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Review

Development and evolution of the subpallium

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ABSTRACT

Among vertebrates, the ventral part of the telencephalon called the subpallium presents common basic developmental, hodological, neurochemical and functional features. It is genetically specified by expression of Dlx genes; its progenitor zones contribute a huge variety of neuronal cell types throughout the telencephalon; it is the origin and substrate of multiple and complex migration and navigation pathways during embryogenesis; and its derivatives, i.e. the basal ganglia and the amygdaloid complex, are highly conserved through evolution. Comparative developmental studies point to a largely common basic plan to generate the subpallium in vertebrates, including comparable progenitor domains and similar migratory cellular movements. In the course of telencephalic evolution however, slight variations have occurred, and the subpallium has probably represented a source for significant novelties and diversification in vertebrate forebrain anatomy and physiology.

Contents

1. Introduction

The vertebrate telencephalon exhibits one of the most heterogeneous collection of neurons in the entire nervous system in terms of morphology, structure, function and genetic specification, making this rostral-most part of the brain one of the most intricate of all biological structures. During the course of vertebrate evolution, the telencephalon is probably also the region of the nervous system which underwent the most dramatic changes and diversification, readily observable in adults as highly variable structures, cytoarchitectonies, neuronal compositions, sizes, or connectivities. Nevertheless, it shows a great degree of conservation across vertebrate species for the successive steps of its development, including specification, signaling, patterning and neurogenesis [1–9].

The telencephalon in all vertebrates is composed by two main territories, the pallium and the subpallium, which both develop from the alar (dorsal) plate of the neural tube. In particular, the subpallium represents an exemplary case of telencephalic complexity

Abbreviations: AEP, peduncular region; DC, dorsal cortex; DP, dorsal pallium; DVR, dorsal ventricular ridge; LGE, lateral ganglionic eminence; LP, lateral pallium; MGE, medial ganglionic eminence; NCX, neocortex; Pa, pallium; PSB, pallium–subpallium boundary; POC, commissural preoptic division; POA, anterior preoptic area; POH, preoptic hypothalamic region; PCX, piriform cortex; Str, striatum; VP, ventral pallium.

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because it not only gives rise to the multiple neuronal types that form the basal ganglia, parts of the amygdala and the septum, but also originates an astonishing diversity of cortical interneurons.

The aim of this paper, through reviewing of the relevant older and recent literature on the development and organization of the subpallium, is to analyze with as much evidences as possible (proliferative domains, neuronal specification, neurochemistry, hodology and function) the degree of conservation or divergence of the subpallium across vertebrates.

2. Development of the subpallium in vertebrates

To a large extent, the definition of different progenitor regions in the subpallium was first based on anatomical landmarks, such as sulci and bulges. Unfortunately, despite the convenience of anatomical references, morphological boundaries do not always coincide with molecular limits, they are often misleading because they may change in position over time, and, most important in an evolutionary perspective, they are not always comparable among species. It is one of the reasons for the exhaustive gene expression analyses conducted during the last years in different species, and which led to the establishment of homology relationships in terms of genetic specification of subpallial territories [10–21].

2.1. Progenitor domains in the mouse subpallium

The developing subpallium includes the basal region of the evaginated telencephalic vesicles and the non-evaginated telencephalon anterior to the optic chiasm [10,23–26]. Within this zone, the boundaries of the histogenetic divisions that give rise to different parts of the adult brain are currently being revised and new hypotheses are being drawn. Combined analysis of the expression of developmental regulatory genes in the proliferative ventricular zone (vz) and the adjacent progenitor subventricular zone (svz) together with phenotypic neuronal markers in the differentiated mantle zone indicate that the mouse subpallium contains more histogenetic divisions than previously suspected [21,27]. The evaginated subpallium (Fig. 1A) consists of the lateral ganglionic eminence (LGE; the striatal division) and the medial ganglionic eminence (MGE; the pallidum proper), that includes the entopeduncular region (AEP), whereas the non-evaginated telencephalon, also called the telencephalic stalk, includes the preoptic area (PO) that contains at least three major subdivisions, a novel commissural preoptic division (POC; at the base of the septum, in relation to the anterior commissure and dorsolateral preoptic area), the anterior preoptic area (POA) at the base of the former, and the preoptic–hypothalamic border region (POH), close to the chiasmatic region [21,27] (Fig. 1A). Inside these major domains, a recent analysis has further subdivided the mouse subpallium into a total of 18 progenitor domains [21].

The LGE is a bulge that forms between the pallium and the MGE during development in mammals. It is defined by the expression of Dlx1/2/5 [23] and in some sub-areas of Isl1, Gsh2, ER81 and Pax6 [21,28–31], and by the lack of vz Nkx2.1 expression [21,32]. The LGE is bordered dorsally by a small domain, named the ventral pallium [10,33] which is characterized in mammals by the expression of Tbr2, Ngn2, and Dbx1, and by the absence of Dlx2 [10,34]. Ventrally, the limit with the MGE is defined by an important vz Nkx2.1 expression [10,27]. The dorsal LGE, currently defined as pLGE1 and pLGE2 (p stands for *p*rogenitor domain; [21]) by the differential expression of Pax6 and ER81 [21,31,35,36] is thought to give rise to interneurons that migrate to the olfactory bulb [31,34,36,37]. It may also contribute distinct populations of postmitotic neurons that form the striatum proper and the autonomic amygdaloid complex (the central amygdala). The remaining LGE progenitor domains, the pLGE3 and pLGE4 as defined by Flames et al. [21], represent striatal progenitors [31] and contain Dlx1/2- and Isl1-cell populations in the svz and Nkx6.2 expression in the ventral portion [21].

The MGE emerges during development as a prominent bulge between the LGE and the septum, but no anatomical landmarks clearly define its caudal and ventral limits, and it consists of multiple progenitor domains [21]. Gene expression-wise the MGE is defined by the expression of Dlx1/2/5 [23], and can be differentiated from the LGE by the strong Nkx2.1, weak Nkx2.2, and lack of Pax6 expression [10,21,30,32]. The MGE derivatives in mammals (besides several types of neurons which populate other telencephalic areas) are defined by strong expression of Nkx2.1 and Lhx6 and they include the globus pallidus (GP), the commissural part of the ventral pallidum and at least a subpopulation of cells of the lateral portion of the bed nucleus of the stria terminalis (BST) [26,27].

The AEP was initially related to cholinergic and other cell groups at the telencephalic stalk, and to the fibre tracts that travel through it, connecting telencephalon and thalamus/brainstem (via the internal capsule/cerebral peduncle) or both hemispheres (via the anterior commissure) [26,38,39]. This former AEP has recently been divided into the "true" AEP related to the peduncle (the area called the entopeduncular area) and the novel commissural preoptic area (or commissural septo-preoptic area; POC) located at the base of the septum and related to the anterior commissure and dorsolateral preoptic area [27]. Based on molecular profiles (i.e. strong expression of Nkx2.1, Lhx6, Lhx7 and lack of Shh), the "new" AEP is likely rostromedially continuous with the pallidal septum and part of the MGE, the pMGE5 of Flames et al. [21]. In addition, the AEP is related to a distinct cell corridor of peptidergic (SOM and NPY) and calbindin-containing (CB) neurons, whereas only the POC, but not the AEP, shows vz expression of Shh [27]. Thus, the AEP, whose derivatives are in general found at the level of the anterior commissure, is a distinct histogenetic subdivision that appears to produce SOM and CB cells that spread into specific parts of the so-called extended amygdala, parts of the medial amygdala and BST [27] (Fig. 1A).

The POA is defined anatomically as the region immediately in front of the optic recess, at the limit between the telencephalon and the diencephalon. In terms of genetic specification the POA is notably different from the rest of the subpallium. Its vz is defined by the expression of Nkx2.1, Nkx2.2, and by the lack of detectable levels of Gsh2, Lhx6, Lhx7, Olig2 and Shh [21].

Finally, the POH constitutes the border of the subpallium, recently defined as a thin territory separating longitudinally the POA from the magnocellular hypothalamus [40]. It contains progenitor cells that express Dlx2, Pax6, Olig2, and Gsh2; it lacks expression of Nkx2.1, Shh, Nkx6.2, and Dbx1, and has been divided in two areas because the POH1 but not the POH2 expresses high levels of Nkx2.2 [21].

In addition to the contribution from these intrinsic subpallial progenitor domains, the subpallium receives immigrant cells from other regions including the pallium, the thalamic eminence and the hypothalamic territories [10,27,41].

2.2. Neurogenesis and neuronal specification

A model for telencephalic development and neurogenesis [42] proposed that the molecular mechanisms which specify progenitor zones by restricted and combinatorial expression of transcription factors (previous sections) are also at work to control the production of neurons with specific neurotransmitter and neurite projection phenotypes. Hence, the Pax6/neurogenin1-expressing pallium would generate glutamatergic neurons, whereas the Dlx/Mash1-expressing subpallium would produce GABA and cholinergic cells. Moreover, neurons born from a given progenitor zone and positioned in the differentiating/mantle zone through classical radial