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Research Report

A comparative study of bioradiography in human brain slices and preoperative PET imaging

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ABSTRACT

Novel autoradiography (bioradiography) images in human neocortical brain slices which were obtained at operation from seven patients with intractable epilepsy who had received a 2-[^{18}F]fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) examination preoperatively, were acquired in Krebs–Ringer medium (control condition) and that with high K^+ (high K^+ condition) containing FDG and compared with FDG-PET uptake. The FDG uptake images in rat brain slices were also acquired as a reference and compared with that in humans. In the slices incubated under high K^+, FDG uptake in both human and rat gray matter was significantly enhanced, whereas that in the white matter was not. But the variance of uptake was larger in humans than the rats. This might indicate the different degree of progress of epilepsy in the sampled brain tissues. The uptake rates of FDG in human gray matter under the control condition showed an inverse correlation with those seen in PET, which were evaluated as sampled and contralateral gyri (SG/CG) and sampled gyri and cerebellar cortex (SG/CB) ratio. On the contrary, it showed a weak positive correlation with PET under the high K^+ condition. The uptake rates of FDG in human gray matter expressed as a high K^+/control ratio, closely matched that observed by FDG-PET, which were evaluated as the SG/CG ratio and the SG/CB ratio. Our experimental system provides useful information for the interpretation of PET data in epileptics and the theoretical basis to interpret the results of metabolic studies using living human brain tissues for further use in pharmacological manipulation.

Introduction

Bioradiography is a novel autoradiographic method to estimate metabolism and physiological function in living tissues using positron emitter-labeled compounds for positron emission tomography (PET) (Matsumura et al., 1995; Murata et al., 1996; Sasaki et al., 2002a,b). It offers the following advantages: (1) dynamic changes in metabolic activity can be followed in living tissue, (2) environmental conditions of tissue slices can be easily controlled as required, and (3) radioligand delivery to

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the tissue is not influenced by blood flow. This method has been used to study glucose metabolism, neuroreceptor assays and neurotransmitter release in animal brain tissues (Matsumura et al., 1995; Murata et al., 1996; Sasaki et al., 2002a,b).

Surgery has been recognized as an effective treatment for certain epileptic patients, such as those with medically intractable temporal lobe epilepsy (TLE) (Cascino et al., 2004). Presurgical imaging using PET, single photon emission tomography, and magnetic resonance imaging (MRI) is used to assess the feasibility of surgery and to decide the scale of excision in regions with spike activity (Casse et al., 2002; Matheja et al., 2000). The brain regions estimated to have low glucose metabolism by 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG)-PET are diagnosed as the excision extent including epileptogenic foci (Casse et al., 2002). Noninvasive molecular-imaging techniques such as PET have potential roles in disease diagnosis and therapy, but diagnosis as in the case of epilepsy is influenced by several factors and problems, for example, biodegradation of the radioligand, influence of blood flow on radioligand delivery, and limited spatial resolution. In order to confirm PET diagnosis, glucose metabolism in living human brain tissue *in vitro* was compared with preoperative FDG-PET findings using bioradiography with FDG in brain slices obtained at operation from patients with intractable epilepsy.

Results

The experimental flowchart is shown in Fig. 1. All seven patients underwent excisions of pathological lesions and the area with epileptogenecity surrounding them identified by presurgical FDG-PET, MRI, and intraoperative cortical electroencephalography (EcoG). In all cases, a significant amelioration of seizures was achieved by surgery. This indicated that the epileptic foci and the pathological brain surrounding them were precisely detected and resected. In all the patients, cortical gyri sampled for slice analysis were not the epileptic foci themselves but the gyri surrounding the focus from where an abnormal EcoG pattern was recorded. Though three of seven patients harbored low-grade gliomas, the proliferation rate of tumor cells determined from the labeling rate with a monoclonal antibody (MIB-1) against nuclear antigen Ki-67 (Ki labeling index) was very low (<1% in two and 5% in one) and therefore none of them were invasive tumors. No tumor cells were identified in the sampled gyri of three of tumor patients. Therefore, we concluded that the sampled cortical gyri used for autoradiographical analysis was the cortex outside the main lesions but influenced by chronic epileptic conditions (Table 1).

As shown in Table 2 and Fig. 5, FDG uptake in the sampled gyri was lower than that in the contralateral gyri or cere-

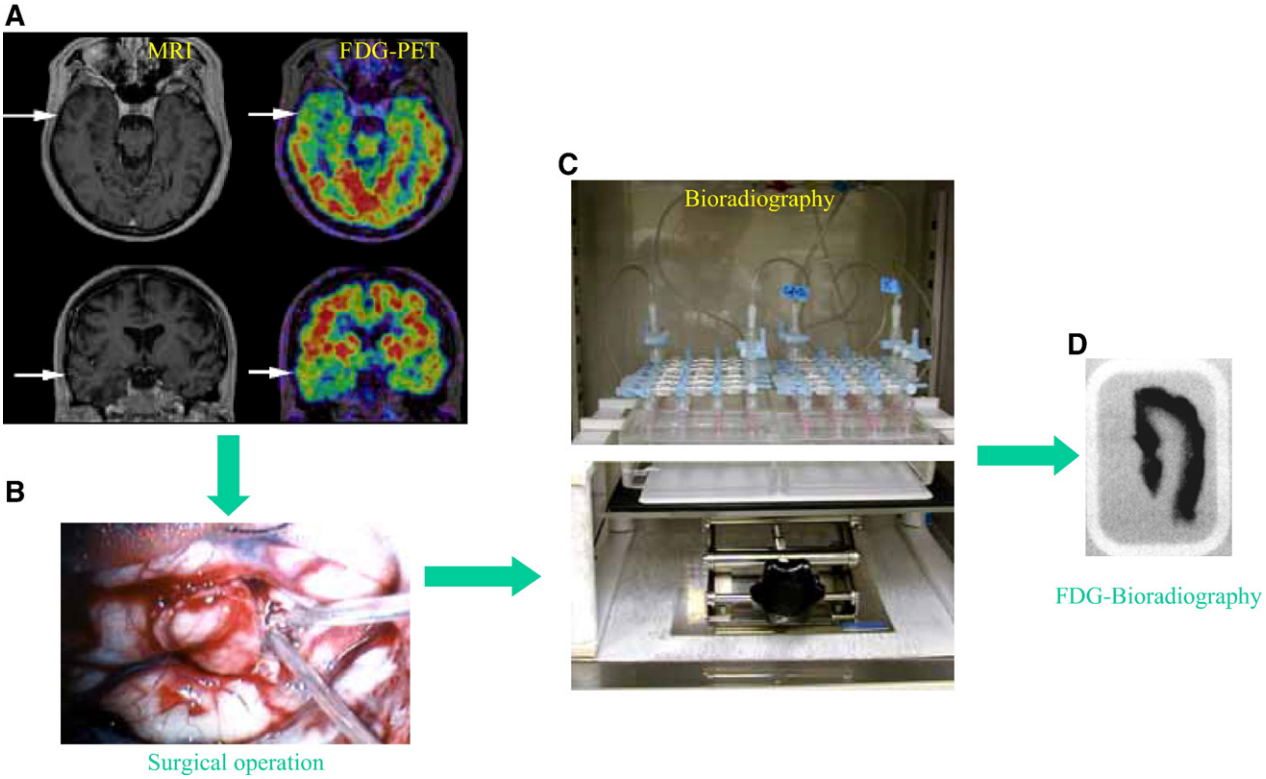

Fig. 1 – Flowchart for bioradiography in human brain slices. (A) The presurgical evaluation of patients with medically intractable epilepsy was performed with FDG-PET co-registered to MRI. FDG-PET showed hypo-glucose metabolism in the right temporal cortex (arrow). (B) Epileptic foci and the epileptogenic cortical gyrus surrounding them were surgically excised (arrow). The former was subjected to routine pathological analysis and the latter to bioradiographical analysis. (C) Bioradiography for analysis in vitro using human and animal brain slices. (D) FDG bioradiographic image of an excised human brain slice.