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[C-11]LABELING OF BIOLOGICALLY ACTIVE SUBSTANCES CONTAINING QUATERNARY AMMONIUM STRUCTURES AND THEIR TISSUE DISTRIBUTIONS.
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In biologically active substances, many quaternary ammonium compounds are present. Among them, choline derivatives are the typical compounds. Acetylcholine (Ach) is one of the important neurohumoral transmitters and choline (Ch) is regarded as the precursor of them. It is expected that [C-11]Ach or [C-11]Ch is useful for the study of cholinergic receptors as a positron tracer in vivo. The [C-11]labeling method of Ach or Ch is as follows : (1) trap of [C-11]CH_3I (2) reaction of starting materials with [C-11]CH_3I (3) separation of [C-11]labeled products and unreacted starting materials by column chromatography. [C-11]Ach or [C-11]Ch was obtained in high radiochemical purity within 60 min. (radiochemical yield (r.y.) [C-11]Ach : 51-57 %, [C-11]Ch : 48-55 %) The [C-11]labeling of cytidine diphosphate choline (CDP-choline) was also performed with a few modifications of the above method. (r.y. 23 %) This compound is the active form of choline and expected to be applied as a positron tracer in the study of phospholipid formation. By administrating [C-11]Ach, [C-11]Ch and [C-11]CDP-choline to rats, it has been demonstrated that they show the similar tissue distributions and are mainly accumulated in the adrenal, kidney, moderately in the heart and low in the brain.

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DEVELOPMENT OF RADIOPHARMACEUTICALS FOR THROMBUS DETECTION (V) : A NEW PLATELET SPECIFIC LABELING AGENT, I-125 IODINATED METARAMINOL.
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In our search for platelet specific labeling agent, l-metaraminol hydrogen D-tartrate (MA), an agent for the treatment of hypotension, caught our attention since it is recognized as a drug actively incorporated by platelets. An easy and efficient iodination using chloramine-T method yielded new low toxic and platelet specific agent, I-125 MA. Platelet labeling with this new radiopharmaceutical could be easily performed in plasma by 30 min incubation at 37° C reaching efficiency of 44.5±3.5% at 2-3 x 10^8 cells/ml, and 63.0±3.1% at 24x10^8 cells/ml. Pharmacological studies indicated the specific incorporation of I-125 MA by active transport system similar to that for 5-HT as well as passive diffusion. The labeled platelets fully retained their cellular functions in vitro. In vivo studies carried out in rabbits with induced thrombi in femoral artery showed rather rapid disappearance of radioactivity from circulating blood and the high thrombus-to-blood activity ratio of 19.8±4.3 within 30 min after the injection. Thus, the thrombus imaging with I-123 MA labeled autologous platelets using single emission CT studies is highly promising.

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PREPARATION AND BASIC STUDY OF Ga-67-DF-FRAGMENT E(1,2) FOR THE DETECTION OF THROMBUS.
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Fragments E1,E2 and E3 are dimeric molecules derived from plasmic digestion of cross-linked fibrin. Fragments E1 and E2 have the unique property of binding to polymers of fibrin. This affinity to thrombus makes fragment E1 and E2 interesting for development into a radiopharmaceutical. The mixture of fragments E1, E2 and E3 was separated from fdp(fibrin degradation products) by a combination of column gel filtration on sepharose CL-6B and urea treatment(1). In order to separate E3 from fragment E fraction, fragment E fraction was chromatographed on a DEAE-cellulose column with stepwise elution of sodium chloride. Gallium-67 labeled fragment E(1,2) was prepared as a new thrombus imaging agent, using DF as a bifunctional chelating agent. Ga-67-DF-fragment E(1,2) was injected into rabbits with induced thrombus. The thrombus-to-blood ratios were 6.3 and 9.1 at 6 and 20 hours after injection respectively. These results suggest that Ga-67-DF-fragment E(1,2) is a promising thrombus imaging agent.

Ref.: (1) Budzynski, A.Z., et al: J.Biol. Chem., 254: 4925-4932, 1979

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PREPARATION AND BIODISTRIBUTION OF Ga-67 LABELED FIBRINOGEN CONJUGATED WITH WATER SOLUBLE POLYMER CONTAINING DEFEROXAMINE; A NEW APPROACH TO PROTEIN LABELING.
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It has been reported that Ga-67 labeled proteins conjugated with deferoxamine(DFO) such as HSA, fibrinogen(Fib),urokinase are promising as radiopharmaceuticals. In our further investigation on Fib, we found that metalic impurities in Ga-67 solution affect the labeling efficiency, because the stable metalic ions such as Fe ions block the chelation site on Fib. When a large number of DFO molecules are introduced into Fib to solve this problem, the the Fib itself is denaturalized. Therefore, Ga-67 labeled Fib of high specific activity suitable for diagnostic use is difficult to prepare without denaturalization.

We have introduced "spacers" such as dialdehyde starch(DAS) and polyacrolein(PA) to link Fib to a large number of DFO without losing bioactivities of Fib. These "spacers" DAS and PA contain many aldehyde groups that are capable of reacting with amino groups of DFO and Fib. The Ga-67 Fib-DAS-DFO obtained with this technique showed high specific activity and also high bioactivity. These results suggest that Ga-67 Fib-DAS-DFO is an excellent agent for detection of thrombi.

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