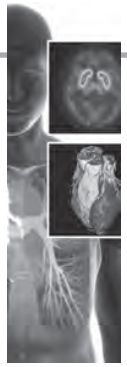

Biodistribution and kinetics of ^{67}Ga-β-neurotoxin using SPECT molecular imaging

Irene Vergara-Bahena[1] & Luis Alberto Medina*[1,2]

[1]*Unidad de Investigación Biomédica en Cáncer INCan/UNAM*

[2]*Instituto de Física Universidad Nacional Autónoma de México*

**Author for correspondence:*

Tel.: +52 (55) 56225186

Fax: +52 (55) 56225009

medina@fisica.unam.mx

At least venomous snake bites 2000 persons each year in US. The severity of envenomation depends of the snake specie, its size, location of the bite and quantity of venom injected; but also depends of the health of the victim, age, size, and the time it takes to receive medical care. The envenomation is a medical emergency that requires fast attention to avoiding fatalities; in this sense, knowledge about distribution and kinetics of venom is valuable information that significantly helps to clinicians for treating it.

The main reported method for detecting and quantify venom or isolated toxins, in experimental envenomation, is the immunoassay ELISA. However, it has some limitations; for example, it needs significant volume of blood for quantitation, requires to sacrifice the animal to obtain organs and tissues, and sometimes the quantification is not possible due to the integrity of the antigen was lost during procedures of extraction from tissues. Biodistribution study of toxins and venoms by radiolabeling molecular imaging presents several advantages such as: 1) allows the tracking of toxins in blood for long in the same alive animal, reducing the number of animals used in each experiment; 2) permits to measure the accumulation in organs at different times without sacrifice the animal; 3) the distribution by lymphatic system, which is a common route for distribution of snake toxins, can easily distinguished.

Radiolabeling molecular imaging techniques are powerful tools for studying physiological processes on a cellular level as well as biodistribution and kinetics of radiolabeled biomarkers proposed for diagnostic and therapy. Imaging modalities can be distinguished based on whether they are structural (CT and MRI) or functional imaging techniques (SPECT and PET) [1]. Single Photon Emission Computed Tomography (SPECT) uses radioactive tracers and a radiation detector scanner with specific performance to localize (radio)activity distribution within the body that a computer constructs into two- or three-dimensional images; this information is used to detect a physiological abnormality or to track the kinetics of radiolabeled molecules *in vivo* and in real time. Principal radionuclides routinely employed for SPECT imaging include the gamma emitters ^{99m}Tc, ^{111}In, ^{67}Ga and ^{131}I.

In the field of toxinology, significant efforts have been done to study the pharmacokinetics (PK) and the envenoming development caused by snake venoms. In order to determine the PK of venoms or isolated toxins some researchers have took advantage of radiolabeling techniques, especially by radioiodination. In 1997 Riviere *et al.*, performed an elegant experiment in order to improve the antivenom therapy. They analyze the PK of the *Vipera aspis* venom radiolabeled with ^{125}I and its modification in presence of the antivenom; their results made a great contribution in the field of toxinology providing invaluable information to design and improve the antivenom therapy. Unfortunately, incomplete knowledge still exists with regarding to absorption, biodistribution and elimination of most of venoms or isolated toxins.

Several works have reported the radiolabeling of isolated toxins or complete venoms using ^{99m}Tc, which is the most common radionuclide employed in molecular imaging; for instance, the tityustoxin from the scorpion *Tityus serrulatus*, a bee venom and the *Crotalus durissus terrificus* snake venom; all of them with successful results [2-4]. By considering that antivenoms are essentially antibodies or their fragments, they also could be radiolabeled on the same way that some therapeutic antibodies used in radioimmunotherapy of cancer and used to evaluate its behavior in the presence of the venom.

We recently reported the use of ^{67}Ga to radiolabeling a β-neurotoxin (β-NTx) from venom of the eastern coral snake *Micrurus fulvius* and its biodistribution by SPECT molecular imaging [5]. The ^{67}Ga is an excellent radionuclide for long-time tracking of β-NTx, since it has a large half-life time (3.2 days) and emits three main gamma energies (93.3, 184.6 and 300.2 keV) that are suitable for SPECT imaging; its cost and availability, as compared with ^{111}In, a radionuclide with 2.8 days half-

life and "clean" gamma energies (171 and 245 keV), make it accessible to study envenoming development. In that work we confirmed the participation of the lymphatic system in the absorption and biodistribution of the β-NTx; its elimination by renal route was also observed. A significant result was to confirm the hypothesis that a venom depot subsists after inoculation from where the β-NTx gradually moves into the blood circulation through lymphatic vessels [6-8].

Radiolabelling molecular imaging approach could have an important contribution in the field of toxinology; for instance, to detect, quantify and to know the elimination route of immunocomplexes (toxin-antivenom), which has not been possible by using conventional methods as ELISA. This approach could also be useful for better understanding of tissue damage caused by some snake and spider toxins at cutaneous or muscular level. Also, can be functional to study some toxins that possess potential therapeutic properties against relevant diseases as cancer.

Conclusion

Radiolabeling molecular imaging is a potential technique that could be extended to study the PK and biodistribution of venoms and/or toxins from poisonous animals, as well as antivenoms.

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