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Structural Basis of Developmental Plasticity in the Corticostriatal System

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A B S T R A C T

Previous studies have shown that in developing monkey corticostriatal fibres terminate around striatal cytoarchitectonic compartments – cell islands, showing transfiguration around 105th embryonic day (E105) of gestation. In the present study we have analyzed these striatal cytoarchitectonic islands and acetylcholinesterase (AChE) rich patches in the developing human brain considering them as structural indicators of the development of the corticostriatal pathways. Postmortal brain tissue of 27 fetuses and prematurely born infants, ranging from 11–34 postovulatory weeks (POW) whose deaths were attributed to non neurological causes, were processed by Nissl method, AChE histochemistry and imunocytochemical technique (synaptophysin). All specimens are part of the Zagreb Neuroembryological Collection. Initial AChE patches, presumably corresponding to the dopaminergic islands, were seen as early as 10 POW whereas cytoarchitectonical cell islands were not observed until 14 POW. The main developmental change occurs between 20–24 POW when AChE negative cell poor zones develop around cell islands. This transient AChE pattern of striatal organization reaches its peak around 28 POW, being most prominent along lateral border of putamen. In one case of periventricular hemorrhagic lesion with premortem survival period we have found reorganization of AChE patches in the putamen which indicates structural plasticity of corticostriatal pathways. In conclusion we propose that cell poor zones serve as »waiting« compartments for growing corticostriatal fibers which approach striatum through subcallosal bundle and external capsule. The period of the existence of striatal compartments (14–30 POW) is a sensitive period for structural plasticity and vulnerability after periventricular lesions.

Key words: *human brain, striatal islands, AChE patches, transient pattern, waiting period*

Introduction

Recent studies using histochemical[1–7] and modern imaging techniques opened new possibilities of studying development of pathways in normal human brain as well as structural reorganization of these pathways after perinatal brain lesion[8,9–12.] The main focus in these studies was on the thalamocortical, corticospinal and corticocortical pathway systems[4,7,10,13,14]. The corticostriatal system, which is essential for the motor behaviour[15,16] is largely unexplored. In a classical paper of Patricia Goldman[16] on primate brain, it was shown that developing corticostriatal projection reaches putamen as early as 69th embryonic day (E69), the terminals are uniformly distributed until E95 and cytoarchitectonic compartmentalization of this projection begins after E105 (gestation period in this species lasts 165 days). In the cytoarchitectonical studies it was shown that in the human brain inhomogeneities appear rather early, i.e. around 15 POW[17–19]. These inhomogeneities of the human fetal striatum were demonstrated by different immunohistochemical and cytochemical markers[18,20–23]. Recently a number of chemically distinct compartments were described in adult striatum[24–27] and their distribution was discussed in the framework of other chemical compartments such as AChE poor zones, so called »striosoms« of Graybiel and Ragsdale[22]. The compartmental organization of adult striatum has multiple levels[28] and one of them is related to the distribution of cortical inputs. However the relationship of adult compartments with fetal chemical compartmentalization[4,20–23] and cytoarchitectonical cell islands[16,18] remained till now unclear.

We performed the present study to explore whether analysis of the cytoarchitectonical and histochemical inhomogeneities in the developing human putamen may

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help for delineation of developmental periods of growth of corticostriatal projections as was shown in experimental studies[16]. The comparative phases of development of the human and monkey brain were determined in previous studies[1–3].

In the present study we aimed to analyse cyto- and chemo-architectonics during »waiting« period, i.e. the developmental period spanning between fibers entering the putamen and their selection of modular or matrix targets. We expect that this period is crucial for structural plasticity of corticostriatal pathways which was elegantly demonstrated in monkeys[15]. The intention of this paper was to obtain normal structural and developmental data necessary for imaging studies and pathological studies after perinatal brain lesions.

Material and Methods

The present observation is based on data obtained from 27 fetal and prematurely born infants' brains ranging from 11 till 34 postovulatory weeks (POW). The specimens were obtained from medically indicated or sponta-

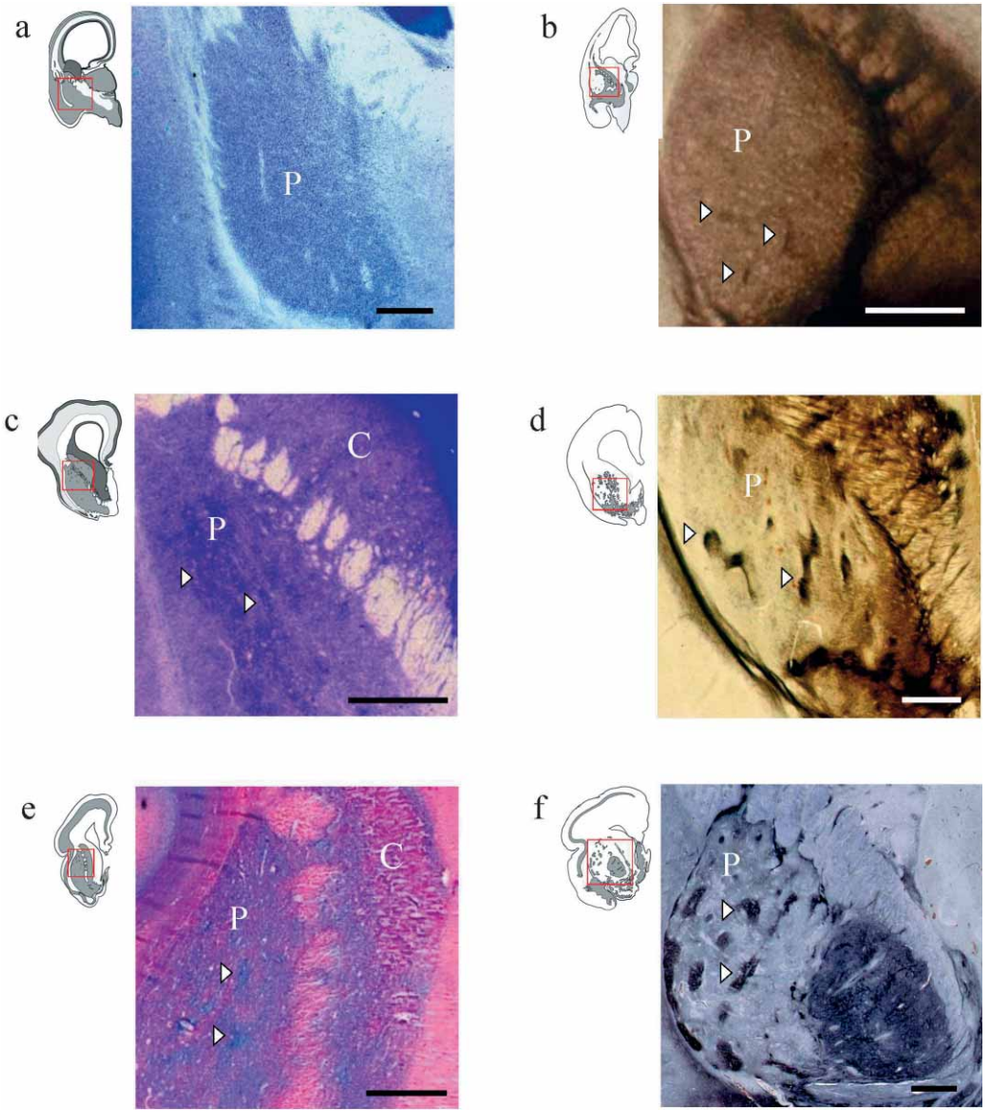

Fig. 1. Transversal sections through the human striatum showing cellular organization at different fetal ages. On Nissl preparations cytoarchitectonical organization appear homogenous at the 10 POW (a) and first cellular islands can be seen at the 14 POW (c). Initial AChE patches were seen as early as 10 POW (b) and they are more pronounced at the 15 POW (d). Compartmental organization of the developing human striatum can be also seen using PAS-AB histochemistry (e, 18 POW) and imunocytochemistry against synaptophysin (f, 21 POW). Arrowheads point to cellular islands/AChE patches. POW = postovulatory weeks, P = putamen, C = caudatus. Scale bar: 500 μm

neous abortions at the School of Medicine, University of Zagreb. The ages of the fetuses were estimated on the basis of their crown-rump lengths (CRL) (120–270 mm) and/or pregnancy records and expressed as weeks from ovulation[29]. In addition, we analyzed the brains of four prematurely born infants aged 28, 29, 30 and 34 POW whose deaths were attributed to respiratory disease or sudden infant death syndrome. We also studied one case of premature born infant (28 POW) having periventricular hemorrhagic infarction in both caudates, diagnosed by computed tomography (CT), which died 4 months postnatal. The procedure for the human autopsy material was approved and controlled by the internal Review Board of the Ethical Committee at the School of Medicine.

Whole brains were fixed by immersion in 4% paraformaldehyde in 0.1 M phosphate buffer, (pH 7.4), embedded in paraffin and serially sectioned at 15–20 mm and alternately stained by Nissl method and acetyl-cholinesterase histochemistry (AChE). For the visualization of acid-sulphated glycoconjugates selected sections were also processed by Periodic Acid Schiff-Alcian Blue (PAS-AB) histochemical staining. To demonstrate the pattern of synaptophysin expression, which is indicative of synaptogenesis in the human fetal striatum[23], immunocytochemical labelling was performed. All specimens are part of the Zagreb Neuroembryological Collection. Images of selected histological sections were captured through a charge-coupled device (CCD) camera or Nikon scanner and processed using Adobe Photoshop.

Results

Initial AChE patches were seen in the putamen as early as 10 POW. These initial inhomogeneities are in form of very small patches and are few in number (Figure 1b). During this period cytoarchitectonical organization as seen on Nissl preparation appears homogenous (Figure 1a). First cellular islands discernible on Nissl preparations appear after 14 POW (Figure 1c). These islands are surrounded by rather homogenous matrix. During the same period the AChE reactive patches were distributed throughout putamen (Figure 1d). This compartmentalization becomes more and more pronounced as visible on figures 2a and 2b. After 18 POW this cytoarchitectonical inhomogeneities display a variety of shapes as well as different staining properties, ranging from dark stained to more loosely cell packed islands (Figure 2a).

The cytoarchitectonical compartmentalization of AChE rich patches forms a mosaic which is characteristic for fetal developmental period. The fetal mosaic shows island-matrix compartmentalization on Nissl and patch-matrix on AChE preparations. The preterm mosaic shows more complex pattern due to the appearance of Nissl pale and AChE negative perimeters around cell islands and around AChE positive patches respectively (Figure 2a,

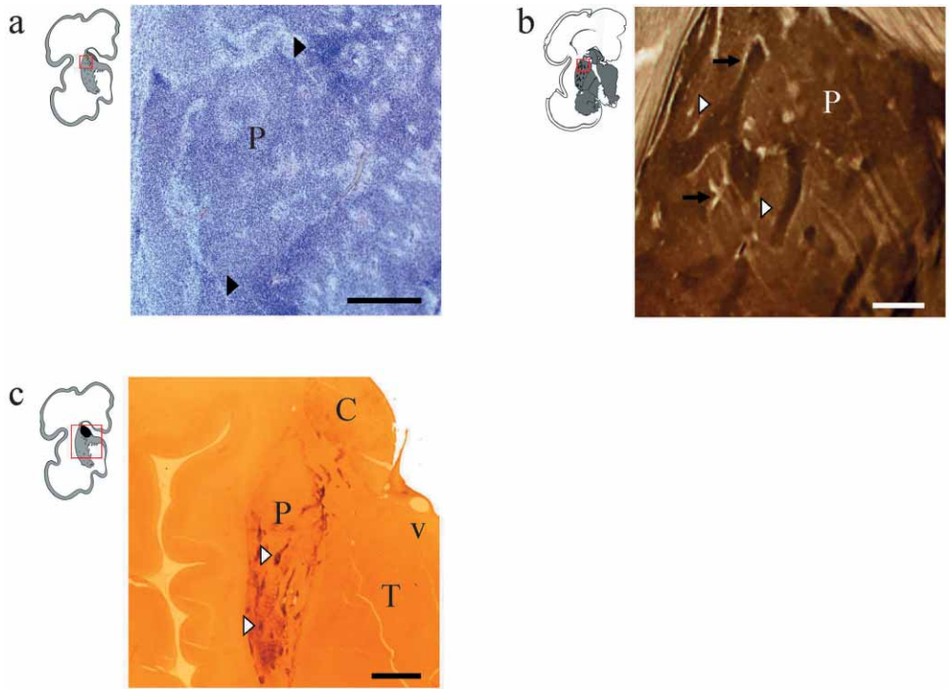

Fig. 2. Appearance of Nissl pale perimeters around cell islands (a, 32 POW) as well as AChE negative zones around AChE positive patches (b, 28 POW). Arrowheads indicate cell islands, arrows point to cell-poor zones. A case of periventricular hemorrhagic lesion with premortem survival period (c, 4 postnatal months). POW = postovulatory weeks, P = putamen, C = caudatus; T = thalamus, v = vena thalamostriata. Scale bar: A = 500 μm; B, C =1mm

b). This developmental change occurs between 20–24 POW and lasts until 34 POW. This pattern starts to diminish after 34 POW.

During existence of fetal (patch – matrix) and preterm (patch – cell free perimeters – matrix) mosaic of compartmental organization we have seen evidence of compartmental distribution of extracellular matrix molecules. As revealed by Periodic Acid Schiff-Alcian Blue (PAS-AB) histochemistry striatal patches contain high amount of glycosaminoglycan related molecules (Figure 1e). Synaptophysin reactivity, which indicates synaptogenesis in the fetal striatum, is also distributed in patches (Figure 1f).

In one case of periventricular hemorrhagic lesion with premortem survival period we could not find clear modular organization of the striatum in the lesion region (Figure 2c) whereas in the caudal putamen there was a reorganization of the AChE positive patches which indicates structural plasticity of corticostriatal pathways.

Discussion

We have confirmed that putamen shows clearly cytoarchitectonical and histochemical compartmentalization between 15–34 POW. This transient pattern of organization is very different from the adult system of striosoms and other immunocytochemical compartments described in human putamen[24–27,30]. Other studies of prenatal development of the human striatum have also shown transient nature of compartmental organization[20,21,31]. We propose that this transient pattern of compartmentalization corresponds to the nigrostriatal[16,30] input. We point to this period of existence of transient organization as a »waiting« period, because the corticostriatal fibres seem to arrive early and grow over prolonged period[16]. Hence it is our hypothesis that at the end of the »waiting« period (28 POW) corticostriatal fibres form cell-free »waiting« zone around cell islands, before entering their targets. The significance of the similar »waiting« zone was already shown in the human and monkey cortex[1–5,13,19,32]. We predict that lesions after »waiting« period will have different effect on corticostriatal system than lesions before. From our data it is obvious that the final stage of the »waiting« period corresponds well to the preterm period.

It may be questioned whether transient cytoarchitectonic compartments and chemically distinct patches can be related to the growth of corticostriatal system. In this respect it is essential to refer to results of Goldman-Rakic paper[16], in which there was a close correlation between cell islands and input from the cortex. We suggest that cytoarchitectonical defined compartments should be a basic reference for all histochemical and immunocytochemical markers seen in developing striatum.

The lack of cytoarchitectonical correlates makes difficult to compare our results with results of Graybiel and Ragsdale[33]. In this period we have seen AChE negative zones while Graybiel and Ragsdale described AChE reactive perimeters. However some of their results pointed at similar AChE negative zones in putamen as we have illustrated in our material[33].

The hypoxic-ischemic lesions in preterm infants can damage basal ganglia and could have profound effect on future motor behaviour[34,35]. It is very likely that this basal ganglia lesions affect corticostriatal system. The striatum can be easily delineated on ultrasound examination which offers reliable possibility to study perinatal brain lesion during this critical period. However, the compartments of striatum seem to be so small that can not be distinguished on magnetic resonance imaging while ultrasound is not precise enough to study inhomogeneities.

At the moment, it is difficult to answer an important question whether the contralateral striatal projection in human cerebrum exists during development and whether this projection can compensate the lesions which are predominantly unilateral. The small contralateral corticostriatal projection was seen in monkey and this projection can show reactive structural plasticity if the input from the contralateral cortex is removed[15]. The future MRI-studies with better resolution may help to solve this question.

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STRUKTURNA PODLOGA RAZVOJNE PLASTIČNOSTI KORTIKOSTRIJATALNOG SUSTAVA

S A Ž E T A K

Dosadašnje studije pokazale su da tijekom razvitka kortikostrijatalna vlakna u majmuna završavaju oko strijatalnih citoarhitektonskih odjeljaka – staničnih otočića, pokazujući promjenu oko 105. embrionalnog dana (E105) gestacije. U ovoj studiji istraživali smo citoarhitektonske otočiće te na acetil-kolin esterazu (AChE) pozitivna područja strijatuma ljudskog mozga smatrajući ih strukturnim pokazateljem razvitka kortikostrijatalnih putova. Postmortalno moždano tkivo 27 fetusa te prerano rođene djece, starosti 11–34. tjedna nakon ovulacije (TNO) obrađeno je Nissl metodom, AChE histokemijom i imunocitokemijom (synaptophysin). Analizirani materijal dio je Zagrebačke neuroembriološke zbirke. Prva AChE pozitivna područja, koja vjerojatno odgovaraju dopaminergičkim otočićima, bila su vidljiva sa 10 TNO, dok su se citoarhitektonski stanični otočići na Nissl preparatima mogli uočiti tek nakon 14 TNO. Glavna promjena tijekom razvitka događa se između 20–24. TNO kada se oko staničnih otočića pojavljuju AChE negativne zone. Ovakav prolazni obrazac AChE reaktivnosti najbolje se može uočiti oko 28. TNO uz lateralnu granicu putamena. U jednom slučaju periventrikularnog krvarenja kod prematurusa sa preživljavanjem, našli smo reorganizaciju AChE pozitivnih područja u putamenu što upućuje na strukturnu plastičnost kortikostrijatalnih putova. Pretpostavljamo stoga da zone siromašne stanicama služe kao »čekaonice« za rastuća kortikostrijatalna vlakna koja pristupaju strijatumu kroz subkalozalni snop te preko kapsule eksterne. Razdoblje prisutnosti strijatalnih odjeljaka (14–30 TNO) predstavlja zapravo osjetljivi period za strukturnu plastičnost i vulnerabilnost nakon periventrikularne lezije.