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Streptozotocin (STZ) and schistosomiasis mansoni change the biodistribution of radiopharmaceutical sodium ^{99m}Tc-pertechnetate in mice

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ABSTRACT

Introduction: Technetium-99m (^{99m}Tc) is a radionuclide commonly used in nuclear medicine to obtain ^{99m}Tc-radiopharmaceuticals, which can be used to evaluate either physiological processes or changes related to diseases. It is also used in some experimental studies. Streptozotocin (STZ) administration to rodents causes lesions in very early stages and induces severe and permanent diabetes. Most morbidity of schistosomiasis mansoni is attributed to a granulomatous inflammatory response and associated liver fibrosis. This study was designed to investigate whether STZ administration and schistosomiasis modify the biodistribution of the radiopharmaceutical sodium ^{99m}Tc-pertechnetate.

Methods: Adult female mice were infected by exposure to 100 *Schistosoma mansoni* cercariae (BH strain, Belo Horizonte, Brazil) and euthanized after nine weeks. STZ was administered by a single intraperitoneal injection of 100 mg/kg body weight, 3 or 15 days before euthanasia. Each animal received 100 μl of sodium (Na) ^{99m}Tc-pertechnetate ($^{99m}TcO_4^-$) (740 kBq). The animals were divided into four groups: A, uninfected; B, infected; C, uninfected + STZ; and D, infected + STZ. Blood, brain, thyroid, heart, lungs, liver, spleen, pancreas and kidneys were removed. The radioactivity was counted and the percentage of the injected dose of $Na^{99m}TcO_4$ per gram of the organ (% ID/g) was determined.

Results: Three days after the STZ injection, there was a decrease of $Na^{99m}TcO_4$ uptake by the liver, lungs, pancreas and kidneys ($p < 0.05$) in group D when compared with group A. After 15 days, the decrease of $Na^{99m}TcO_4$ uptake occurred also in the brain, thyroid, heart, spleen and blood ($p < 0.05$) in group D.

Conclusion: We demonstrated modifications on the biodistribution of $Na^{99m}TcO_4$ due to STZ administration and schistosomiasis, possibly due to physiological alterations in some organs.

Advances in Knowledge and Implications for Patient Care: The biodistribution of radiopharmaceutical $Na^{99m}TcO_4$ should be carefully evaluated in subjects with diabetes and/or schistosomiasis infection.

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1. Introduction

Technetium-99m (^{99m}Tc) is the most widely available radionuclide for the labeling of radiopharmaceuticals used in nuclear medicine [1]. Moreover, it has been used in experimental investigations with animals [2]. It has important physical characteristics, low cost and general usefulness [3,4]. In addition, several ^{99m}Tc-radiopharmaceuticals are used as tools for clinical evaluations [1,5,6] and in other studies [2,3,7,8]. The radiopharmaceutical sodium (Na) ^{99m}Tc-pertechnetate ($Na^{99m}TcO_4$) has been widely used in studies involving the thyroid and salivary glands [1,9,10]. Nevertheless, the subjection of $Na^{99m}TcO_4$ to appropriate radiochemical reactions permits the acquisition of several ^{99m}Tc-radiopharmaceuticals used in different clinical examinations [1,5–7]. It is also used in experimental investigations [11–13], including studies of parasitic diseases [8,14] and diabetes [15].

Diabetes mellitus is a chronic disorder caused by the depletion or malfunction of insulin-producing beta-cells in the endocrine pancreas or by resistance to this hormone [16]. This leads to changes in the metabolism of carbohydrates, proteins and fat [17]. High concentrations of glucose [17], poor wound healing, immune system dysfunction [18,19] and higher susceptibility to bacterial and fungal infections characterize the disease [20,21]. In rodents, drug-induced diabetes mellitus

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is achieved using streptozotocin (STZ), which decreases the action of nicotinamide adenine (NAD) of pancreatic islet β cells, containing glucose receptor GLUT-2 [22], by inhibiting DNA synthesis, and consequently, irreversibly blocks the production of insulin [23,24]. This drug causes severe hyperglycemia similar to type 1 diabetes in humans [23,25]. Moreover, degenerative cellular effects have been highlighted in very early stages of diabetes [26].

Together with non-communicable diseases such as diabetes, neglected tropical diseases (NTDs) mostly affect people who live in extreme poverty, causing chronic and debilitating effects [27]. Schistosomiasis mansoni is an endemic NTD in Africa, the Caribbean and South America, with an estimated 200 million people infected [28]. Schistosomes are blood-dwelling flukes that are highly dependent on host metabolism [29], mainly glucose [30]. Much of the morbidity of schistosomiasis is attributed to the egg-induced granulomatous inflammatory response and associated liver fibrosis [31].

The normal bioavailability and elimination pattern of a radiopharmaceutical can be altered under pathophysiological conditions because of the changes in the tissues. Other factors, besides the state of the disease, can also interfere and affect the bioavailability of radiopharmaceuticals. These factors include drugs (synthetic and natural) and dietary conditions [32]. Little data are available about the effect of parasitic diseases on the biodistribution of ^{99m}Tc-radiopharmaceuticals in laboratory models. In this study, we examined the effect of STZ and/or schistosomiasis mansoni infection on biodistribution of $Na^{99m}TcO_4$ in mice.

2. Materials and methods

2.1. Animals and experimental infection with Schistosoma mansoni

Forty female Swiss Webster mice, 60 days old, from the Laboratory Animal Breeding Center (CECAL), Oswaldo Cruz Institute, Rio de Janeiro, RJ, Brazil, were housed in polypropylene cages (40 × 33 cm) at constant temperature (21 ± 1 °C) and humidity (60 ± 10%) with a 12 h light–dark cycle. The mice were fed standard chow (Nuvilab CR-1-Nuvital Nutrients Ltda., Colombo, Paraná, Brazil) and water *ad libitum*. The animals were divided into four groups, in each experiment (n = 5 per group): A, uninfected; B, infected; C, uninfected that received STZ; and D, infected that received STZ.

All protocols were approved by the ethics committee for the use of animals of State University of Rio de Janeiro, under protocol number CEUA/013/2013.

Mice (n = 20) were each infected transcutaneously by exposure to ~100 *S. mansoni* cercariae (BH strain, Belo Horizonte, Brazil) [33]. The establishment of infection was confirmed by fecal examination using the quantitative Kato-Katz method [34], 43 days after exposure to infection.

2.2. Drug treatment

Mice were treated with a single intraperitoneal injection of 100 mg/kg body weight of STZ (Sigma-Aldrich, MO, USA) freshly dissolved in 0.01 M citrate buffer at pH 4.5 (Sigma-Aldrich, MO, USA) [35]. The drug was administered at 3 or 15 days before euthanasia.

The stock solution used in this experiment was 50 mg of STZ diluted in citrate buffer, and injected within 15 min of preparation. Body weight was determined (BioPrecisa, JH2102 scale) before the application of STZ. The control animals received 0.9% saline solution.

In order to reduce death due to hypoglycemic shock, STZ-treated mice received a 5% glucose solution instead of water during the first 24 h after STZ administration [36].

2.3. Administration of the ^{99m}Tc-radiopharmaceutical

Nine weeks post-infection, each of the 40 mice received 0.1 ml (740 kBq) of $Na^{99m}TcO_4$, freshly eluted from a ^{99}Mo-^{99m}Tc generator of the Nuclear Medicine Service of Pedro Ernesto Hospital, associated with State University of Rio de Janeiro, through intraperitoneal injection.

2.4. Euthanasia

The mice were euthanized by cervical dislocation 10 min after exposure to $Na^{99m}TcO_4$, in the 3rd or 15th days after STZ injection.

2.5. Biochemical determinations and uptake of the radiopharmaceutical

Blood samples were collected by cardiac puncture for biochemical determinations, without previous fasting. Blood glucose levels were measured using glucometer test strips (G-Tech Free SD Biosensor, Inc.). Animals with glucose levels higher than 190 mg/dL were considered diabetic [37].

Brain, thyroid, heart, lungs, pancreas, liver, spleen, and kidneys were collected and weighed on a precision balance (BioPrecisa, model JH2102) [12]. The radioactivity of the blood sample and organs was measured using a well gamma counter (Packard Instrument Company, model C5002, USA) provided with a sodium iodide crystal NaI (Tl), containing thallium impurities. After radioactivity counting, (i) the percentage of total injected dose of ^{99m}Tc (% ID) in organs and (ii) the percentage of the injected dose of ^{99m}Tc per gram of tissue (% ID/g) absorbed in each organ were calculated.

2.6. Statistical analysis

The values are presented as means ± SEM. The data obtained from glucose dosage were analyzed using the Student t-test. The data obtained (%ID/g) were also analyzed using the Mann–Whitney test. All statistical analyses were performed with the program BioEstat 5.3 (Instituto de Desenvolvimento Sustentável Mamirauá, Brazil). p-values <0.05 were considered statistically significant.

3. Results

The results obtained from the blood glucose determination are shown in Table 1. Mice treated with STZ had elevated blood glucose levels compared to their untreated counterparts. As expected, on day 3 the level of glucose did not show pairwise statistical differences ($p > 0.05$) between STZ groups and control. In addition, the levels of glucose of the animals without STZ treatment were considered normal [37]. The levels of glucose increased significantly on the 15th day (>54.9%; $p < 0.05$), whereas controls showed reduced levels. The glucose level of 228.4 ± 26.1 mg/dL was considered to be a standard blood concentration to indicate diabetes in the animals.

When the evaluation of the effects of schistosomiasis on the biodistribution of the radiopharmaceutical $Na^{99m}TcO_4$ was performed on the 3rd day after STZ administration (Table 2), it was noted that the %ID/g in liver was significantly lower (<48.5%, $p < 0.05$) between infected animals (group B) and the uninfected group (group A). The thyroid is an important target of $Na^{99m}TcO_4$, (Table 2) and the %ID/g, as expected, was higher, but no statistical differences between infected animals and uninfected group were found. Although an increase in the %ID/g was identified in the spleen, this alteration also was not significant.

Table 1
Blood glucose determination 3 and 15 days after treatment with STZ (mg/dL) (mean ± SEM).

Glucose levels	Groups		p
	Without treatment with STZ	Treated with STZ	
3 days	185.4 ± 13.4	197.4 ± 10.2	0.4840
15 days	147.5 ± 12.7	228.4 ± 26.1	0.0164

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