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# Distinct Origin of GABA-ergic Neurons in Forebrain of Man, Nonhuman Primates and Lower Mammals

Zdravko Petanjek<sup>1,2</sup>, Ana Dujmović<sup>1,2</sup>, Ivica Kostović<sup>1</sup>, Monique Esclapez<sup>3</sup>

<sup>1</sup> Croatian Institute for Brain Research, School of Medicine, University of Zagreb, Zagreb, Croatia

<sup>2</sup> Department of Anatomy, School of Medicine, University of Zagreb, Zagreb, Croatia

<sup>3</sup> INSERM U751, Facultas de Medecine Timone, Marseille, France

## ABSTRACT

*In this mini-review we present recent data about origin of GABA-ergic (gama-aminobutyric acid) neurons in the mammalian forebrain, including the diencephalon and telencephalon. The interest in GABA-ergic neurons, which in cerebral cortex mostly correspond to local circuit neurons (interneurons), has increased in the past decade. Many studies have shown that in lower mammals all hippocampal and almost all neo-cortical GABA-ergic neurons are born in the specific region named ganglionic eminence, and not locally in proliferative layers all around telencephalic vesicle. The ganglionic eminence, that represents a region with thick proliferative-subventricular layer in the ventral (basal) part of telencephalon, was classically thought to give neurons to basal ganglia and septal nuclei, whereas proliferative layers of dorsal telencephalon give neurons to cerebral cortex including hippocampus. It was thought that neurons migrate from proliferative layer to their target region following a radial orientation. However, data in lower mammals showed that this is the case only for glutamatergic principal cells, i.e. projection neurons. GABA-ergic neurons use long distance tangential migration, parallel to pial surface to reach, from ganglionic eminence, their targeting layer in the cerebral cortex. Especially intriguing, but frequently neglecting, several studies suggest that mammalian evolution might use different developmental rules to provide GABA-ergic neurons to an expanding brain. In this review we focus on specific events underlying GABA-ergic neuron development in human and non-human primates. Disturbances of the GABA-ergic network are found in many neurological and psychiatric disorders, some of them might result from altered production or migration of these neurons during development. Therefore, it is crucial to understand human-specific mechanisms that regulate the development of GABA-ergic neurons.*

**Keywords:** GABA, interneurons, cerebral cortex, thalamus, ganglionic eminence, human

## Introduction

The forebrain comprises a complex set of structures that derive from the most anterior region of the neural tube, the prosencephalon<sup>1-7</sup>. The prosencephalon consists of the diencephalon and telencephalic vesicles, which emarginated from the dorsal part of the rostral diencephalon. The telencephalon includes two major regions: the pallium (roof), and the subpallium (base). The pallium gives rise to the cerebral cortex and hippocampus, whereas the subpallium gives rise to basal ganglia and septal nuclei. Two major neuronal types are produced in proliferative layers of forebrain<sup>8</sup>, projectional neurons and local circuit neurons (interneurons). In cerebral cortex projectional neurons are mainly glutamatergic<sup>9,10</sup> whereas interneurons synthesize mainly GABA

(gama-aminobutyric acid) that is major inhibitory neurotransmitter in mature (adult) brain<sup>11-19</sup>.

The interneurons comprise 20 to 30% of cortical neurons serving an instrumental role in modulating cortical output<sup>20-47</sup>. These functions are conducted by a remarkable diversity of distinct subtypes that are distinguished by axonal and dendritic morphology, biochemical markers, connectivity and physiology. During mammalian, and especially primate evolution number and complexity of GABA-ergic neurons increased more than is the case to projection neurons. Recent data showed that GABA-ergic neurons in the forebrain have different mechanisms of proliferation and migration compared to gluta-

matergic projectional neurons<sup>21,22,48–53</sup>, and even more; there are significant changes during mammalian evolution regarding origin of cortical and thalamic GABA-ergic neurons<sup>54–57</sup>. Therefore, in this review we will focus on two aspects of evolutionary changes in GABA-ergic neuron origin in the forebrain, the origin of GABA-ergic neurons in cerebral cortex and of the GABA-ergic neurons in thalamic nuclei.

### Origin of GABA-ergic neurons in mammalian thalamus

During brain evolution, considerable enlargement of the cortical areas of the cortex is accompanied by an increase of corresponding thalamic nuclei in the diencephalon<sup>55,58–67</sup>. The number of neurons increases preferentially in limbic and association group of nuclei, whereas that in the specific relay nuclei appears to be conserved. The most remarkable progression is present in dorsal human thalamic nuclei connected with associative cortex (e.g. pulvinar nucleus, mediodorsal nucleus), that are in relative size even much larger than those in other primates. In addition, the increase in neuron number is not proportional for all neuronal types, so there is a relative increase in number of GABA-ergic neurons in ascend of evolution. For example, in rodents, there is a lack of GABA-ergic neurons in dorsal thalamic nuclei, except in lateral geniculate nucleus. In addition, the percentage of these neurons in ventrobasal thalamic nuclei is much lower than in higher mammals. In primate brain, GABA-ergic neurons represent approximately 30% of the neurons in each thalamic nucleus<sup>54,68,69</sup>.

During the embryonic period in human (first 2 months of gestation), the wall of the thalamus, similar to that of all neural-tube derived regions, includes the ventricular, intermediate and marginal zones<sup>7,8</sup>. Experimental autoradiographic studies in mammals demonstrated that all thalamic neurons arise from the diencephalic ventricular and subventricular zones<sup>70–75</sup>, distinct from the telencephalic proliferative layers<sup>3,7,8</sup>. In human fetuses, the comparative histological analyses together with measurements of supravital incorporation of tritiated thymidine indicated that the thalamic neurons were generated during the embryonic and early fetal period of development<sup>7,8,76–79</sup>.

However, Rakic and Sidman<sup>77</sup> found that the major period of human pulvinar growth was from the eighth to the thirty-fourth week of gestation, when the diencephalic proliferative layers apparently no longer generate neurons, while the ganglionic eminence attains its maximal size and proliferative activity<sup>7,8,54,55,80,81</sup>. Results of our group described in human fetuses in detail a transient structure, the gangliothalamic body, extending from the ganglionic eminence to the thalamus. The gangliothalamic body was well developed from the eighth to the thirty-fourth week of gestation in all rostro-caudal thalamic regions, containing a streams of bipolar cells in the tangential direction, which suggests that they are migrating to a wide range of thalamic nuclei<sup>81</sup>. Some

of thalamic nuclei may gain new neurons in the period that postdates the initial outgrowth and even penetration of the thalamic fibers into the cortical plate<sup>82–110</sup> suggested that the ganglionic eminence probably supplies additional local circuit neurons.

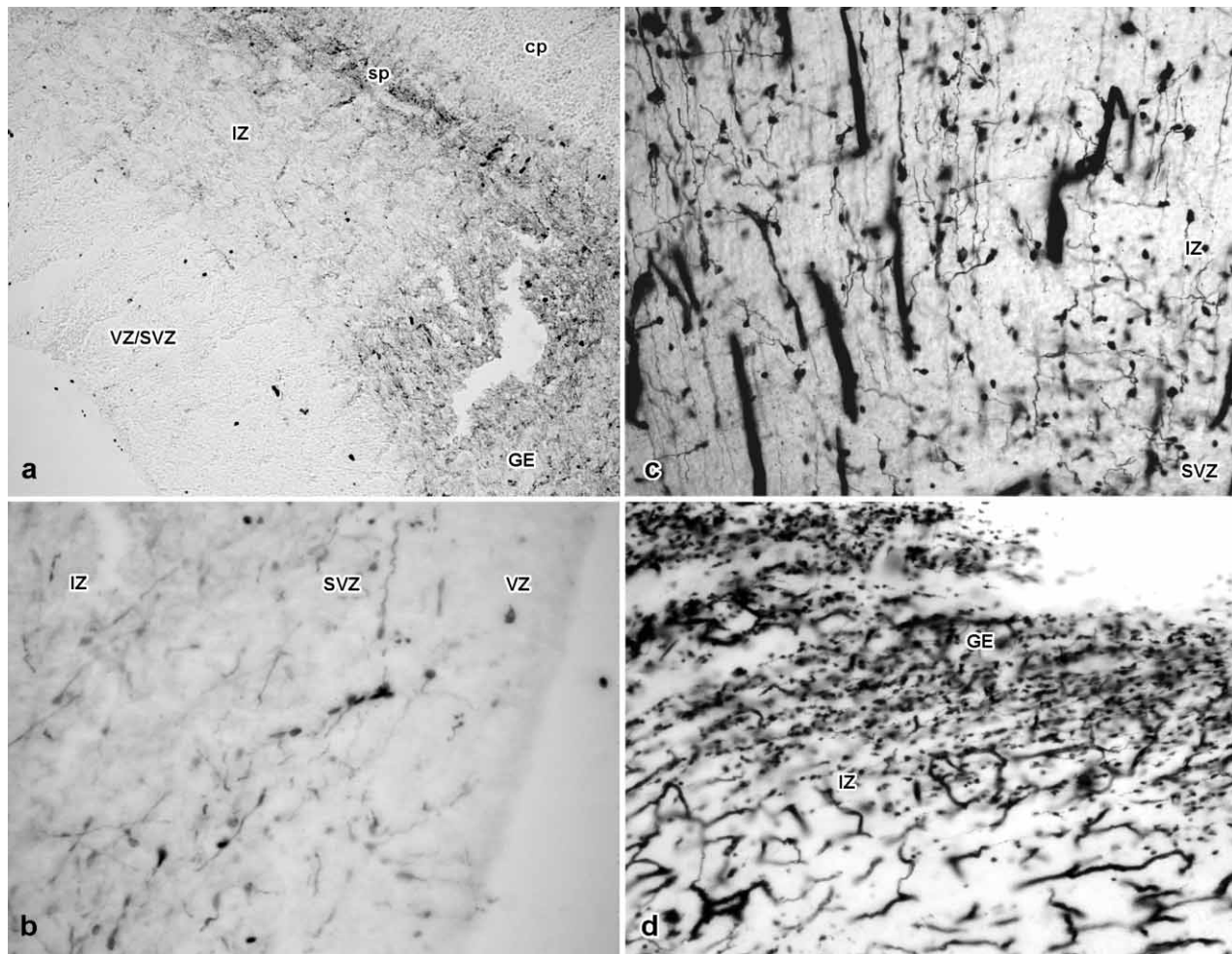
Direct evidence in human brain that cells actually migrate from the ganglionic eminence to the thalamus came from Letinić and Rakic study<sup>54</sup>. Using vital dye labeling in organotypic slice cultures they show that in human brain, a contingent of neurons migrate from the ganglionic eminence of the ventral telencephalon to the dorsal thalamic association nuclei of the diencephalon, while in monkeys and mouse this was not the case. These later findings are supported by previous studies performed in other mammalian species that did not observed such telencephalo-diencephalic migration<sup>8</sup>. However Kornack and collaborators<sup>111</sup> described a discrete telencephalo-diencephalic cell migration in the developing monkey brain. Using retroviral-mediated gene transfer analysis, these authors showed that during late gestation, the posterior thalamus gains new cells that arise from nearby mitotically active telencephalic proliferative layers, and translocate into the diencephalon. In contrast to human fetal brain, gangliothalamic body was not observed, because the number of cells traveling from telencephalon to diencephalon in the monkey is too small to form a distinct structure.

All these data showed significant changes in the neuronal organization of thalamic GABA-ergic circuitry through mammalian evolution, with new migration pathways involved. In addition, they suggest that during mammalian brain evolution regions connected to each other anatomically and functionally co-evolve<sup>58,59</sup>.

### Origin of GABA-ergic neurons in cerebral cortex of nonprimate mammals

Classical studies, as well as modern retroviral lineage analyses, concur to establish that projection neurons, in all species examined, originate in the ventricular layer zone (VZ) of the dorsal telencephalon and migrate along radial glial fibers, crossing the intermediate zone (IZ), to the overlying cortical plate<sup>8,112–133</sup>. Data from *Emx1*<sup>IREScree</sup> mouse<sup>2,134</sup> showed that radial glia, Cajal-Retzius cells, glutamatergic neurons, astrocytes, and oligodendrocytes of most pallial structures originate from pallial proliferative layers<sup>135</sup>.

However, it is well recognized that cells disperse in the forebrain in patterns that do not coincide with the plane of the glial fiber system<sup>8,136–142</sup>. Lineage experiments indicate that separate progenitors give rise to cortical glutamatergic projection neurons and GABA-ergic neurons<sup>143–147</sup> and that clones of GABA-ergic neurons are tangentially dispersed, whereas radially arranged clones are formed primarily of projection neurons<sup>57,148–151</sup>. Immunohistochemical analysis has revealed that post-mitotic migrating like GABA-containing neurons within the intermediate zone and lower marginal zone have a morphology and orientation consistent with a lateral to



*Fig. 1. Frontal section of monkey brain stained with calretinin antibody (a,b) at stage of E47 (embryonic day) (a) and stage E56 (b). Note unipolar migrating like cells leaving ganglionic eminence (GE) and entering the intermediate zone (IZ) in tangential orientation (a). Note intensive calretinin staining in the subplate (sp) located below the cortical plate (cp). At later stages the subventricular (SVZ) and intermediate zone contain numerous tangentially and nonradially oriented unipolar migrating like cells, whereas no cells were found in the ventricular zone (VZ) (b). Golgi staining of frontal sections of the human fetal brain at 22. week of gestation (c,d). Note the same distribution of nonradially oriented migratory like cells in the dorsal telencephalic wall (c) as in the monkey brain (b). At that stage numerous unipolar migrating like cells are still leaving the ganglionic eminence and entering the intermediate zone (d).*

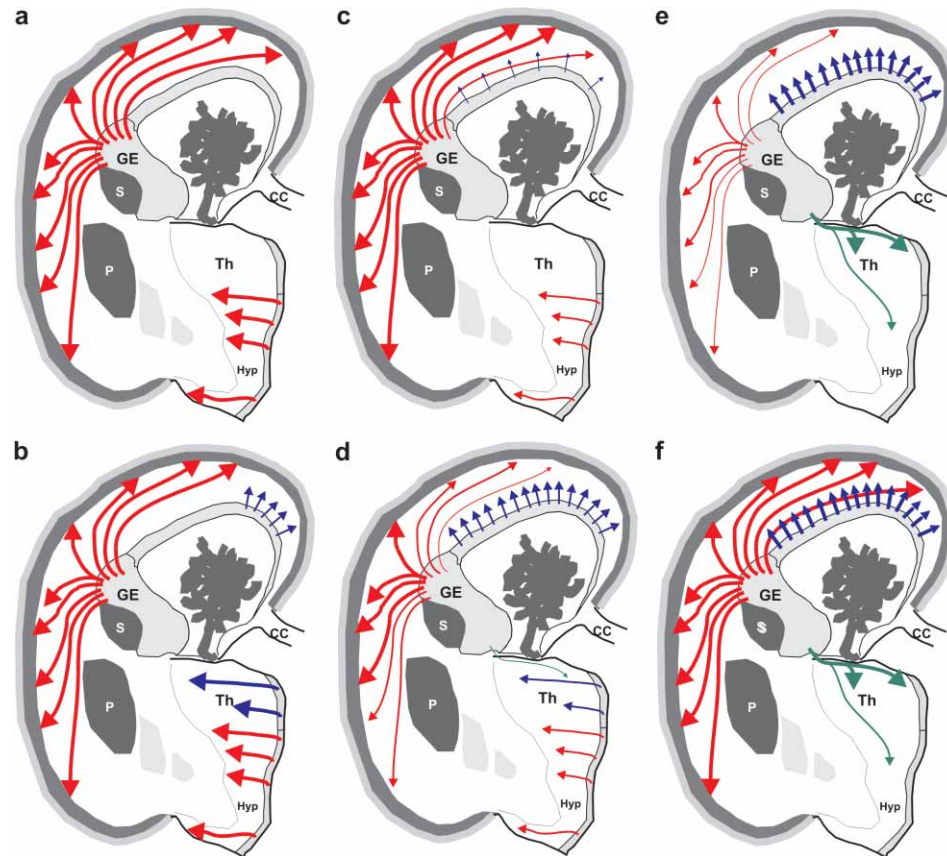
medial migration, from the ganglionic eminences into the neocortex<sup>152,153</sup>. Studies of cultured brain slices have revealed that cells containing GABA migrate tangentially from the ventral telencephalon into the neocortex<sup>49,55, 154–169</sup>. In addition, several lines of knockout mice that display abnormalities in proliferative tissues of the ventral telencephalon show marked reductions in the numbers of cortical GABA-immunoreactive neurons present in the neocortex at birth. These include mutants for the transcription factors *Dlx1* and *Dlx2* that show 75% decrease in neocortical GABA neurons at P0 (postnatal day)<sup>155,170</sup>; *Nkx2.1* – 50% decrease in neocortical GABA-ergic cells at E18.5 (embryonic day)<sup>171</sup>; and *MASH1* that show 50% decrease in neocortical GABA-ergic neurons at E18.5<sup>172,173</sup>.

These studies have provided compelling evidence that GABA-expressing cells are derived from the ganglionic

eminences of the ventral telencephalon and migrate tangentially through the intermediate zone into the cerebral cortex (Figure 1). It was shown that ganglionic eminence gives also rise to GABA-ergic projection neurons of the striatum and globus pallidus<sup>80,159,174–177</sup>, as well as to GABA-ergic neurons of the olfactory bulb<sup>155,162</sup>. The ganglionic eminence may also generate the cholinergic projection neurons of the nucleus basalis and cholinergic interneurons of the striatum<sup>80,159</sup>.

Division of the developing telencephalon into progenitor domains in which neuronal fate may be restricted to a particular neurotransmitter phenotype questioned which mechanisms may control region-specific neurogenesis and neurotransmitter specification. *Mash-1* and *Dlx1/2* expression was showed to be major transcription factors involve in the specification of GABA-ergic phenotypes in the forebrain. The basic helix–loop–helix gene *Mash1*





*Fig. 2. Schematic drawings of changes in origin and routes of GABA-ergic neuron migration in forebrain based on the literature data and showed on schematised frontal section of human fetus at 14. week of gestation at the level where ganglionic eminence (GE), thalamus (Th), hypothalamus (Hyp), caudate nucleus (S), putamen (P) and corpus callosum (CC) is present. During early embryonic stages (a,b) the major source of cortical GABA-ergic neurons is the ganglionic eminence and the neurons migrate tangentially in the cortex (red arrows); in rat (a) it seems that all GABA-ergic neurons are produced in the ganglionic eminence, whereas in monkey (b) proliferation of GABA-ergic neurons is very early present also in the pallial (cortical) proliferative on the most dorsal part of the telencephalon (blue arrows). Note, that in the diencephalon of the rat (a) GABA-ergic interneurons are produced only in the ventral diencephalic proliferative layers (red arrows), so that dorsal thalamic nuclei do not contain GABA-ergic neurons. In the monkey (b) GABA-ergic diencephalic neurons are produced also in dorsal proliferative layers (blue arrows), so they are found in the dorsal thalamic nuclei too. It is supposed that dynamics of interneuron production found in the monkey (b,d) is also present in the human fetal brain. Later on during gestation (c,d) more cells are produced in dorsal proliferative layers, so that even in rodent (c) some small percentage of the GABA-ergic neurons is produced in dorsal proliferative layers, whereas according to Letinić and collaborators<sup>55</sup> in human (d) the number of dorsal producing GABA-ergic neurons is increasing, whereas in the ganglionic eminence production is decreasing. Regarding to this suggestion in more later stages of neurogenesis (e), that were not present in rodent brain, the major proliferation of cortical GABA-ergic neurons is present in dorsal (cortical) proliferative layers, and not in the ganglionic eminence. However, the most recent preliminary data of our group<sup>211</sup> suggest another possibility, because size of ganglionic eminence as density of migrating like cells leaving it has reached the peak around 22. week of gestation (f). Note that proliferation of neurons in the diencephalic proliferative layers is in the middle of gestation decreasing, and later is not present at all. In human (e,f), there is a huge stream of cells invading thalamic nuclei from the ganglionic eminence (green arrows), whereas in monkey only few neurons were found to undertake this route (d). In lower mammals this is not present (c).*

plays an important role in neurogenesis of the striatum<sup>80,172,173,175,178</sup>. Ectopic expression of Mash1 in the cortex induces expression of GAD67 (glutamate decarboxylase)<sup>179</sup>. In addition, the transcription factor Dlx2 induces GAD67 and GABA expression when expressed within cortical cells from Dlx1/Dlx2 mutant mice<sup>155,170, 174,180–183</sup> or in slices of wild-type prenatal neocortex<sup>184,185</sup>. That in single mutants for this two genes no complete absence of GABA-ergic cells was described<sup>155,170–173</sup>, it is possible that there are other genes that could specify phenotype

for some subpopulation of GABA-ergic neurons in the forebrain.

### Origin of GABA-ergic neurons in cerebral cortex of macaque monkey and humans

The primate neocortex displays an exponential increase, in size compared with that of other mammals, whereas subcortical structures show only linear increa-

ses<sup>60,186–188</sup>. Such evolution of the neocortex disturbs the scaling of shared developmental processes between cortical and subcortical structures (Figure 2). Therefore, one can imagine that an exclusive ventral telencephalic production of cortical GABA-ergic neurons as in rodents, would imply that in primate these neurons have to travel very long distances before reaching their targeted layer. Interestingly the study of Letinić and collaborators<sup>55</sup> provides evidence that mammalian evolution uses different developmental rule to resolve this issue. The authors demonstrate that the dorsal telencephalic proliferative layers are the major source of neocortical GABA-ergic neurons in humans. The study identifies a distinct population of Mash1-expressing progenitors for GABA-ergic neurons in the human dorsopallial proliferative layers. Mash1 was present only in progenitors that give rise to cortical plate neurons that express GABA and *Dlx*, and not in progenitors that give rise to pyramidal neurons. In addition several studies have shown that an ectopic Mash1 expression in rodents is sufficient to upregulate *Dlx1/2* in neocortical neurons, whereas an ectopic *Dlx* expression may induce the GABA-ergic phenotype in the same cells<sup>155,170,180–183</sup>. This data suggest that Mash1 transcription factor may induce GABA-ergic neuronal production in the human dorsopallial VZ/SVZ by upregulating *Dlx* genes.

Letinić and collaborators<sup>55</sup> also suggested that this dorsal telencephalic origin of GABA-ergic neurons might be humanspecific, as the telencephalo-diencephalic migration of GABA-ergic neurons. This hypothesis was based also on the fact that rodents and primates display significant differences in production of cortical cells. For example most retroviral labelling studies indicate that SVZ in rodent is predominantly a gliogenic compartment<sup>8,189–194</sup>, in contrast, the SVZ is a main region for neurogenesis in monkey and human<sup>55,192,193,195,196</sup>. However, reports<sup>8,154,197,198</sup> suggest that in rodents some, *Dlx* expressing progenitors in the SVZ of the dorsal telencephalon derive from truly pallial progenitors, as has been proposed to occur in humans<sup>55</sup>, indicating that the idea that the source of GABA-ergic neuron in the cortical VZ/SVZ is unique to humans needs to be counterbalanced.

In rodent disruptions of ganglionic eminence development results in only partial losses of cortical GABA-ergic cells<sup>154,171,172,174,199</sup> and pallial (cortical) progenitor cells are able to generate GABA-expressing neurons in vitro<sup>143,200–202</sup>. It should be mentioned that the production of GABA-ergic neurons in the rodent cortical (pallial) proliferative layers accounts at best for only a small fraction of the interneurons present at maturity<sup>49</sup>. In the ferret, neurons destined for neocortical layers II and III continue to be generated during early postnatal life<sup>203–205</sup>. The spatial origin of these cells within the telencephalon<sup>49</sup> showed that very few (less than 5%) of them labeled for the interneuron markers GABA or GAD67 originate from the cortical proliferative layers.

Data obtained in transgenic mouse suggest that in rodents more than 95% of cortical GABA-ergic cells express *Dlx5/6* at some stage of their development and suggesting that most cortical GABA-ergic neurons are derived from the subpallium<sup>184,185,206,207</sup>. However, our results showed that in macaque as in human a large proportion of GABA-ergic neurons are produced in the proliferative layers of the dorsal telencephalon<sup>208,209</sup>.

Therefore, all this data demonstrate different production sources for cortical as well as diencephalic GABA-ergic neurons during evolution. The dorsal telencephalic origin, in addition to the ventral one for cortical GABA-ergic neurons in humans might reflect a boosting of pre-existing developmental mechanisms. The novel source of Mash1 progenitors in humans might arise from the evolutionary duplication of comparable cells in the ganglionic eminence. Some light Mash1 immunoreactivity observed in dorsal proliferative layers during neurogenesis in mice<sup>210</sup>. Such data support this hypothesis.

The possibility that some of Mash1-expressing progenitors in the primate neocortical VZ/SVZ in fact arrived from the ganglionic eminence at earlier embryonic stages and continue to divide locally in neocortical proliferative layers was mentioned by Letinić and collaborators<sup>55</sup>. However, this and our<sup>208,209</sup> data strongly suggest that neocortical GABA-ergic neurons are born in the VZ/SVZ of the dorsal telencephalon as a distinct neuronal stem cell lineage. In favor of this hypothesis are some experimental results from studies in rodents; it seems that a single genetic switch is all that it takes — misexpression of Mash1 in cortical neurons results in their transformation to the interneuron type<sup>179</sup>. Also, after 14.5 embryonic day (E) in the mouse, many *Dlx*-expressing cells appear to migrate from the subcortical SVZ directly into the SVZ of the neocortex. Some of these cells express the postmitotic neuronal marker Tuj1 and at E16.5 they are not proliferating based on the lack of labeling with antibodies against proliferating cell nuclear antigen (PCNA)<sup>154</sup>. The slice transplant experiments of E14.5 ganglionic eminence, pulsed with BrdU for 4 hours before fixation at 2 days in vitro, also found that ganglionic eminence cells did not proliferate after migration into the cortex<sup>198</sup>. Surprisingly, although *Dlx1* expressing cells in the cortical SVZ were negative for PCNA at E16.5, at P0 many of them co-label with PCNA and these appear to be proliferating<sup>154</sup>. So it seems that Mash1 expression in a minority of cortical progenitors induces *Dlx* genes. A slice transplantation assay<sup>154</sup>, modified by the use of GFP-expressing donor tissues<sup>198</sup> showed that large number of cells from the subcortical donor tissue migrated into the cortex of the host slice<sup>154,198</sup>. Although many of these cells migrated into the cortical proliferative layers, and although a large number of the cortical proliferative layers cells incorporated BrdU, double labeled cells were extremely rare at any of the three ages. Migration of GFP-labeled cells (post-mitotic neurons) from the ganglionic eminence into the cortical proliferative zones was robust, as was production in the cortical proliferative layers. However, the percentage of GFP

expressing cells that incorporated BrdU within the cortical proliferative layers remained extremely small, showing that GABA-ergic neurons produced in cortical-pallial proliferative layers originate from truly cortical, »pallial« progenitors, and not from progenitors invading this layer from ganglionic eminence.

All above presented data are in line with the interpretation that large dorsal (pallial-cortical) production of interneurons in primate cortex is an „answer« to an increased number of GABA-ergic neurons to an expanding neocortex. However, our recent preliminary findings, describing tangential migration in the human fetal brain during second trimester of gestation, suggest another hypothesis<sup>211</sup>. We found that at the 22. week of gestation density of tangentially migrating cells increased compared to earlier stages, especially in the stream leaving the ganglionic eminence, that during this period shows an increase in size. Increase in number of tangentially migrating like cells up to second half of gestation becomes more important in the view that radial migration has decreased substantially. This suggests that intensive production of interneurons continued into the second half of gestation, while the production of projection neurons is decreasing rapidly. In addition, the number of cortical neurons that are produced by ganglionic eminence seems to increase during midgestation. Such observation seems not to support previous hypothesis. It is more likely that relatively increased number of cortical

interneurons is supported by protracted production of neurons in ganglionic eminence, as appearance of dorsal (pallial) production of interneurons. It is also possible that huge dorsal production of interneurons in primate brain is principally connected with production of some specific interneuron subpopulation.

In conclusion, we have to mention that studies on cortical GABA-ergic neurons development are very limited in monkeys and humans. It is also obvious that research performed in rodents will not provide sufficient evidence to understand mode and tempo of interneuron development in the human brain. Disturbances of the GABA-ergic network are found in many neurological and psychiatric disorders and some could result from altered development<sup>53,85,212–237</sup>. Therefore, understanding of the human specific mechanisms, that regulate the development of GABA-ergic interneuron subtypes, is a crucial pre-required step for future neurobiological studies of these diseases. Therefore, we found that further research of GABA-ergic neuron development in the primate brain has to be highly encouraged.

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## Z. Petanjek

Croatian Institute for Brain Research, Department of Anatomy, School of Medicine, University of Zagreb, Zagreb, Croatia.  
E-mail: zpetanjek@net.hr

## PORIJEKLO GABA-ERGIČKIH NEURONA U PREDNJEM MOZGU ČOVJEKA, DRUGIH PRIMATA I NIŽIH SISAVACA

### SAŽETAK

U ovom osvrtu pružamo pregled novih spoznaja o porijeklu inhibicijskih neurona koji sintetiziraju GABA (gama-amino-maslačnu kiselinu) u prednjem mozgu (proencefalonu) sisavaca, što uključuje kranji mozak (telencefalonu) i međumozak (diencefalonu). Zanimanje za GABA-ergičke neurone, koji u kori velikog mozga (korteksu) uglavnom odgo-varaju neuronima lokalnih krugova (interneuronima), značajno je poraslo u proteklom desetljeću. Kao posljedica toga, potpuno se promijenilo prijašnje vjerovanje, te su novi rezultati pokazali da se u nižih sisavaca svi hipokampalni i gotovo svi kortikalni GABA-ergički neuroni rađaju u specifičnom području, tzv. ganglijski brežuljak, a ne lokalno u proliferativnim slojevima uzduž cijele ventrikularne stijenke telencefalona. Ganglijski brežuljak, koji je zapravo područje ventralnog (bazalnog) telencefalona gdje je izrazito zadebljan proliferativni-subventrikularni sloj, smatrao se

izvorom neurona bazalnih ganglija i septalnih jezgara, dok su se proliferativni slojevi dorzalnog telencefalona smatrali izvorom svih kortikalnih i hipokampalnih neurona. Također se smatralo da se neuroni kreću od proliferativnih slojeva do svog konačnog odredišta prvenstveno mehanizmima radijalne migracije, ali su novi podaci pokazali da je to slučaj samo za projekcijske glutamatergičke neurone. GABA-ergički neuroni koriste mehanizam tangencijalne migracije, prelazeći velike udaljenosti od ganglijskog brežuljka do svih dijelova kore velikoga mozga krećući se paralelno s pijačnom površinom. Posebno intrigantni, ali uglavnom zanemareni, su podaci o razlikama u porijeklu GABA-ergičkih neurona koje se javljaju tijekom evolucije u sisavaca. U ovom radu posebno smo se usredotočili na specifična događanja tijekom razvoja GABA-ergičkih neurona majmuna i čovjeka. U većini neuroloških i psihijatrijskih bolesti dolazi do odstupanja unutar GABA-ergičke mreže neurona, prvenstveno kao posljedica poremećenog razvoja. Zbog toga je za razumijevanje neurobiologije ovih poremećaja potrebno istražiti mehanizme specifične čovjeku koji reguliraju razvoj različitih podvrsta GABA-ergičkih interneurona.