	1.8 ± 0.01	1.6 ± 0.03	1.5 ± 0.01	1.2 ± 0.06	1.10 ± 0.02
Brain	7.1 ± 0.12	4.85 ± 0.6	1.4 ± 0.02	0.83 ± 0.06	0.62 ± 0.03
Thyroid	1.3 ± 0.05	0.9 ± 0.02	0.7 ± 0.03	0.55 ± 0.01	0.32 ± 0.01
Brain/blood	0.25	0.2	0.23	0.24	0.52

amount of histamine till reaching the maximum value of 98% at 3 mg (Figure 4). The formed complex remained stable with increasing the amount of histamine up to 10 mg. So the optimum amount of histamine was 3 mg (Liu et al. 2004; Sanad 2007).

Effect of pH of the reaction mixture

As shown in Figure 5, at pH 2, the labeling yield of ^{99m}Tc-histamine complex was small and equal to 75.5% and this yield increased with increasing the pH of the reaction mixture where pH 4 gave the maximum labeling yield of 98%. By increasing the pH greater than 4, the labeling yield decreased again till it became 55.5% at pH 6 where colloid was the main impurity (35.2% at pH 6) after pH 6 more colloidal solutions are formed (Liu et al. 2004).

Effect of reaction time

Figure 6 describes the effect of incubation time on the radiochemical purity of ^{99m}Tc-histamine complex. At 1 min post labeling, the yield was small and equal to 85.6% which increased with time till reaching its maximum value of 98% at 30 min. The yield remains stable at 97.9% for a time up to 6 h (Liu et al. 2004).

Stability test

In vitro stability of ^{99m}Tc- histamine was studied in order to determine the suitable time for injection to avoid the formation of the undesired products that result from the radiolysis of complex. These undesired radioactive products might be accumulated in non-target organs. The results of stability showed that the ^{99m}Tc-histamine is stable up to 24 h and that at 37°C, resulted in no release of radioactivity (n = five experiments) from the ^{99m}Tc-histamine, as determined by paper chromatography (Motaleb et al. 2011).

Partition coefficient for ^{99m}Tc- histamine

The partition coefficient values were 1.48 ± 0.02, showing that the ^{99m}Tc-histamines are lipophilic and can cross the blood–brain barrier.

Biodistribution of ^{99m}Tc-histamine

The biodistribution patterns of ^{99m}Tc-histamine is shown in Table 1, the ^{99m}Tc-histamine was injected in normal mice via intravenous route and was distributed all over the body organs and fluids. All radioactivity levels are expressed as average percent-injected dose per gram (%ID/g ± SD). ^{99m}Tc-histamine was removed from the circulation mainly through the kidneys and urine (approximately 37.8% injected dose at 2 h after injection of the tracer). The liver uptake decreased markedly with time for ^{99m}Tc-histamine from 8.11 ± 0.3, at 5 min till reaching 1.3 ± 0.02 at 4 h (Sanad 2013; Motaleb et al. 2012). The high accumulation of ^{99m}Tc-histamine in lungs is decreased markedly with time from 30.5 ± 0.2, at 5 min till reaching 3.5 ± 0.6 at 4 h (Suhara et al. 1998; Sanad and Ibrahim 2013; Ibrahim and Sanad 2013; Sanad and El-Tawoosy 2013). The biodistribution data showed substantial uptake of 7.1 ± 0.12 (%ID/g ± SD) in the brain at 5 min post-injection. After this time point, radioactivity dropped to 4.85 ± 0.6 at 15 min post-injection. The maximum brain uptake of ^{99m}Tc-histamine (7.1 ± 0.12) is higher than that of currently used radiopharmaceuticals for brain imaging, ^{99m}Tc-ethyl cysteinate dimer (^{99m}Tc-ECD) and ^{99m}Tc- hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO) which have maximum brain uptake of 4.7% and 2.25%, respectively (Walovitch et al. 1989; Neirinckx et al. 1987); therefore, ^{99m}Tc-histamine could be successfully used for brain SPECT.

Conclusion

Histamine can be labeled easily with ^{99m}Tc using 50 μg stannous chloride dihydrate ($SnCl_2 \cdot 2H_2O$) as a reducing agent and 3 mg histamine at pH 4 for 30 min at room temperature to give ^{99m}Tc-histamine complex with a radiochemical yield of 98%, which is higher than that of the commercially available kit. Biodistribution studies showed that the uptake of ^{99m}Tc-histamine in the brain (7.1% ± 0.12) is higher than that of currently used radiopharmaceuticals for brain imaging, ^{99m}Tc-ethyl cysteinate dimer (^{99m}Tc-ECD) and ^{99m}Tc-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO), respectively. ^{99m}Tc-histamine could be used for brain SPECT. Furthermore, ^{99m}Tc histamine could be considered as a novel radiopharmaceutical for brain imaging.

Competing interests

The author declares that he has no competing interests.

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