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BRAIN RESEARCH

Research Report

The Lurcher mouse: Fresh insights from an old mutant

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ABSTRACT

The Lurcher mouse was first discovered in 1954 as a spontaneously occurring autosomal dominant mutation that caused the degeneration of virtually all cerebellar Purkinje cells and most olivary neurons and granule cells. More recent molecular studies revealed that Lurcher is a gain of function mutation in the δ2 glutamate receptor (GluRδ2) that converts an alanine to threonine in the highly conserved third hydrophobic segment of GluRδ2. The mutation converts the receptor into a constitutively leaky cation channel. The GluRδ2 receptor is predominantly expressed in cerebellar Purkinje cells and in the heterozygous Lurcher mutant (+/Lc). Purkinje cells die due to the mutation in the GluRδ2 receptor, while olivary neurons and granule cells degenerate due to the loss of their Purkinje cell targets. The purpose of the review is to provide highlights from 5 decades of research on the Lurcher mutant that have provided insights into the developmental mechanisms that regulate cell number during development, cerebellar pattern formation, cerebellar physiology, and the role of the cerebellum in CNS function.

1. Introduction

The Lurcher mouse (+/Lc; gene symbol, Grid2^{Lc}) is a neurological mutant characterized by a wobbly, lurching gait which is caused by the extensive postnatal degeneration of key neurons in the olivocerebellar circuit, principally, the Purkinje cells and their primary afferents, granule cells and olivary neurons. The +/Lc mutant was discovered as a spontaneous mutant in the mouse colony of the Medical Research Council Radiobiological Research Unit at Harwell, England in 1954. The first description of the mutant was published in 1960 by R.J.S. Philips (Phillips, 1960). In addition to describing the ataxic characteristics of the Lurcher mutant, Dr. Philips showed that the mutated gene was on chromosome 6 and the mutation was semi-dominant, with homozygous mutants dying around birth. Heterozygous animals are viable, and, since 1960, the +/Lc mutants have provided a fertile source for a large variety of studies aimed at understanding CNS function, from development to behavior. The identification of the gene that is mutated in Lurcher, the δ2 glutamate receptor (GluRδ2; gene

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symbol, Grid2), in 1997 (Zuo et al., 1997), has inspired a fresh round of studies of the Lurcher mutation that are providing new insights into how the CNS functions, from the molecular biology of glutamate neurotransmitter receptors to the pathways of neuronal cell death and survival. The goal of this review is to highlight the role that the Lurcher mutant has played in a wide array of anatomical, physiological, behavioral, and molecular studies of the CNS, and, hopefully, to indicate promising future research directions that depend on the Lurcher mutant.

2. Early descriptions of the mutant

Once the +/Lc mutant was identified, initial studies quickly focused on the obvious degeneration of the cerebellum as a primary site of the genetic lesion in the heterozygous +/Lc mutants. The early histological studies determined that, in the adult +/Lc mutants, the cytoarchitecture of the cerebellum was severely disrupted with the loss of virtually all Purkinje cells and the vast majority of the granule cells and olivary neurons (Fig. 1; Caddy and Biscoe, 1975; Caddy and Biscow, 1976; Wilson, 1975, 1976). Swisher and Wilson's (1977) qualitative analysis of the postnatal development of the +/Lc mutant established that cerebellar development begins normally in the +/Lc mutant, but signs of Purkinje cell abnormalities and pyknotic cells in the molecular layer are apparent by 3–4 days after birth (P3–4). Depending on the lobule, some Purkinje cells appear necrotic by P4, and there are gaps in the Purkinje cell layer by P5, suggesting that Purkinje cells have started to degenerate. The most comprehensive analysis of the +/Lc mutant was published by K.W.T. Caddy and T.J. Biscoe in 1979 in the *Philosophical Transactions of the Royal Society of London Series B* (Caddy and Biscoe, 1979). In this major developmental study, Caddy and Biscoe qualitatively and quantitatively described the process of neurodegeneration of the cerebellar Purkinje cells, granule cells, and olivary neurons in the +/Lc cerebellum. Their study showed that reductions in +/Lc Purkinje cell numbers can be detected between P8 and P10 closely followed by the death of granule cells and olivary neurons. Virtually all of the Purkinje cells have degenerated by 3 months after birth, while eventually 90% of the granule cells and 75% of the olivary neurons degenerate. There is, however, no loss of deep cerebellar neurons (or a limited loss of ~20%, see Heckroth, 1994). On the basis of Golgi staining and electron microscopy, Caddy and Biscoe showed that many +/Lc Purkinje cells have an abnormal, stunted morphology with multiple primary dendrites, although, depending on the age of the mouse, some +/Lc Purkinje cells can appear normal. Somatic spines on the +/Lc Purkinje cells persist longer that in the wild type. At the ultrastructural level, many of the +/Lc Purkinje cells that are obviously degenerating show evidence of disorganized cytoplasm with free ribosomes and spherical mitochondria that fill the dendrites.

A subsequent Golgi and ultrastructural study of Purkinje cells in young +/Lc mutants by Dumesnil-Bousez and Sotelo confirmed and extended these early findings (Dumesnil-Bousez and Sotelo, 1992). +/Lc Purkinje cell abnormalities become apparent by P8: these abnormalities include perinuclear clumps of chromatin in the nuclei, a delay in the development of the cell body and dendrites, and the formation of axonal swellings on Purkinje cell dendrites in the white matter tracts. The external granule cell layer is also smaller at P8. However, synaptogenesis between Purkinje cells and parallel fibers, climbing fibers, and basket cell axons appears to proceed normally, at least through P10. After P10, the rate of parallel fiber synaptogenesis declines compared to wild type, few climbing fibers translocate from their initial soma contacts to their peridendritic locations (see also Heckroth et al., 1990), and basket cell axons fail to completely surround the Purkinje cell bodies.

In contrast to the multiple defects in +/Lc Purkinje cells, other cerebellar interneurons, including olivary neurons, appear to have a normal ultrastructure until they degenerate (Caddy and Biscoe, 1979). The number of granule cells and olivary neurons is normal in +/Lc mutants until approximately P8, when their numbers fail to keep pace with wild-type numbers and then decline to approximately 10% and 25% of wild-type values, respectively. The number of stellate and basket cells was not quantified until recently (Zanjani et al., 2002) where it was found that the density of stellate and basket cells was the same as in the wild-type molecular layer, indicating that there must be extensive loss of molecular layer interneurons since the volume of the molecular layer is reduced in the +/Lc mutant. The number of Golgi neurons has also not been quantified, though Caddy and Biscoe (1979) note that they seem to be as numerous in the +/Lc cerebellum as in the wild type. If the density of Golgi neurons appears normal in the +/Lc mutant, this may again indicate that there is extensive loss of Golgi neurons as the volume of the granule cell layer is drastically reduced in the +/Lc mutant. The sole major cell type that appears to avoid

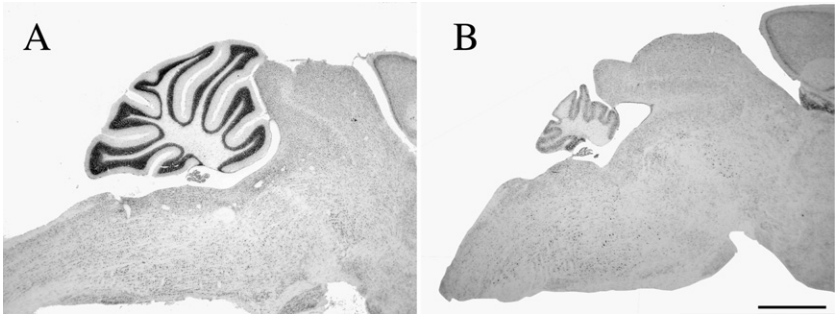

Fig. 1 – Photos of sagittal sections of the hindbrain and midbrain of adult wild-type (A) and +/Lc (B) mutant mice. Scale bar is 1 mm.