Targeting of myocardial necrosis and apoptosis using a novel small molecular probe, bis(zinc(II)-dipicolylamine) complex (Zn-DPA)

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Objective. This study was designed to investigate the feasibility of a rationally-designed small molecule probe, bis(zinc(II)-dipicolylamine) coordination complex (Zn-DPA), for targeting apoptosis and necrosis indicative of a recent myocardial ischemic insult based on cell membrane anionic phosphatidylserine content. Methods. The targeting properties of Zn-DPA were first investigated using ex vivo fluorescent imaging. An ischemic-reperfused rat heart model was created by ligation of the left coronary artery followed by reflow. The fluorescent-labeled Zn-DPA was intravenously injected in rats subjected to 30-min and 5-min myocardial ischemia followed by 2-hr reperfusion. Ninety minutes post-injection, the rat hearts were excised and sectioned for postmortem analysis and imaging. ⁹⁹ᵐTc labeling of Zn-DPA was carried out with a preformed ⁹⁹ᵐTc(I) tricarbonyl complex cation [⁹⁹ᵐTc(CO)₃(H₂O)₃]⁺ by exchange of the water molecules in the precursor for the aromatic N-heterocyclic nitrogens in DPA. In vivo and ex vivo cardiac images of ⁹⁹ᵐTc-labeled Zn-DPA (⁹⁹ᵐTc-Zn-DPA) were acquired using a high-resolution SPECT imager called FastSPECT II and autoradiography in the ischemic-reperfused rat hearts. Myocardial ischemic area, infarction, and apoptosis were evaluated by histological and immunochemical assay. Results. Zn-DPA was successfully labeled with ⁹⁹ᵐTc and a consistent production with radiochemical purity greater than 95% was obtained. Myocardial infarction was clearly observed in the rat hearts with 30 minutes ischemia and 2-hours reperfusion, but not in the hearts with 5-minute ischemia. In vivo hot spot uptake of ⁹⁹ᵐTc-Zn-DPA was detected in the ischemic rat hearts. Postmortem autoradiograph and fluorescent imaging showed that Zn-DPA accumulated not only in infarcted myocardium, but also in ischemic viable myocardium. The uptake of Zn-DPA was related to myocardial cell death including necrosis and apoptosis. Conclusions. We have preliminarily demonstrated the usefulness of fluorescent and ⁹⁹ᵐTc labeled Zn-DPA for hot-spot detection of recent myocardial ischemic insults. This novel small molecule probe might have a promising potential for imaging of apoptosis with unique radiopharmaceutical characteristics, including more favorable blood clearance and biodistribution for imaging than a protein, and capability of radiolabeling with ⁹⁹ᵐTc, a radionuclide with broad clinical utility.