ELSEVIER

Update TRENDS in Neurosciences Vol.27 No.7 July 2004

Full text provided by www.sciencedirect.com
SCIENCE DIRECT

Research Focus

Lipids make smooth brains gyrate

David J. Price

Genes and Development Group, Hugh Robson Building, George Square, Edinburgh EH8 9XD, UK

The surface area of the cerebral cortex has increased massively during mammalian evolution and this change has been accompanied by folding of the cortical sheet into gyri. The molecular mechanisms that control cortical size are poorly understood. A recent study suggests that the regulation of cortical size might involve phospholipids, by showing that their addition to cultured embryonic mouse cortices increases cortical size and induces folds resembling gyri.

The size of each region of the mammalian brain is dictated in large part by the number of cells it contains. During development, each region acquires its mature complement of cells through a combination of cell division, cell death and cell migration. The total number of divisions among the progenitor cells of a region is a major determinant of its eventual size, although size can be further modified through the removal of significant numbers of postmitotic cells by naturally occurring cell death [1,2] and the redistribution of some postmitotic cells between regions by cell migration [3]. Naturally occurring cell death can also remove progenitor cells, thereby reducing the productivity of the progenitor population [2,4]. Several classes of molecule have been implicated in the control of cell division, cell death and cell migration in the developing brain, including transcription factors, secreted peptides and proteins, intracellular and extracellular proteins, and neurotransmitters [5–12]. In a recent paper, Kingsbury *et al.* [13] add to this list by providing evidence that extracellular lipids could also be important regulators of cell number in the developing brain. They show that the application of a lipid, lysophosphatidic acid (LPA), to embryonic mouse cerebral cortex increases the number of cells it contains and, intriguingly, causes the formation of folds resembling the cortical gyri of higher mammals.

How does LPA increase cortical cell number?

Kingsbury *et al.* [13] added LPA to embryonic mouse cerebral hemispheres in culture and found that this increased the thickness of the cerebral cortical wall (both its proliferating and differentiating layers) by ~30% and induced cortical folding in up to ~85% of cases. Although the increase in the surface area of the cortex due to folding was not quantified, images of treated cortices shown in their paper suggest that it was an order of magnitude greater than the increase in cortical thickness. LPA treatment appeared to decrease the proportions of cortical progenitor cells undergoing naturally occurring cell death, to promote the exit of these progenitors from the cell cycle and, as a result, to increase the overall numbers of proliferating and differentiating cells in the cortex (Figure 1). Importantly, there was no response to LPA treatment in cortices from mutant mice lacking the two LPA receptors normally expressed in embryonic cortex (LPA_1 and LPA_2) [14–16]; the explanation for this requirement was almost certainly that LPA added to the culture medium acted specifically via these LPA receptors. There is, however, no clear requirement for LPA_1 and LPA_2 during normal cortical development *in vivo*, because mice lacking these receptors can develop to adulthood with no detectable defects in cortical organization [17,18]. In future it will be crucial to identify a physiological role for LPA in normal cortical development using additional tools that might, for example, allow interference with the potential action of endogenous LPA at the time of cortical development but not before. This might reduce the opportunities for compensation for an early loss of LPA signalling.

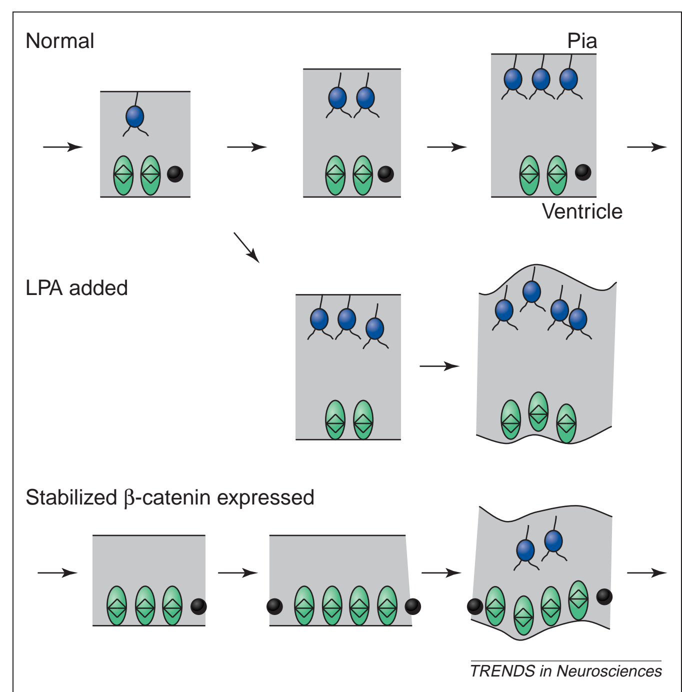

Figure 1. Summary of the effects of lysophosphatidic acid (LPA) added *in vitro* [13] and of stabilized β-catenin expression in transgenic mice [19] on cortical development. During normal development (top row), there is gradual expansion of the cortex as cells proliferate on the inner, ventricular side of the telencephalic wall (green cells) to generate postmitotic neurons that migrate to the outer side of the wall (blue cells); some cells in the proliferating zone die (black dots). Addition of LPA (middle row) inhibits cell death, promotes the production of postmitotic neurons, increases cortical cell number and causes cortical folding. Stabilization of β-catenin (bottom row) reduces the proportion of proliferating cells exiting the cell cycle, increases the size of the proliferating pool and also causes cortical folding.

Corresponding author: David J. Price (david.price@ed.ac.uk).
Available online 27 April 2004

How does LPA induce cortical folding?

Possibly the most interesting result reported by Kingsbury *et al*. [13] was that LPA induced cortical folds resembling gyri characteristic of the cortices of higher mammals. Recently, Chenn and Walsh [19] reported that the expression of a stabilized form of the protein β-catenin in CNS progenitor cells in transgenic mice increased cerebral cortical surface area, but not cortical width, and induced the formation of cortical folds. The cause of this cortical enlargement appeared to be an abnormal expansion of the cortical progenitor population resulting from increased re-entry of progenitors into the cell cycle, but did not seem to involve any change in the number of cortical cells undergoing naturally occurring cell death (Figure 1). Although LPA and β-catenin are very different molecules and their application or stabilization increased cortical cell number in different ways, both caused a similar morphological change – that is, a disproportionate increase in cortical surface area over cortical width and the formation of cortical folds. This suggests that if for any reason developing cortex is confronted with an excess of cortical cells, it expands tangentially rather than radially, increasing its surface area much more than its depth.

The surface area of the cerebral cortex is at least 1000 times greater in humans than in mice and yet the depth of the human cortex, which varies from 1.5–4.0 mm, is only 2–3 times greater than the depth of the mouse cortex. Why have evolution and the experimental manipulations of Chenn and Walsh [19] and Kingsbury *et al*. [13] caused a disproportionate increase in the surface area of the cortex? Although administration of LPA and expression of stabilized β-catenin have different mechanisms of action, they both affect primarily the progenitor population that resides at the ventricular surface of the cortical wall, altering the proportion of progenitors that either die or exit the cell cycle to differentiate. Enlargement of the cortical progenitor population has occurred through cortical evolution and has resulted in an expansion of the proliferative zone tangentially rather than radially. It could be that constraints dictated by the processes involved in cell division in the proliferative zone restrict the extent to which it can expand radially. Addition of progenitor cells to the developing cortex for whatever reason might, therefore, cause mainly tangential expansion of the proliferative zone and hence tangential expansion of its overlying derivative, the cortical sheet. If it were possible to increase experimentally the number of postmitotic cells generated from each progenitor without increasing the size of the progenitor pool, it would be interesting to discover whether cortical surface area would still increase disproportionately or whether the main change would be to cortical depth under these circumstances.

Why does the increased surface area of the cortex that is observed through evolution, and that results from administration of LPA or expression of stabilized β-catenin, become folded? It is easy to imagine that the formation of gyri in the cortices of higher mammals confers the advantage of allowing a relatively large sheet of cortical cells to be compressed into as small a volume as possible, so optimizing the efficiency of numerous processes such as the growth of axons to connect the parts of the brain together. The formation of gyri is not, however, analogous to crumpling a sheet of paper into a ball, because the positions and sizes of many cortical gyri are similar from individual to individual of higher species. The mechanisms that have evolved to produce gyri in higher mammals must, therefore, be very elaborate. It is not clear whether the experimental manipulations of Kingsbury *et al*. [13] and Chenn and Walsh [19] are able to induce processes that approach in complexity those that produce the gyri of higher mammals; it would be interesting to know whether the patterns of gyri produced by their experimental manipulations showed any features that were reproducible between individuals. A notable aspect of the study by Kingsbury *et al*. [13] is the folding of cultured hemispheres developing in the absence of any constraints normally imposed by the skull. A cortical sheet whose surface area is expanding abnormally rapidly within a normally developing skull might be expected to buckle and fold, but this seems more surprising if there is no skull. It is still possible that LPA induces cortical folding directly, perhaps in parallel with its effect on cortical cell number, or that other tissues such as the subcortical structures remaining in the cultured hemispheres constrain the expanding cortical sheet and so make it fold. If these possibilities can be excluded then a remarkable result will remain: namely, that the cortex, even in lower mammals, has evolved an intrinsic mechanism causing it to fold in response to an increase in its surface area.

Concluding remarks

The findings described here point to phospholipids as potential contributors to the control of cerebral cortical size. Further work is needed to establish a clear physiological role for these molecules in this regulatory process during normal development *in vivo*. The results raise the interesting hypothesis that mechanisms intrinsic to the cortical sheet itself generate complex patterns of sulci and gyri in response to an increase in cortical cell number.

References

1 Kuan, C.Y. *et al.* (2000) Mechanisms of programmed cell death in the developing brain. *Trends Neurosci.* 23, 291–297

2 Blaschke, A.J. *et al.* (1996) Widespread programmed cell death in proliferative and postmitotic regions of the fetal cerebral cortex. *Development* 122, 1165–1174

3 Marin, O. and Rubenstein, J.L. (2001) A long, remarkable journey: tangential migration in the telencephalon. *Nat. Rev. Neurosci.* 2, 780–790

4 Blaschke, A.J. *et al.* (1998) Programmed cell death is a universal feature of embryonic and postnatal neuroproliferative regions throughout the central nervous system. *J. Comp. Neurol.* 396, 39–50

5 Ghosh, A. and Greenberg, M.E. (1995) Distinct roles for bFGF and NT-3 in the regulation of cortical neurogenesis. *Neuron* 15, 89–103

6 LoTurco, J.J. *et al.* (1995) GABA and glutamate depolarize cortical progenitor cells and inhibit DNA synthesis. *Neuron* 15, 1287–1298

7 Xuan, S. *et al.* (1995) Winged helix transcription factor BF-1 is essential for the development of the cerebral hemispheres. *Neuron* 14, 1141–1152

8 Antonopoulos, J. *et al.* (1997) Activation of the GABAA receptor inhibits the proliferative effects of bFGF in cortical progenitor cells. *Eur. J. Neurosci.* 9, 291–298

9 Mabie, P.C. *et al.* (1999) Multiple roles of bone morphogenetic protein signaling in the regulation of cortical cell number and phenotype. *J. Neurosci.* 19, 7077–7088

10 Vaccarino, F.M. *et al.* (1999) Changes in cerebral cortex size are

governed by fibroblast growth factor during embryogenesis. *Nat. Neurosci.* 2, 246–253

11 Raballo, R. *et al.* (2000) Basic fibroblast growth factor (Fgf2) is necessary for cell proliferation and neurogenesis in the developing cerebral cortex. *J. Neurosci.* 20, 5012–5023

12 Estivill-Torrus, G. *et al.* (2002) Pax6 is required to regulate the cell cycle and the rate of progression from symmetrical to asymmetrical division in mammalian cortical progenitors. *Development* 129, 455–466

13 Kingsbury, M.A. *et al.* (2003) Non-proliferative effects of lysophosphatidic acid enhance cortical growth and folding. *Nat. Neurosci.* 6, 1292–1299

14 Hecht, J.H. *et al.* (1996) Ventricular zone gene-1 (*vzg-1*) encodes a lysophosphatidic acid receptor expressed in neurogenic regions of the developing cerebral cortex. *J. Cell Biol.* 135, 1071–1083

15 Contos, J.J. and Chun, J. (2001) The mouse lp_{A3}/*Edg*7 lysophosphatidic acid receptor gene: genomic structure, chromosomal location, and expression pattern. *Gene* 267, 243–253

16 McGiffert, C. *et al.* (2002) Embryonic brain expression analysis of lysophospholipid receptor genes suggests roles for $s1p_1$ in neurogenesis and $s1p_{1\text{-}3}$ in angiogenesis. *FEBS Lett.* 531, 103–108

17 Contos, J.J. *et al.* (2000) Requirement for the lp_{A1} lysophosphatidic acid receptor gene in normal suckling behavior. *Proc. Natl. Acad. Sci. U. S. A.* 97, 13384–13389

18 Contos, J.J. *et al.* (2002) Characterization of lpa_2(*Edg*4) and lpa_1/lpa_2(*Edg*2/*Edg*4) lysophosphatidic acid receptor knockout mice: signalling deficits without obvious phenotypic abnormality attributable to lpa_2. *Mol. Cell. Biol.* 22, 6921–6929

19 Chenn, A. and Walsh, C.A. (2002) Regulation of cerebral cortical size by control of cell cycle exit in neural precursors. *Science* 297, 365–369

0166-2236/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tins.2004.04.008

The unexpected consequences of a noisy environment

Xiaoqin Wang

Laboratory of Auditory Neurophysiology, Department of Biomedical Engineering, Johns Hopkins University School of Medicine, 720 Rutland Avenue, Ross 424, Baltimore, MD 21205, USA

A recent study found that the functional organization of auditory cortex was disrupted when rats were exposed to a moderate level of continuous noise during early development. However, this detrimental effect on auditory cortex could be remedied later by stimulating the noise-reared rats with structured sounds. These findings suggest that the endpoint of the ‘critical period’ could be extended well into adult life, which has significant implications for our understanding of cortical plasticity.

In a modern society, we are constantly exposed to a noisy environment: for example, while driving a car during daily commuting; from the never-ending air conditioner in the office and at home; and from earth-shaking rock concerts. People usually give little thought to what these noises could do to our brains beyond the obvious hearing loss that one experiences after being exposed to loud sounds. Previous studies have shown that prolonged exposure to high-intensity noises results in damage to hair cells, the auditory receptors that convert the acoustic information into neural signals for the brain. Hair cells in infants and young children often suffer permanent damage due to prolonged and untreated middle ear infections. As one might expect from the work of Hubel and Wiesel on visual cortex development and its susceptibility to distorted visual inputs [1], the damage to hair cells and resulting interruption of auditory inputs should lead to alterations in the central auditory system, including cortex [2]. However, the nature of such plasticity in auditory cortex is not fully understood. What is even less well known but far more interesting is how auditory cortex responds to distorted acoustic inputs when peripheral receptors are intact. Recent studies showed that if one artificially manipulated acoustic inputs to the auditory system during early development, altered neural representations of sounds emerge in auditory cortex [3,4]. How far could auditory cortex be degraded if distorted acoustic inputs were prolonged, akin to the situation in which an infant suffers severe hearing loss owing to an untreated middle ear infection? Is such degradation a non-reversible process? A recent study by Chang and Merzenich [5] sheds light on these fundamentally important questions. Their results show that constant exposure to moderate levels of noise results in severe distortion of neuronal frequency tuning and disruption of tonotopic organization of auditory cortex, but that such alterations seem to be reversible later in life if structured auditory inputs are provided.

Corresponding author: Xiaoqin Wang (xwang@bme.jhu.edu).
Available online 11 May 2004

Tonotopic organization of mammalian auditory cortex

The auditory cortex of adult mammals is organized according to sound frequency. This organization, or ‘tonotopic map’, is most clear in the primary auditory cortex (A1), where individual neurons have well-defined frequency tuning properties. In immature animals, the tonotopic map is not as well organized as in adults and A1 neurons tend to have broad frequency tuning. As infants grow into juveniles and adults, a refined tonotopic map progressively emerges. In adult animals, the tonotopic map is reorganized in situations where permanent hearing loss is induced or if animals are extensively engaged in behavioral training [6–8]. Studies show that the tonotopic organization is much more susceptible to perturbations of acoustic inputs in infancy than in older animals, giving rise to the concept of a ‘critical’ or sensitive period of development, after which plasticity is more restricted