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New scenarios for neuronal structural plasticity in non-neurogenic brain parenchyma: The case of cortical layer II immature neurons

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ABSTRACT

The mammalian central nervous system, due to its interaction with the environment, must be endowed with plasticity. Conversely, the nervous tissue must be substantially static to ensure connectional invariability. Structural plasticity can be viewed as a compromise between these requirements. In adult mammals, brain structural plasticity is strongly reduced with respect to other animal groups in the phylogenetic tree. It persists under different forms, which mainly consist of remodeling of neuronal shape and connectivity, and, to a lesser extent, the production of new neurons. Adult neurogenesis is mainly restricted within two neurogenic niches, yet some gliogenic and neurogenic processes also occur in the so-called non-neurogenic tissue, starting from parenchymal progenitors. In this review we focus on a population of immature, non-newly generated neurons in layer II of the cerebral cortex, which were previously thought to be newly generated since they heavily express the polysialylated form of the neural cell adhesion molecule and doublecortin. These unusual neurons exhibit characteristics defining an additional type of structural plasticity, different from either synaptic plasticity or adult neurogenesis. Evidences concerning their morphology, antigenic features, ultrastructure, phenotype, origin, fate, and reaction to different kind of stimulations are gathered and analyzed. Their possible role is discussed in the context of an enriched complexity and heterogeneity of mammalian brain structural plasticity.

Contents

Abbreviations: BrdU, 5-bromo-2′-deoxyuridine; CNS, central nervous system; CAMKII, Ca(2+)/CaM-dependentproteinkinase II; CNGA-3, cyclic nucleotide-gated ion channel-3; DCX, doublecortin; DLL, pan distalless; GABA, γ-aminobutyric acid; GAD, glutamic acid decarboxylase; GFAP, glial fibrillar acidic protein; GFP, green fluorescent protein; MAP-2, microtubuleassociated protein-2; NeuN, neuronal nuclear antigen; Ng2, nerve/glial antigen 2 proteoglycan; NMDA, N-methyl-D-aspartate; NR1, subunit 1 of the NMDA receptor; OPCs, oligodendrocyte progenitor cells; p-CREB, phosphorylated cAMP response element-binding protein; PSA-NCAM, polysialylated form of the neural cell adhesion molecule; SGZ, subgranular zone; SVZ, subventricular zone; ST8SiAII, ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 2; ST8SiAIV, ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 4; Tbr1, T-box brain-1; TUC4, TOAD/Ulip/CRMP-4; TuJ1, class III beta-tubulin.

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1. Introduction

Plasticity is the ability to make adaptive changes related to the structure and function of a system. Such capability is of paramount importance in the nervous system, which is devoted to dynamically interact with the internal and external environment. Further knowledge of neural plasticity physiological role(s) also draws interest for regenerative medicine, in the perspective of modulating plastic changes to foster repair within the damaged nervous tissue.

Due to its heterogeneity, plasticity is one of the most often used, yet most poorly defined terms in Neuroscience. In this review we will restrict our interest to structural plasticity, by referring to all types of changes, which modify the shape and structure of the central nervous system (CNS; Bonfanti, 2006; Theodosis et al., 2008) and then focusing on a population of immature neurons in the layer II of certain regions of the adult cerebral cortex.

Structural plasticity can occur in different forms and for this reason it has become a very wide field of investigation. Although a highly conserved feature in evolution, structural plasticity shows striking quantitative/qualitative differences among animal species. The situation of substantial 'general plasticity' and cell renewal existing in the oldest living metazoans is strongly reduced in vertebrates (Koizumi and Bode, 1991), although some fish, amphibians and reptiles still exhibit a great neurogenic potential and good CNS regenerative capability (Sirbulescu and Zupanc, 2010; Endo et al., 2007; Lopez Garcia et al., 2002). In birds and mammals a transition between regeneration permissive and non-permissive stages occurs soon after birth (Whalley et al., 2009). Hence, in the large-sized/architecturally-complex brain of mammals, structural plasticity is a compromise established between a need for neural circuit invariability and the requests for its adaptive modification, which suggests that most of such plasticity deals with pre-existing neural elements (reviewed in Bonfanti, 2011). This is reasonable, since a fundamental feature of mature CNS parenchyma is its connectional, neurochemical and functional specificity, which allows specific cell types to be connected and to act in a relatively invariant way (Frotscher, 1992). The neural networks are initially sculpted by experience during the sensitive periods and then they are stabilized at different postnatal developmental stages (reviewed in Spolidoro et al., 2009). The architectural specificity is maintained in the adult through a vast cohort of membrane-bound and extracellular matrix molecules, mainly involving adhesion molecules and their receptors with permissive and/or instructive functions (Gumbiner, 1996; Bonfanti, 2006).

On these bases, the discovery of neural stem cells (Reynolds and Weiss, 1992) and adult neurogenesis in the mammalian brain (Lois and Alvarez-Buylla, 1994; Gould, 2007; Kempermann et al., 2004) were viewed as a breakthrough in neurobiology, leading to hypothesize a regenerative medicine able to heal traumatic, vascular and neurodegenerative pathologies in our nervous system (reviewed in Arenas, 2010; Lindvall and Kokaia, 2010). Yet, no substantial, efficacious therapies based on cell replacement are at present available in the CNS. Adult mammalian neurogenesis is confined within two small brain regions – the forebrain subventricular zone (SVZ) and the hippocampal subgranular zone (SGZ) – which are germinal layer-derived sites under the control of a highly regulated microenvironment (Gage, 2000; Kriegstein and Alvarez-Buylla, 2009). As a consequence, outside the two privileged areas harbouring neural stem cells, the mammalian nervous system is largely made up of non-renewable, non-regenerative tissue (Sohur et al., 2006; Gould, 2007; Ponti et al., 2010; Bonfanti, 2011; Bonfanti and Peretto, 2011). Yet, recent reports of progenitor cell populations capable of proliferation in many brain, cerebellum, and spinal cord regions, suggest that a slow glial cell renewal (and also genesis of young neurons in some mammalian species; see below) can also occur physiologically (Horner et al., 2002; Dayer et al., 2005; Luzzati et al., 2006; Ponti et al., 2008; reviewed in Nishiyama et al., 2009; Bonfanti and Peretto, 2011) and/or after injury (Ohira, 2010) in the so-called non-neurogenic parenchyma.

All these forms and 'levels' of plasticity, which have been progressively revealed during the last decades, have increased the complexity in the landscape of mammalian brain structural plasticity.

1.1. Heterogeneity of plasticity in the so-called non-neurogenic tissue

The prevalent view in modern neurobiology considers the non-neurogenic mammalian tissue as intrinsically plastic under the profile of synaptic connections (Holtmaat and Svoboda, 2009; Bavelier et al., 2010; Chen and Nedivi, 2010; Fu and Zuo, 2011; see Table 1), which can structurally change connectivity without changing the number and type of neurons. On the other hand, evidences for adult parenchymal gliogenesis and neurogenesis can increase the heterogeneity of such plasticity by introducing new structural modifications through the addition of new cellular elements (Bonfanti and Peretto, 2011).

1.1.1. Structural plasticity affecting pre-existing elements

In addition to the striking plasticity existing in early life, some experience-dependent structural changes also persist during adulthood (Sale et al., 2008; Holtmaat and Svoboda, 2009). Although the large-scale organization of axons and dendrites is remarkably stable for most of the animal lifespan, a subset of synaptic structures can display cell type-specific, experience-dependent structural plasticity in terms of formation/elimination of synapses (Holtmaat and Svoboda, 2009; Chen and Nedivi, 2010; Fu and Zuo, 2011; see Table 1). Axonal sprouting occurs during spatial learning (Ramirez-Amaya et al., 2001), and in response to environmental enrichment (Galimberti et al., 2006). Structural plasticity involving pre-existing cells and circuits can also occur after a lesion in the form of compensatory events, i.e. synaptic formation/elimination and axonal sprouting/pruning (see Table 1). For example in mice, after stroke, dendrites become plastic in the vicinity of a cerebral infarct and these structural changes might provide a substrate for the long-term functional changes in the representational cortical maps (Brown et al., 2009). Due to the extreme heterogeneity of CNS neural tissue and circuitries, the outcomes of lesion-induced compensatory plasticity would be highly variable, exiting into a wide range of events depending on the specific site and type of injury (Darian-Smith and Gilbert, 1994; Chen et al., 2002; Dancause et al., 2005).