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Review

# The relevance of symmetric and asymmetric cell divisions to human central nervous system diseases

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ABSTRACT

During development of the embryonic central nervous system (CNS), large numbers of neurons and glia are generated from the neuroepithelium and its progenitor derivatives as a result of symmetric and asymmetric cell divisions. We describe the biology of symmetric and asymmetric cell divisions in the CNS as gleaned from animal models, and discuss the relevance of these processes to human CNS development and disease.



## 1. Introduction

During embryonic central nervous system (CNS) development, large numbers of neurons and glia are generated from the neuroepithelium and its progenitor derivatives. Symmetric and asymmetric cell divisions are highly regulated processes that occur during this developmental phase. Much of our understanding of the mechanisms underlying symmetric and asymmetric divisions in the CNS stems from studies of invertebrate and vertebrate models such as *Drosophila* and mice. Although these processes are far less well understood in humans, it is probable that a common thread exists from flies to humans, as studies from various disciplines, including medical genetics and cancer biology, have implicated human disease-causative genes/molecules whose homologues participate in symmetric and asymmetric cell divisions in animal models. We provide a broad overview of the biology of symmetric and asymmetric cell division in the CNS, and discuss the relevance of these processes to human CNS development and disease.

## 2. Early CNS development

A brief recapitulation of early CNS development, particularly the cerebral cortex, is instructive before describing the biology of symmetric and asymmetric cell divisions. The earliest structure in the embryo from which the CNS originates is a region of the ectoderm called the neural plate. The neural plate subsequently undergoes a series of morphogenetic changes resulting in the formation of the neural tube. The rostral neural tube develops into the prosencephalon (forebrain), from which the telencephalic vesicles (cerebral hemispheres) derive. The lumen of the neural tube becomes the ventricles in the telencephalon[1] (Fig. 1).

The telencephalic primordium is initially composed solely of proliferating neuroepithelial cells, the descendants of the neural plate.[2] These neural stem cells, originally a single pseudostratified layer of cells, subsequently generate the entire neocortex, which in humans is composed of several cell layers, the important ones being the ventricular zone (VZ), subventricular zone (SVZ), intermediate zone, cortical plate and marginal zone (Fig. 2). The VZ and SVZ both contain dividing cells, and are the main regions of interest in this review (see Section 3).

At birth, billions of neurons and glia are present in the human cerebral cortex.[3] This is the consequence of highly regulated symmetric and asymmetric cell divisions in the CNS.

## 3. Symmetric and asymmetric cell divisions in embryonic neurogenesis

Broadly, symmetric and asymmetric divisions refer to daughter cells acquiring similar or different fates, respectively, following mitosis of a mother cell.[4,5] Divergent fates in daughter cells may be recognized by various characteristics: (i) morphological, such as cell size and shape; (ii) molecular, such as the segregation of proteins into only one daughter cell; or (iii) behavioral, such as the subsequent descendant types produced by either of the daughter cells.[5,6] Symmetric and asymmetric divisions have been described in diverse systems of varying complexity, including simple unicellular organisms such as bacteria and yeast.[5] However,

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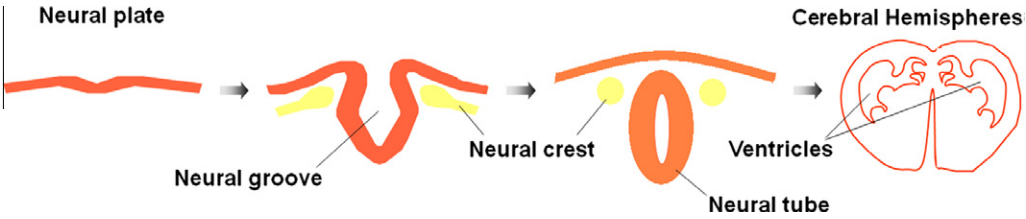


**Fig. 1.** Diagram of early development of the central nervous system from the neural plate.

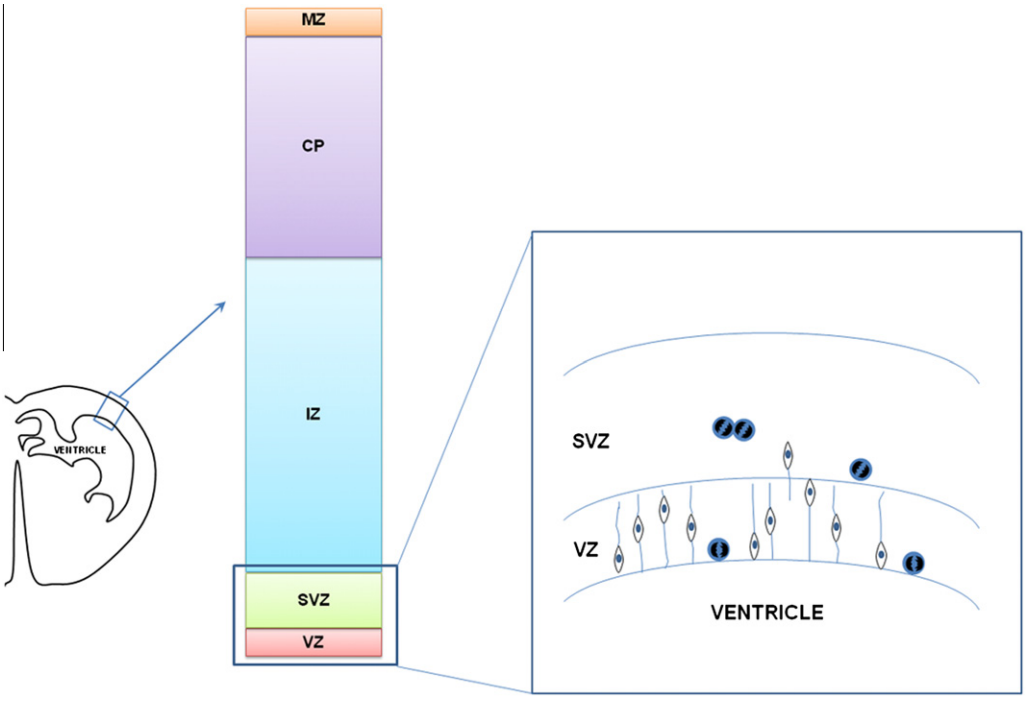


**Fig. 2.** Diagram of the zones of the developing human cerebral wall. The ventricular zone (VZ) and subventricular zone (SVZ) represent the proliferative compartments during neurodevelopment. CP = cortical plate, IZ = intermediate zone, MZ = marginal zone.

a description of symmetry and asymmetry in the context of neurogenesis in the mammalian brain is most relevant for this review.

The neuroepithelial cells are the original neural stem cells from which the cerebral cortex is derived. At the onset of neurogenesis, the neuroepithelial cells downregulate certain epithelial characteristics and develop astroglial properties – these descendants are termed radial glia.[7] Radial glia reside in the VZ, and assume the progenitor, stem cell-like role of the neuroepithelial cells, although they are more fate-restricted progenitors.[8,9] Both neuroepithelial cells and radial glia divide at the apical aspect of the VZ, and thus can be collectively referred to as apical progenitors.[10] During neurogenesis, another neuronal progenitor cell type appears and divides at the basal aspect of the VZ, subsequently forming the SVZ.[11] These are termed basal progenitors, and because they derive from apical progenitors, are also termed intermediate progenitors.

Both symmetric and asymmetric divisions occur during neurogenesis. Apical progenitors can undergo three different types of divisions: (i) symmetric, proliferative divisions leading to the formation of two apical progenitors; (ii) asymmetric, self-renewing divisions leading to the formation of an apical progenitor and an intermediate (basal) progenitor; and (iii) asymmetric, self-renewing divisions leading to the formation of an apical progenitor and a neuron.[6,7] Basal progenitors undergo symmetric, differentiating divisions leading to the formation of two neurons.[11] These various types of divisions are illustrated in Fig. 3.

## 4. The molecular basis of fate determination

One mechanism for fate determination of daughter cells following symmetric and asymmetric cell divisions is the partitioning of fate-determining molecules during mitosis of the mother cell. The idea that specific molecules can be partitioned unequally to daughter cells and behave as fate determinants had been hypothesized over a century earlier, following observations of cell divisions in simple organisms (reviewed in [5]). However, this hypothesis was only experimentally validated a little under two decades ago, with the identification of the first asymmetrically segregated cell fate determinant – Numb[12] (reviewed in [13]). Numb was the first of many asymmetrically segregated determinants discovered in *Drosophila*, and was a starting point for similar studies into asymmetric divisions in vertebrates. Molecules that have been reported to undergo asymmetric segregation in the vertebrate CNS (*in vivo* or *in vitro*) include the Notch1,[14] Numb,[15–17] LGN,[18] epidermal growth factor receptor (EGFR),[19] Tripartite motif-containing protein 32 (TRIM32)[20] proteins and Minibrain (Mnb) messenger RNA.[21]

The mechanisms underlying fate-determinant partitioning during mitosis, particularly during asymmetric cell division, have been extensively characterized.[22,23] We draw attention to one particular mechanism, the orientation of the cleavage plane during mitosis, because of its relevance to a genetic cause of human CNS malformations, which we describe in Section 6.