Brain Research Bulletin 66 (2005) 297–302

BRAIN RESEARCH BULLETIN

www.elsevier.com/locate/brainresbull

Expression patterns of developmental regulatory genes show comparable divisions in the telencephalon of *Xenopus* and mouse: insights into the evolution of the forebrain

Loreta Medina*, Aurora Brox, Isabel Legaz, Margarita García-López, Luis Puelles

Department of Human Anatomy, Faculty of Medicine, University of Murcia, 30100 Murcia, Spain

Available online 24 February 2005

Abstract

In this study, we review data on the existence of comparable divisions and subdivisions in the telencephalon of different groups of tetrapods based on expression of some developmental regulatory genes, having a particular focus in the comparison of the anuran amphibian *Xenopus* and the mouse. The available data on *Xenopus*, mouse, chick and turtle indicate that apparently all tetrapod groups possess the same molecularly distinct divisions and subdivisions in the telencephalon. This basic organization was likely present in the telencephalon of stem tetrapods. Each division/subdivision is characterized by expression of a unique combination of developmental regulatory genes, and appears to represent a self-regulated and topologically constant histogenetic brain compartment that gives rise to specific groups of cells. This interpretation has an important consequence for searching homologies, since a basic condition for cell groups in different vertebrates to be considered homologous is that they originate in the same compartment. However, evolution may allow individual cell groups derived from comparable (field homologous) subdivisions to be either similar or dissimilar across the vertebrate groups, giving rise to several possible scenarios of evolution, which include both the evolutionary conservation of similar (homologous) cells or the production of novel cell groups. Finally, available data in the lamprey, a jawless fish, suggest that not all telencephalic subdivisions were present at the origin of vertebrates, raising important questions about their evolution.

Keywords: Ventral pallium; Lateral pallium; Claustrum; Pallial amygdala; DVR

1. Introduction

The telencephalon is the most rostrodorsal region of the brain and contains the superior centers involved in control of sensorimotor, autonomic and endocrine functions, in emotional behavior, as well as in cognitive functions such as learning and memory. Classical studies established that in mammals the telencephalon contains the cerebral cortex, the basal ganglia, the claustrum, the amygdala, the septum and other basal forebrain areas that include the basal nucleus of Meynert. For more than a century, comparative neurobiologists have tried to unravel the evolutionary origin of these structures and to find their homologues in other vertebrates, with a particular focus in the cerebral cortex and basal ganglia. This task turned out to be extremely difficult due to the complex and apparently variable morphological organization of the diverse cell groups in the telencephalon of mammals and non-mammals (for review, see [62]). With the development of histochemical/immunohistochemical and tract-tracing techniques and their use by comparative neurobiologists after the late 1960s, major advances were achieved in our understanding of the organization of the telencephalon. In particular, the basal ganglia could be identified consistently in the telencephalon of several non-mammalian vertebrates, including birds, reptiles, amphibians and jawed fish, as well as in the lamprey, a jawless vertebrate [26,29–31,39,42,43,50,51,66]. However, the origin of other parts of the mammalian telencephalon, including the cerebral cortex, the claustrum and the amygdala, remains partially uncertain and ideas on their evolution are still controversial [1,15,25,45,49,62].

* Corresponding author. Tel.: +34 968 364340; fax: +34 968 363955.
E-mail address: lmedina@um.es (L. Medina).

0361-9230/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.brainresbull.2005.02.003

The discovery of developmental regulatory genes involved in brain patterning, regional specification and morphogenesis, and their use by comparative developmental neurobiologists have opened new scenarios for studies of brain evolution [2,3,8,9,19,20,34,48]. Developmental regulatory genes encode signaling proteins or transcription factors that regulate the expression of other genes, and are involved in different aspects of development, including patterning, specification, cell proliferation (growth) and cell differentiation. These genes show highly conserved sequences and positionally stereotyped expression patterns, and have become very useful tools for comparing brain regions across vertebrates. Here, we review recent evidence suggesting that in tetrapods the telencephalon consists of the same basic histogenetic divisions/subdivisions, which are characterized by expression of unique combinations of developmental regulatory genes [2,3,8,9,19,20,32,34,48]. This approach has allowed more precise identification of homologous pallial subdivisions in *Xenopus*, sauropsids and mouse, supporting a fundamental subdivision of the conventional lateral pallium into novel lateral and ventral pallial sectors [48]. These lateral and ventral pallial subdivisions give rise to parts of the piriform cortex, claustrum and amygdala in mouse, and we discuss whether similar cell groups are produced in the corresponding pallial subdivisions of *Xenopus*.

2. Telencephalic divisions/subdivisions and their derivatives in mouse based on gene expression patterns

A large amount of data indicates that, during development, the telencephalon in mouse becomes divided into two major molecularly distinct domains: the pallium and the subpallium [11–13,16,32,46,48,60,64,67]. These two major divisions show distinct expression of several developmental regulatory genes and give rise to different cell groups (Fig. 1(A)). For example, the subpallium expresses *Dlx* family genes (such as *Dlx*1, *Dlx*2 and *Dlx*5) and *Gsh*1/2, and gives rise to the basal ganglia, part of the amygdala (including the central, medial and intercalated nuclei), a major part of the septum, and some basal telencephalic cell groups that include the bed nucleus of the stria terminalis (BST), the extended amygdala and the corticopetal cholinergic neurons [12,32,48,64,67,68]. The pallium expresses *Pax*6, *Emx*1/2, *Neurogenin*2, *T-brain* family genes (*Tbr*1 and *Tbr*2), and the LIM homeodomain gene *Lhx*9, and gives rise to the cerebral cortex, the claustrum, part of the amygdala (including the basolateral complex and the cortical amygdalar areas) and a small part of the septum [4,5,11,13,23,32,48,52,57,58,60,61,64,68]. Several studies involving lack-of-function of a single gene or a pair of these genes (using knockout mice) have shown their importance in patterning and morphogenesis of the telencephalic pallium and subpallium (for example, [4,5,35,61,64,67,68]).

Both pallium and subpallium can be further subdivided into smaller molecularly distinct domains [48]. For example, the subpallium includes striatal, pallidal and anterior entopeduncular subdivisions showing expression of distinct combinations of *Dlx*2/5, *Nkx*2.1 and *Sonic hedgehog* genes [44,48,56,63]. The pallium, classically divided in three parts, also can be subdivided by differential expression of several developmental regulatory genes, including *Lmo*2, *Emx*1 and *Lmo*3 [10,48,65]. The LIM-only genes *Lmo*2 and *Lmo*3 are expressed strongly in either the medial (hippocampal) or the lateroventral (piriform lobe) pallial territories, respectively, but their expression is weak in the dorsal pallium [10,65]. Other developmental regulatory genes are expressed across the pallium in gradients: for example, *Emx*2 and *Pax*6 are expressed in opposing gradients in the pallium, from caudomedial to rostrolateral levels or viceversa [4,5], and the LIM homeodomain gene *Lhx*2 is expressed strongly in the dorsomedial pallium, gradually diminishing into the lateroventral pallium [10,52]. The three pallial territories are differently affected by mutations targeting distinct regulatory genes involved in pallial development. For example, in the absence of the LIM homeodomain gene *Lhx*2, the medial and dorsal pallial sectors are severely shrunken [10,65]. In contrast, the piriform lobe, as characterized by its normal markers *Lmo*3 and *Dbx*1, appears relatively normal-sized (see below [65]). This suggests that these subdivisions are self-regulated histogenetic compartments, whose distinct development is controlled by specific networks of regulatory molecules, and which give rise to specific neuronal populations (see discussion of the concept of "compartment" in [47]).

In addition to the classical subdivision of the pallium in medial, dorsal and lateral domains, Puelles et al. proposed the existence of a distinct ventral pallial subdivision on the basis of differential *Emx*1 expression: while the majority of the pallium expresses strongly *Emx*1, the ventral pallium shows only some *Emx*1 signal at its pial surface [48] (this territory poor in *Emx*1 was previously described and named "intermediate zone" [59]). Puelles et al. included this territory as part of the pallium based on its expression of typical pallial marker genes, such as *Tbr*1 in the mantle and *Pax*6 in the ventricular zone [48]. Later studies have corroborated the existence of a distinct ventral pallial territory based on its selective expression of the homeobox gene *Dbx*1 during early development [32,68]. As a result, the classical piriform lobe includes two subdivisions, a lateral pallium and a ventral pallium (this involves a re-definition of the classical "lateral pallium", which used to include all the "piriform lobe"). Based on differential expression of *Emx*1, *Cadherin*8 (*Cad*8) and *Semaphorin*5*A* (*Sema*5*A*), the lateral and ventral pallia appear to give rise to different parts of the claustral complex and pallial amygdala [32,48]. Thus, the lateral pallium apparently gives rise to the dorsolateral claustrum, basolateral amygdalar nucleus and posterolateral cortical amygdalar area (all showing high *Emx*1 and *Cad*8 expression, but low or no *Sema*5*A* signal) [32]. On the other hand, the ventral pallium appears to give rise to the ventromedial claustrum, endopiriform nuclei (except a posterior part), lateral and ba-