Decreased benzodiazepine receptor density in the cerebellum of early blind human subjects

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Abstract

As a first approach to study the effect of early visual deprivation on the GABA-ergic inhibitory system, the distribution of benzodiazepine receptors (BZR) was accurately estimated using [11C]Flumazenil ([11C]FMZ). Measurements were carried out in five subjects who became blind early in life and in five sighted control subjects. The interactions between [11C]FMZ and BZR were described using a non-linear compartmental analysis which permitted to estimate the BZR synaptic density independently of other model parameters. The distribution of BZR in the visual areas and other cortical regions of blind subjects was qualitatively and quantitatively similar to that of controls. However, the BZR density in the cerebellum was significantly lower in blind than in control subjects (P<0.01). Our findings suggest that modifications of the cerebellar neural circuitry may be concomitant to the already observed compensatory reorganization in cerebral areas of blind subjects. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

Positron emission tomography (PET) studies have shown that the glucose metabolism in primary and associative visual areas of early blind (EB) subjects at rest is comparable to that measured in sighted control (SC) subjects with the eyes open, i.e. to the normally active visual cortex [58,59]. Brain energy metabolism studies have demonstrated that the metabolic state of the EB visual areas is related to neuronal activity [13]. Furthermore, the glucose utilization in the cerebellum of EB subjects was significantly lower than in blindfolded SC subjects contrasting the findings in the visual areas [13].

The increased metabolism in EB visual cortex has been attributed to the alteration of the phase of synaptic elimination following the synaptogenesis process during brain development, due to the lack of visual stimuli [58].

According to this hypothesis, synaptic contacts would be more numerous and/or hyperactive in EB visual areas [13,58]. Besides, the decreased glucose metabolism level in the EB cerebellum suggests that early visual deprivation may also alter the cerebellar neural organization.

The synaptogenesis process and the later phase of synaptic elimination observed in primate cerebral cortex are accompanied by similar changes in several neurotransmitter receptor densities (dopaminergic, adrenergic, serotonergic, cholinergic, and GABAergic receptors) [36,37]. Moreover, since the interaction between neurotransmitters affects the neuronal cytoarchitecture and cortical developmental processes [17,21,30,31], the combination of morphological and neurochemical studies may provide further insight on the effects of sensory deprivation.

As a first approach to study in vivo the chemical circuitry of the human brain in the case of early blindness, we have used [11C]Flumazenil ([11C]FMZ) to quantify the benzodiazepine (BZ) receptor density of EB and SC...
subjects. $^{[11]}C$FMZ is a BZ antagonist widely used in human brain studies using positron emission tomography (PET). BZ receptors (BZR) are functionally associated to GABA$_{A}$ receptors which are made up of pentameric assemblies of subunits ($\alpha$, $\beta$, $\gamma$, $\delta$, $\rho$) that form a chloride channel. The Cl$^-$ conductance increases when GABA binds to the $\beta$-subunit and the effect is facilitated when BZ binds to the $\alpha\gamma$ subunit complex in the same channel [11,53]. FMZ binds to most of the GABA$_{A}$ receptors resulting from different subunit combinations in mammalian brain, except to those containing $\delta$ subunit [53]. The FMZ affinity for receptors containing $\alpha_k$ subunit is lower than the affinity for receptors with $\alpha_1$ subunit [27,53]. GABA$_{A}$ receptors containing $\alpha_k$ subunit are only expressed in cerebellar granule cells and represent 45% of all GABA$_{A}$ receptors in the rat cerebellum [26].

The kinetics of in vivo ligand binding of FMZ to central BZR was described using a nonlinear three compartment model [15]. The model parameters were accurately estimated by using a three-injection protocol which guarantees a unique solution and small parameter estimation uncertainties [15,16]. The input curve to the compartmental model was obtained by applying a metabolite correction method which estimates the relative fraction of $^{[11]}C$FMZ in the total radioactivity in plasma curve from the tissue kinetic data without the need for actual FMZ metabolite measurements [52].

Labeling and quantification of BZR using $^{[11]}C$FMZ may provide information on the effects of early blindness on the distribution of GABA$_{A}$ receptors in the cerebral and cerebellar cortex of human subjects. The effect of visual deprivation on the distribution of GABA neurons and its receptors in visual brain areas has been mainly studied in cases of monocular deprivation in adult monkeys [8,21–23]. However, the effect of early binocular deprivation on GABA distribution, to our knowledge, has not been reported, neither in animals nor in humans. This study may provide insight on the contribution of such inhibitory synapses to the measured abnormal metabolism in the EB visual cortex and cerebellum [13,58].

## 2. Materials and methods

### 2.1. Subjects

Five male volunteers with peripheral blindness of early onset (Table 1) and five sighted control subjects participated in this study. EB subjects had no residual light perception, but were otherwise neurologically normal. EB and SC subject mean ages were 49±17 and 42±13 years, respectively ($P=0.46$). None of the subjects was under any medication. All subjects gave their informed consent before undergoing the PET acquisition. These experiments comply with the Declaration of Helsinki and were approved by the Medical Ethics Committee of the School of Medicine at the Université Catholique de Louvain.

### 2.2. Synthesis of $^{[11]}C$FMZ

$^{[11]}C$FMZ ([Methyl-$^{[11]}C$] Ro 15-1788) was labelled by N-alkylation of the desmethyl compound (Ro 15-5528) with anhydrous $^{[11]}C$methyl iodide in acetone by use of sodium hydroxide as base [20]. $^{[11]}C$FMZ was purified by semi-preparative reverse phase using high-performance liquid chromatography (HPLC). The HPLC columns used were Alltech Econosil with 0.01M H$_2$PO$_4$ / acetonitrile and 70/30 as eluent. The radiopharmaceutical formulation has been performed following a method that uses a C$_{18}$ Sep-Pak Plus cartridge from Waters [7].

### 2.3. Experimental protocol

The experimental protocol lasted 90 min and consisted of three injections of $^{[11]}C$FMZ and/or unlabeled FMZ [15]. Firstly, an injection of about 370 MBq of $^{[11]}C$FMZ with high specific activity was performed and 30 min later a displacement injection of 0.7 mg of unlabeled FMZ was performed. At 60 min, a coinjection of approximately 160 MBq of $^{[11]}C$FMZ and 1.2 mg of unlabeled FMZ was made. The specific activity of the first injection ranged from 5300 to 16200 MBq/$\mu$mol. Each time, the FMZ was injected as a bolus of 30 s through a 22-gauge catheter (Abbocath™) in a forearm vein. A 24-gauge catheter (Abbocath™) was inserted in the radial artery of the other arm under local anesthesia with bupivacaine for blood sampling. After the labeled tracer injections (at 0 and 60 min), blood samples (~0.2 ml) were withdrawn manually as quickly as possible (every 3 or 4 s) for the first 2 min. Thereafter, the sampling interval increased progressively to about 10 min. The selected timing allowed a good sampling of the plasma curve for the 30-s bolus injection. The plasma curves were corrected for $^{11}$C decay and expressed in pmol/ml by using initial specific activity of $^{[11]}C$FMZ.

### 2.4. PET imaging

PET studies were performed using the ECAT EXACT HR from CTI/Siemens, a whole body high spatial res-
olution scanner. Transaxial resolution is approximately 4 mm full width at half maximum (FWHM) at the center of the field of view (FOV), and decreases to 6.75 mm FWHM at 20 cm from the center. The axial resolution is 4 mm FWHM at FOV center [61]. Acquisition was performed in three-dimensional (3D) mode and images were reconstructed using the 3D reprojection (3DRP) algorithm [32] including scatter correction [60]. A Hanning filter with a 70% relative frequency cutoff was used in both transaxial and axial directions to achieve a quasi isotropic spatial resolution of about 8 mm in the whole brain. For each subject, a 15-min transmission scan was performed prior to tracer administration to estimate attenuation correction. The transmission scan used three rotating 68Ge rod sources with electronic windowing, so attenuation is scatter free. A sequence of 16 frames was obtained after each injection (8×15, 3×60, and 5×300 s), and 47 contiguous transaxial slices were reconstructed with a voxel size of 2 mm in tomographic direction and 3.125 mm in axial direction. The head of each subject was positioned in the scanner FOV by aligning two sets of low power laser beams with the canthomeatal and the mid-saggital lines. Adhesive bands were used to minimize head movements during the study.

Three-dimensional magnetic resonance images (MRI) were obtained on a 0.5 Tesla Philips Gyroscan unit using the Fast Field Echo technique. T-1 weighted images (TR=30 ms, TE=13 ms, flip angle=30°, slice thickness=2 mm) were obtained in the bicommissural (AC–PC) orientation.

2.5. Data analysis

2.5.1. Kinetic model

The kinetics of in vivo ligand binding of [11C]FMZ to central BZ receptors was based on compartmental analysis [15]. The model considered here includes the plasma space together with two extra-vascular compartments representing the ligand in tissue (free and non-specifically bound FMZ) and the ligand specifically bound to BZR (Fig. 1). This model is non-linear with four rate constants (k1, k2, k_on, k_off) plus the concentration of the receptor sites available for binding (B_max). The rate constants k1 and k2 describe simple diffusive transport of FMZ between the plasma and free tracer compartments. The association and the dissociation rate constants (k_on and k_off, respectively) describe the FMZ exchange between the free and specifically bound tracer compartments. The equilibrium dissociation constant (K_d) was obtained from the ratio between k_off and k_on. When describing in vivo reversible binding, K_d corresponds to the ligand concentration at which half of the receptors are bounded to the ligand. If a ligand act at low concentrations on a receptor, the K_d value is low and the ligand is said to have high affinity for those receptors. The complete description of the compartmental model can be found in the work of Delforge et al. [15].

The vascular compartment in the model only accounts for the concentration of [11C]FMZ in plasma because none of the [11C]FMZ metabolites crosses the blood–brain barrier (BBB) [14]. For each subject, the contribution of radioactive metabolites to the total plasma curve was estimated by applying a mathematical correction method not requiring additional [11C]FMZ metabolite measurement [52]. The model equations were solved numerically by applying the Levenberg–Marquardt method [48] and parameter coefficients of variation were obtained from the covariance matrix resulting from the sensitivity function matrix of the weighted least-squares minimization [9,16]. Programs were implemented in MATLAB® (The MathWorks, Inc., Natick, MA).

2.5.2. Regions of interest

Before delineating regions of interest (ROI), PET and MRI data were processed as follows. First, a summed PET image was obtained from the first 16 frames after the first [11C]FMZ injection. Then, for each subject, the summed PET image was realigned to the MRI using the AIR package [62,63], SPM96 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) was used to normalize the matching MRI and summed PET images in the Talairach and Tournoux coordinate system [56] with a 2-mm cubic voxel. The accuracy of realignment and normalization procedures were assessed with an interactive home made image display software [44] implemented in IDL language (IDL Research System, Inc.).

![Fig. 1. Compartmental model for [11C]FMZ–BZR interactions. The intravascular compartment represents the concentration of non-metabolized [11C]FMZ in plasma, C_p(t). Extravascular compartments account for free ligand, C_f(t), and [11C]FMZ bound to BZR, C_b(t). The rate of binding of the free ligand depends on the association rate constant k_on and on the receptor density available for binding [B_max – C_b(t) – C_f(t)]. B_max denotes the concentration of BZR. C_f(t) is non-zero when unlabeled FMZ is introduced in the system. The rate of dissociation of bound FMZ from BZR is k_off. The variables with an asterisk denote labeled concentrations.](image-url)
Subsequently, the spatial transformer obtained for the summed PET image normalization was applied to each frame of the kinetic PET study. Since MRI was not available for one of the control subjects, a FMZ template was obtained by averaging the normalized PET images of the four other control subjects. This template was then used to normalize the summed and kinetic PET images in the Talairach and Tournoux coordinate system.

Using the image analysis program Mediman [10], ROIs were delineated by taking in consideration the activity on the normalized static PET image and anatomical landmarks on the MRI. ROIs were named following the Talairach and Tournoux nomenclature [56]. For all subjects, volumes of interest (VOIs) were subsequently obtained from several ROIs drawn on consecutive planes all over the cerebral cortex and on the cerebellum. Special attention was made on the ROIs in the occipital region where the primary and associative visual cortices were considered separately. Since the spatial resolution of PET and MRI images does not allow to distinguish the exact border between the striate cortex and the visual areas surrounding it, the primary visual cortex included BA-17 and part of BA-18. In addition to the occipital regions in the cerebral cortex, VOIs were obtained in the parietal, temporal and frontal regions. The template of VOIs was subsequently projected on each normalized kinetic study and the \([^{11}\text{C}]\text{FMZ}\) time activity curves (TACs) were obtained by using Mediman. TACs corresponded to the mean radioactivity concentration on the defined VOI corrected for \(^{11}\text{C}\) decay. For each VOI, the BZR density \(B_{\text{max}}\) and the four rate constants were obtained by fitting the kinetic model to the experimental TACs.

3. Results

The fitting of the compartmental model to the experimental TACs allowed the estimation of the five compartmental parameters for all the brain regions considered in all subjects. For \(B_{\text{max}}\) and \(K_a\), the standard variations obtained from the covariance matrix for all subjects were mostly below 12 and 25%, respectively.

The overall distribution of \([^{11}\text{C}]\text{FMZ}\) in the brain of EB subjects appeared qualitatively similar to that of SC subjects. For all subjects, the highest \(B_{\text{max}}\) value was observed in region BA 17-18, and the lowest values were found in the cerebellum. Fig. 2 shows the mean \(B_{\text{max}}\) in visual areas, parietal, temporal, frontal cortices and cerebellum for the EB and SC groups.

An ANOVA showed no significant main effect for the type of subject factor, \(F(1,8)=3.2, P>0.05\); no significant main effect for the side factor, \(F(1,8)=1.1, P>0.05\); but a significant main effect for VOI factor, \(F(6,48)=77, P<\).05\).

![Fig. 2. \(B_{\text{max}}\) mean values in visual areas (BA 17-18 and BA 19), parietal, temporal, frontal cortices and cerebellum of EB (○) and SC (□) subjects. Brain distribution of BZR in cortical areas is qualitatively and quantitatively similar for all subjects. However, \(B_{\text{max}}\) estimates in the cerebellum is significantly lower (\(P<0.05\), Scheffe criterion) for EB subjects. Error bars correspond to the standard deviation of the group mean values. Units are in pmol/ml.](image-url)
0.05. Similarly, the interaction between type of subject and VOI was significant, $F(6,48)=3.6, P<0.05$. $B_{\text{max}}$ estimates for all the regions considered in the cerebral cortex were similar in both groups of subjects ($P>0.05$) as shown by post-hoc comparisons using a Scheffé criterion. However, the $B_{\text{max}}$ value in the cerebellum of EB subjects appeared significantly lower than that in SC subjects ($P<0.05$, Scheffé criterion). Fig. 3 shows the mean and individual $B_{\text{max}}$ estimates in both cerebellar hemispheres for the EB and SC groups.

Fig. 4 shows the mean $K_d$ for the EB and SC groups in visual areas, parietal, temporal, frontal cortices and cerebellum. A large interindividual variation was observed for $K_d$ estimates in all brain regions considered. However, published $K_d$ estimates using the same analysis method [15] and other methods [34,49] exhibit similar intersubject variability. An ANOVA showed no significant main effect for the type of subject factor, $F(1,8)=0.39, P>0.05$; no significant main effect for the side factor, $F(1,8)=0.02, P>0.05$; but a significant main effect for VOI factor, $F(6,48)=32, P<0.05$. The interaction between type of subject and VOI was not significant, $F(6,48)=2.3, P>0.05$. Post-hoc comparisons for VOI factor using a Scheffé criterion showed that the mean $K_d$ value in the cerebellum was significantly higher than the $K_d$ value in all cerebral cortex VOIs ($P<0.05$).

4. Discussion

In EB subjects, the overall distribution of BZR in visual areas, as well as in other cerebral cortical regions was qualitatively and quantitatively similar to that in SC subjects. However, $B_{\text{max}}$ was significantly lower in the cerebellar cortex of EB subjects as compared to control values. $K_d$ estimates showed no significant differences between both group of subjects in any of the brain areas considered. Although a large interindividual variation was observed for $K_d$, the highest $K_d$ values were found in the cerebellum of all subjects.

4.1. Methodological considerations

The feasibility of obtaining parametric images of BZR density from our studies was limited by the time required in the model fitting procedure. When analyzing kinetic data on a voxel by voxel basis, linear compartmental model using a single [$^{11}$C]FMZ injection protocol [18,33] are less

![Fig. 3. $B_{\text{max}}$ values in the cerebellar hemispheres of EB (○) and SC (□) subjects. Filled symbols correspond to $B_{\text{max}}$ group mean values. Open symbols correspond to individual values estimated from the fitting of experimental and compartmental model kinetic curves. Units are in pmol/ml.](image-url)
time consuming procedures. However, such simplified approach only allows to estimate a quantity related to the ratio of $B_{\text{max}}$ and $K_d$ [18,33].

With our three-injection protocol, no model simplification was required and absolute values for the BZ receptor density were estimated independently of the other model parameters. In addition, normalization of the MRI and kinetic PET data to the Talairach and Tournoux coordinate system allowed us to delineate a template of ROIs on precise anatomical structures and to compare the regional $B_{\text{max}}$ and $K_d$ estimates between subjects on a systematic basis.

4.2. BZR density in the cerebellum

In the cerebellar cortex, $B_{\text{max}}$ was significantly lower in EB subjects as compared to SC values whereas $K_d$ estimates were similar for both groups of subjects. For all subjects, the highest $K_d$ estimates were obtained in the cerebellum. Although our results appear higher than those reported by Delforge et al. [15], they are in agreement with the results of Lassen et al. [34] and Price et al. [49]. The $K_d$ values reported by both authors [34,49] are comparable or even higher in the cerebellum than in other brain structures. The higher $K_d$ estimates in the cerebellum with respect to the cerebral cortex values may be related to the lower affinity of FMZ for BZR on granule cells containing the $\alpha_6$ subunit [27,53]. Since the kinetic data obtained do not allow differentiating between FMZ high and low affinity binding, the $K_d$ estimates may account for the overall tracer affinity for all types of BZR in the cerebellar cortex. Therefore, the $B_{\text{max}}$ values in the EB cerebellum may reflect an overall reduction of all types of BZR to which FMZ binds. The reduction in the GABA$_A$ receptors to which BZR are associated could be compensated by an increase of other types of GABA$_A$ receptors to which FMZ does not bind, for example, those containing a $\delta$ subunit. However, the localization and pharmaceutical properties of $\delta$ subunit-containing receptors make this possibility unlikely [47].

The decreased FMZ binding could result from neuronal loss and/or deafferentation of the EB cerebellum from CNS projections. Nevertheless, the normal neurological and behavioral characteristics of the studied EB subjects prevent to consider this hypothetical fact as pathological condition but as an adaptive mechanism (see below). Likewise, an increase of benzodiazepine-like compounds could produce a reduction on the BZR available for binding. Since all subjects participating in our study were medication free and neurological normal, the only possible source of benzodiazepine would be a putative endogenous ligand or from dietary origin [2,39]. However, both possibilities seem unlikely since the decrease of FMZ binding is restricted to the cerebellum, and given the normal neurological state and general healthy condition of the EB subjects in our study.

Except for granule neurons, all the cells in the cerebellar cortex are inhibitory [38]. Inhibitory connections play a central role in the control of the cerebellar neural network activity as shown by model simulations and experimental...
data. For example, spike timing and spike rate control of the Purkinje cells are affected by the inhibitory contacts from basket and stellate cells in the molecular layer of the cerebellar cortex [24, 25]. Also, the inhibitory connections of the golgi cells synchronize the parallel fiber activity and influence the timing of granule cells spikes by way of the feedback inhibitory loop made up by these two types of neurons and their projections [12]. In vitro results obtained from whole-cell recordings in rat cerebellum have shown that the activation of an excitatory synaptic input in Purkinje cells can induce a long-lasting increase of the postsynaptic GABA$_\text{A}$ receptor sensitivity or ‘rebound potentiation’ [28, 29]. This rebound potentiation controls the excitability of Purkinje neurons, and may be a form of synaptic plasticity in the cerebellum.

Traditionally, the cerebellum has been considered exclusively as a motor control system. However, functional mapping studies have shown activation of the cerebellum during non-motor tasks (e.g. [3, 4, 5, 6]) such as acquisition and analysis of sensory information [19, 54, 55], attention [1], cognitive and language functions [35]. Moreover, the participation of the cerebellum seems to be more important during learning or when performing complex tasks [1, 6]. Since plasticity highly depends on the interaction of sensory with motor experience [50], the motor and/or non-motor character of cerebellar function highlights the importance of the cerebellum during brain development. Furthermore, the EB cerebellar BZR density reduction suggests that the different development of cerebral cortical areas of EB subjects may be concomitant to modifications in the neural network of the cerebellum. Hypothetically, this BZR downregulation could result in lower neuronal threshold that could optimize the use of the remaining sensory information reaching the cerebellum. An additional argument for this hypothesis may be obtained from activation studies showing a regional cerebral blood flow (rCBF) increase both in the visual areas and cerebellum during Braille reading and during non-Braille tactile tasks in case of early blindness [51, 57]. Moreover, the activation of these areas was significantly larger in EB subjects as compared to SC subjects when performing non-Braille tactile tasks [51].

4.3. BZR density in the visual cortex

The effect of early sensory deprivation on the synaptogenesis process and the subsequent phase of synaptic revision in the striate visual cortex has been studied in monkeys who were bilaterally enucleated before birth [5]. The mean synaptic density of the 3 year-old operated animal was found to be similar to that of age matched normal animals. However, in layer IV of the striate cortex, the proportion of synaptic contacts on the dendritic spines was larger than the proportion of contacts on the dendritic shafts, inversely to what was observed in controls. Since a higher proportion of asymmetrical synapses (assumed to be excitatory) was found on spines (65 versus 12% of symmetrical contacts), a higher excitatory state would be expected in EB animals, and as suggested by Bourgeois and Rakic [5], consistent with the hypermetabolism observed in the visual cortex of EB human subjects [58, 59].

With respect to synapses situated on dendritic shafts, about equal proportions of symmetrical (37%) and asymmetrical (39%) contacts were found. Therefore, a reduction of shaft synaptic density would produce a similar relative reduction of both symmetrical and asymmetrical contacts. Since symmetrical synapses in the striate visual cortex of monkeys are mainly inhibitory and use GABA as neurotransmitter [4], a proportional reduction of the GABA receptor density in layer IV would be expected. However, the similar values we obtained for the BZR density in EB and in SC subjects suggest that a small reduction in BZR receptors might not be detected using PET due to the low percentage of inhibitory synapses. In the monkey striate visual cortex, the relative proportion of GABA synapses reaches 17 and 22% in all layers together and in layer IV, respectively [4].

The possibility of finding a normal inhibitory synaptic density together with a higher proportion of excitatory contacts in EB striate cortex cannot be excluded. During maturation, the synaptogenesis and the subsequent synaptic revision processes in the layer IV of monkey striate cortex are accompanied by a redistribution of synaptic contacts [41–43]. During postnatal development, symmetric and asymmetric contacts initially situated on the cell bodies and dendritic shafts, respectively, spread out to dendritic shafts and spines, respectively. However, in the absence of visual modulatory inputs, asymmetric contacts that normally would stay in synaptic shafts continue to extend to the increased number of synaptic spines, whereas symmetrical synapses density in shafts maintain control levels [40].

The resulting alterations between inhibitory and excitatory contributions, leading to a higher proportion of excitatory contacts in the visual areas, may explain the excitatory state found at adult age in the visual areas of EB subjects. In addition and as our results suggest, the possible reduction on the GABA$_\text{A}$ receptor density in the striate visual cortex may be less important than the measured shift of the neural circuitry to a higher excitatory state [13, 58, 59].

5. Conclusion

The principal effect of early visual deprivation on the brain BZR distribution appears to be a diminution of this type of receptor in the EB cerebellar cortex. Our findings suggest that plastic changes in the cerebellum of EB subjects during development would be concomitant to those already observed in the cerebral cortex.

The similar BZR density in the visual areas of EB and SC subjects suggests that the measured excitatory state
may be related to a higher proportion of excitatory synapses and/or to alterations of the neural activity due to the imbalance of excitatory and inhibitory connections.

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