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Assessment of regional $GABA_A$ receptor binding using ^{18}F-fluoroflumazenil positron emission tomography in spastic type cerebral palsy

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Periventricular leukomalacia (PVL) due to hypoxic–ischemic insult to the immature brain, chorioamnionitis and maternal infection are the major etiological factors of spastic type cerebral palsy (CP). Despite advances in preventing and treating certain causes of CP, the number of patients has remained essentially unchanged and the pathophysiological mechanisms related to motor dysfunction remain poorly understood. In this study, statistical parametric mapping (SPM) analysis of cerebral gamma-aminobutyric acid (GABA) receptor PET imaging using [^{18}F]-fluoroflumazenil showed increased $GABA_A$ receptor binding in the bilateral motor and visual cortices in spastic diplegia (SD) type CP patients ($n=20$) compared with normal controls ($n=10$). As $GABA_A$ receptor signaling modulates biological perception and production of movement, complex motor skills and use-dependent plasticity in the motor cortex, increased $GABA_A$ receptor binding in the motor cortex might play a important role in poor motor control. Decreased $GABA_A$ receptor binding was seen in the brain stem in SD CP patients, which appears to be related to spastic symptom.

Keywords: Cerebral palsy; $GABA_A$ receptor; [^{18}F]-fluoroflumazenil; Motor dysfunction; Plasticity

Introduction

Cerebral palsy (CP) refers to a disease with a wide range of posture and motor impairments that result from insult to the immature brain, and it is the most common cause of motor disability in children. The prevalence of CP ranges from 1.5 to 2.5 per 1000 live births, however, the number of CP patients has remained essentially unchanged despite advances in preventing and treating certain causes of CP (Kuban and Leviton, 1994; Winter et al., 2002; Nelson, 2003).

Among the various subtypes of CP, spastic type is the most common. Periventricular leukomalacia (PVL) due to hypoxic–ischemic insults to vulnerable periventricular white matter between 26 and 34 weeks of gestation is believed to be one of the major etiologic factors in spastic type CP patients (Lin, 2003; Himmelmann et al., 2005). Before 32 weeks of gestation, 90% of oligodendrocytes are progenitor cells that are exquisitely sensitive to hypoxic–ischemic injury (Back et al., 1998; Volpe, 2001). Upon ischemia, nerve terminals release excessive glutamate triggering excitotoxicity with an imbalance between excitatory and inhibitory functions (Johnston et al., 2001). In addition, maternal/fetal infection or inflammation and cytokine release are also known to be related to the pathogenesis of PVL (Wu and Colford, 2000; Lin, 2003).

Despite extensive animal experiments, however, no adequate models for preterm infant brain damage have been developed yet. Children with PVL do not always produce clinical features of spastic type CP. Conversely, spastic type CP patients do not always have PVL. In fact, PVL is present in approximately 70–75% of spastic diplegia type CP born before 32 weeks of gestation (Lin,

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2003; Kwong et al., 2004). Therefore, PVL induced by hypoxic–ischemic insult with glutamatergic excitotoxicity could be an important component of the brain injury, but it may not be the sole etiologic factor in the pathogenesis of spastic type of CP. Recently, chorioamnionitis and maternal infection are known to be independent risk factors of CP even in term and near-term infants (Wu et al., 2003; Neufeld et al., 2005). Nevertheless, pathophysiological mechanisms related to abnormal motor functions in spastic type CP remain poorly understood.

In this study, 20 patients with spastic diplegia (SD) type CP underwent central benzodiazepine receptor imaging using a recently developed PET tracer, ^{18}F-fluoroflumazenil ([^{18}F]-FFMZ), that binds to the central benzodiazepine subunit of the $GABA_A$ receptor as [^{11}C]-flumazenil (Chang et al., 2005), and the images were compared with those of normal control (n=10). Currently, central benzodiazepine receptor imaging with [^{11}C]-flumazenil is utilized as an in vivo marker of $GABA_A$ receptor binding since flumazenil (FMZ) is a specific, reversibly bound high-affinity neutral antagonist at the benzodiazepine site of the $GABA_A$ receptor (Olsen et al., 1990; Niimura et al., 1999; Yamauchi et al., 2005). [^{11}F]-FFMZ used in our study has advantages over [^{11}C]-FMZ due to its longer physical half life (120 min) and greater structural similarity to FMZ (Chang et al., 2005).

The aim of our study was to investigate the GABAergic role in abnormal motor functions in CP patients with regard to the imbalance between excitatory and inhibitory functions since cortical activity responsible for movement or motor control depends on the balance between excitatory and inhibitory influences.

Materials and methods

Participants

Twenty patients (14 males and 6 females) who suffered from SD CP were included in this study. The inclusion criteria for SD CP were the children who have the characteristic movement pattern of spasticity such as exaggerated stretch muscle reflex, non-progressive nature of the lesion in immature brain confirmed by brain MRI or metabolic work-up and legs are more involved than arms (Capute and Accardo, 1996).

The patients with clinical history of epilepsy or structural abnormality that can influence the biodistribution of $GABA_A$ receptors on [^{18}F]-FFMZ PET imaging were not included. Their ages ranged from 6 to 20 years (mean 11.15±3.81 years). Thirteen of the 20 SD CP patients were born prematurely with a low birth weight (1.68±0.27 kg). Seven of these 13 patients had history of perinatal hypoxia. All patients born prematurely with low birth weight, and two of the seven patients born at full term with normal birth weight demonstrated PVL on conventional MR imaging. The rest 5 of the 7 patients born at full term did not demonstrate PVL (mean age 10.6±4.09 years old, 3 males and 2 females). The Gross Motor Function Classification System (GMFCS) scales of the SD CP patients were Level 1 in four patients, Level 2 in ten, Level 3 in five and Level 4 in one patient. Patients without PVL also showed abnormal motor function; GMFCS Level 1 in two patients, Level 2 in two, and Level 4 in one patient. Visual function was grossly normal in all but 2 patients (strabismus and astigmatism). The General Visual–Perceptual Quotient (GVPQ) level was evaluated in 12 of the 20 SD CP patients for the evaluation of visual function, and mean GVPQ was 95.41±23.91. Three of the 12 patients showed a lower GVPQ score than normal range (average level 90–110).

Ten healthy volunteers (8 males and 2 females, mean age 21±2.2 years) without any neurological disorders and structural abnormality of the brain were included as normal controls for group comparison of [^{18}F]-FFMZ images. These normal volunteers were students of our medical school.

[^{18}F]-FFMZ PET imaging

Subjects underwent PET imaging using a GE advance PET scanner (GE, Milwaukee, Wisconsin, USA). A transmission scan was performed for 10 min using Ge-68 rod sources for attenuation correction, and emission data were obtained after injection of approximately 5.5 MBq (0.15 mCi)/kg of [^{18}F]-FFMZ. We obtained dynamic scans in 3 normal volunteers in a sequence of 32 frames in 2-D mode (5×10 s, 5×20 s, 5×30 s, 2×60 s, 2×90 s, 5×2 min and 8×5 min) for a total acquisition time of 60 min to evaluate the pharmacokinetic properties of the [^{18}F]-FFMZ. Region of interest (ROI) was drawn over the entire brain, and a time–activity curve was obtained. ^{18}F-fluoroflumazenil uptake in the brain reached its maximum level approximately 10 min after injection followed by biphasic clearance; rapid washout until 20 min after injection and then slow clearance (Fig. 1) as described in a previous pharmacokinetic study using ^{18}F-fluoroflumazenil (Mitterhauser et al., 2004). Based on these results, emission scans for SPM analysis were acquired 20 min after injection of the radiotracer for 20 min in 3-D mode to avoid blood flow effect and non-specific $GABA_A$ receptor binding. The attenuation corrected

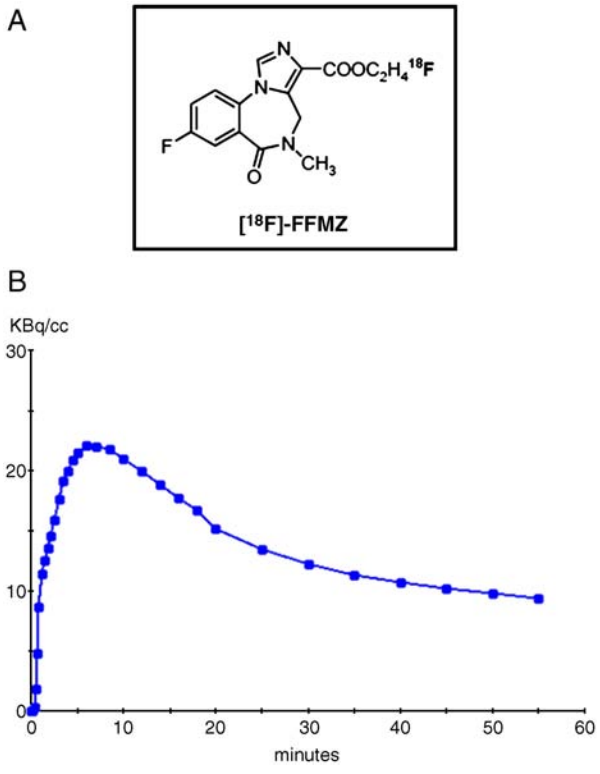

Fig. 1. Chemical form of [^{18}F]-FFMZ (A) and time–activity curve of [^{18}F]-FFMZ uptake after the intravenous injection (B) in normal control.