Brain ischemia and infarction positively visualized by pyruvate-1-11C using positron-emission tomography

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Abstract. We describe positron-emission tomography (PET) scintigraphic findings obtained using pyruvate-1-11C in eight patients with cerebral ischemic hypoxia or infarction. The extraction of 11C by brain tissue from blood after an i.v. injection of 11C-pyruvate was very rapid, being almost complete after a single circulatory passage. Most ischemic lesions were found to be more or less deficient with regard to 11C-extraction capacity. With time, however, the ratio of 11C in ischemic tissue to that in normal tissue was inverted, and the ischemic lesion appeared as a ‘hot’ area in the scintigram. Very old infarcts did not exhibit this phenomenon. These observations indicate the usefulness of an 11C-pyruvate PET scan for the diagnosis of therapeutically restorable brain damage.

Key words: Pyruvate-1-11C – Ischemia – PET

In a previous study, we developed a synthetic method for the production of injectable pyruvate-1-11C, which involved using cyclotron-produced 11CO2 as the precursor and an enzymatic reaction (Hara et al. 1985). Our technique requires a very simple set-up and a short processing time, and produces an extremely high yield of pyruvate-1-11C; thus, we have been able to perform routine clinical studies of the brain using this radiopharmaceutical.

In the brain, pyruvate is metabolized in two separate ways (Blass 1979): under aerobic conditions, it enters mitochondria and finally decomposes into CO2, whereas under anaerobic conditions, it is reduced to lactate which persists in the brain tissue for a long period (Kintner et al. 1983). Pyruvate is supplied to brain cells either as the end-product of intracellular glycolysis or by direct penetration from the blood across the blood-brain barrier (Oldendorf 1973), although the contribution of the latter is comparatively small in physiological terms (Pardridge and Oldendorf 1977). The clearance of pyruvate from blood is very fast, the half-life being less than 30 s in rats (Busch 1955). The glycolytic flux and equilibrium in the brain is regulated in response to the period and degree of oxygen deprivation (Lowry et al. 1964; Hinzen et al. 1972; Drewes and Gilboe 1973; Drewes et al. 1973; Bachelard et al. 1974). The influence of tissue lactic acidosis on the ischemic brain is thought to play an important role in the pathogenesis of cerebral ischemic-anoxic injury (Ginsberg et al. 1980; Welsh et al. 1980; Gardiner et al. 1982; Rehncrona et al. 1981; Kalimo et al. 1981).

In the present study, we attempted to visualize the ischemic brain of stroke patients as a positively delineated zone using positron-emission transaxial tomography (PET) after an i.v. injection of pyruvate-1-11C. We expected the extraction of pyruvate-1-11C from blood – as well as the cerebral clearance of its metabolic product, 11CO2 – to be rapid in well-oxygenated brain tissue, while in ischemic regions, the accumulation of radioactivity due to its entrapment by the lactate produced was anticipated.

Materials and methods

Subjects and scintigraphic procedures

PET studies were performed at the National Nakano Chest Hospital, and eight patients with cerebral ischemia or infarction were investigated. The patient or the family gave informed consent to the study. Quantitative measurements of the cerebral blood flow (CBF), the cerebral metabolic rate of O2 (CMRO2), and the oxygen extraction fraction (OEF; Ackerman et al. 1981) were obtained using the 15O continuous-inhalation technique of Frackowiak et al. (1980) with slight modifications. Pyruvate-1-11C was prepared (Hara et al. 1985) in the cyclotron unit of the hospital located next to the PET scanning room. The patients received no premedication. A dose of 30–40 mCi (11.1–14.8 MBq) 11C-pyruvate was injected intravenously, and the PET scan was started immediately. Images were obtained simultaneously at three slice levels, with counts being made at 5-min intervals for 25 min. 11CO2 gas, which is the precursor for the synthesis of 11C-pyruvate, was produced in a Japan Steel Works cyclotron (9 MeV proton; 10–15 μA extracted beam), and the PET images were generated using a Shimadzu Headtome II scanner. After the PET study had been completed, the patient underwent an X-ray computed tomography (XCT) examination.

Prior to these clinical studies, the time-activity relationships of the blood and brain were examined in an adult volunteer with a body weight of 60 kg. A dose of 5.65 mCi (2.09 MBq) 11C-pyruvate was injected intravenously, and 2-ml aliquots of arterial blood were taken at 1-min intervals. The collected blood was examined for the total radioactivity and the 11CO2 radioactivity (i.e., the volatile 11C fraction measured after the addition of perchloric acid to the blood sample and a subsequent flush with CO2 gas). A PET scan...
was performed serially at 30-s intervals, and the radioactivity concentration in the brain was calculated using a computer of the PET system after the total brain area (except the sinuses) had been delineated as a region of interest (ROI) in the PET image at the OM + 7-cm level. The relationship between readings obtained in a Curie meter, a well-type scintillation counter, and the PET detector was determined using a standard positron source.

Case reports

Case 1. This 74-year-old man with a history of emphysema with hypoxemia and a single episode of syncopal attack had had an abrupt onset of clumsiness of the right hand, paresis of facial muscles below the right eye, and mild dysarthria. He was admitted to the hospital 3 days later. Examination revealed the persistence of these symptoms as well as hyperreflexia of the right extremities. XCT revealed no abnormality in the brain. The neurological symptoms improved markedly within 3 weeks of ictus, and the XCT findings remained normal.

Case 2. This 60-year-old man with a history of hypertension had experienced a sudden onset of right hemiparesis and aphasia 7 weeks before the study. At the time of the PET examination, he exhibited moderate right hemiparesis and right central facial weakness, hyperreflexia of the right extremities, and total aphasia. XCT revealed a small area with slightly decreased density in the left parietal subcortical area. Angiography revealed no abnormalities in the cerebral arterial tree, thus suggesting recanalization of a once-obstructed artery.

Case 3. This 78-year-old woman with a history of hypertension, retinal hemorrhage, and a syncopal attack had experienced the sudden onset of left hemiparesis 2 months before the study. At the time of the study, she had mild left hemiparesis of the pure motor type. XCT revealed a small plaque of decreased density in the right corona radiata.

Case 4. This 58-year-old woman had suddenly developed right hemiparesis and aphasia 3 months before the study. Examination at the time of the PET study revealed right hemiparesis, sensory aphasia (nominal aphasia and paraphasia), and left homonymous hemianopsia. XCT revealed a left temporoparieto-occipital infarct consistent with occlusion of the branches of the left-middle cerebral artery.

Case 5. This 55-year-old man with a history of hypertension and adult-onset diabetes mellitus had experienced the sudden onset of right hemiparesis and total aphasia 4 months before the study. At the time of our study, he showed mild weakness of the right hand, hyperreflexia of the right extremities, and total aphasia. XCT revealed a large area of decreased density in the left hemisphere of the cerebrum involving most of the area around the middle cerebral artery.

Case 6. This 60-year-old man with a history of hypertension and depression had experienced the sudden onset of left hemiparesis 2.5 years before the study, followed by a single episode of generalized convulsion 1 year later. At the time of our study, he exhibited slight mental disturbance, dysarthria, left homonymous hemianopsia, left facial palsy, traces of left hemiparesis, and hyperreflexia of the left extremities. XCT revealed decreased density of the right-frontal temporoparietal area around the right-middle cerebral artery.

Case 7. This 38-year-old man with a history of Kugelberg-Welander disease and myocardial infarction had experienced the sudden onset of left hemiparesis and dysarthria 7 years before the study. At the time of our study, he showed dysesthesia of the left extremities, but no hemiplegia nor dysarthria. XCT revealed an area of decreased density in the right frontotemporoparietal region.

Case 8. This 56-year-old male, who was a heavy drinker with a history of diabetes mellitus, had first exhibited mental disturbance and an unsteady gait 7 years before the study. Examination at the time of our study revealed mild memory disturbance, dysarthria, and bilateral pyramidal tract signs. XCT showed an area of decreased density in the left temporo-occipital region in the area of the left posterior cerebral artery.

Results

Following an i.v. injection of pyruvate-1-11C into a normal human, we examined the time-activity relationships in the arterial blood and brain (Fig. 1a, b). The blood clearance of 11C-pyruvate was very rapid, with the initial biological half-life being less than 3 min. The 11C activity in the brain reached its maximum almost immediately after the injection. The maximum 11C concentration in the brain was close to a value indicative of complete extraction of the radioactivity from the arterial blood during the first circulatory passage. The blood contained 11CO2 radioactivity (produced metabolically) and probably 11C-lactate radioactivity, the presence of the latter being implied by the sluggishness of the clearance from the blood of the nonvolatile 11C fraction, this becoming more marked with time.

To interpret the data for the assessment of the degree of cerebral ischemia, we assumed that the image obtained 0–5 min after the injection of pyruvate-1-11C (early image) represented the blood volume plus blood flow, while the image obtained at 10–15 min and later – in fact the pattern was unchanged – represented the persistance of radiotracer activity in the lactate pool (late image; see Discussion). After injection, pyruvate-1-11C was not only taken up into the brain but was also incorporated in the scalp muscle. The muscle retained 11C activity for a long period due to its preference glycolysis. In the brain, the early image closely resembled the images obtained for the CBF and CMRO2, both of which were decreased in the area where XCT indicated low density. In terms of area, however, the low-CBF and low-CMRO2 areas as well as the low-intensity area on the 11C-pyruvate early image were somewhat larger than the low-density area on the XCT image, particularly when the duration of the disease had been relatively short. On the other hand, the late image obtained with 11C-pyruvate was very different from the early image in the patients whose disease had been of relatively short duration.