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Research Report

Dystonia and cerebellar degeneration in the *leaner* mouse mutant

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ABSTRACT

Cerebellar degeneration is traditionally associated with ataxia. Yet, there are examples of both ataxia and dystonia occurring in individuals with cerebellar degeneration. There is also substantial evidence suggesting that cerebellar dysfunction alone may cause dystonia. The types of cerebellar defects that may cause ataxia, dystonia, or both have not been delineated. In the current study, we explored the relationship between cerebellar degeneration and dystonia using the *leaner* mouse mutant. *Leaner* mice have severe dystonia that is associated with dysfunctional and degenerating cerebellar Purkinje cells. Whereas the density of Purkinje cells was not significantly reduced in 4 week-old *leaner* mice, approximately 50% of the neurons was lost by 34 weeks of age. On the other hand, the dystonia and associated functional disability became significantly less severe during this same interval. In other words, dystonia improved as Purkinje cells were lost, suggesting that dysfunctional Purkinje cells, rather than Purkinje cell loss, contribute to the dystonia. These results provide evidence that distorted cerebellar function may cause dystonia and support the concept that different types of cerebellar defects can have different functional consequences.

1. Introduction

The dystonias are a group of disorders broadly characterized by involuntary excessive muscle activity leading to abnormal twisting or repetitive movement (Albanese et al., 2013). There are many potential etiologies, both inherited and acquire (Fung et al., 2013). Traditionally, the dystonias have been attributed to dysfunction of the basal ganglia, but more recently a number of studies also have implicated the cerebellum (Neychev et al., 2011; Standaert, 2011; Sadnicka

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et al., 2012; Charlesworth and Bhatia, 2013; Filip et al., 2013; Lehericy et al., 2013; Prudente et al., 2014).

The evidence suggesting that cerebellar dysfunction may cause dystonia has raised several important questions that have yet to be addressed. For example, what types of abnormalities in the cerebellum may cause dystonia? Cerebellar lesions, such as those caused by stroke, most often result in ataxia (Caplan, 2005; Deluca et al., 2011), though sometimes they are associated with dystonia (Rumbach et al., 1995; Alarcon et al., 2001; O'Rourke et al., 2006; Zadro et al., 2008; Waln and LeDoux, 2010; Usmani et al., 2011). The majority of cerebellar degenerative syndromes are also associated with ataxia. However, in several of these, ataxia may be combined with dystonia, or the dystonia may be the presenting or dominant motor abnormality (Sethi and Jankovic, 2002; Kuoppamaki et al., 2003; Wilder-Smith et al., 2003; Hagenah et al., 2004; Le Ber et al., 2006; van Gaalen et al., 2011; Jhunjhunwala et al., 2013). The reasons that cerebellar defects may sometimes cause ataxia or dystonia are unknown, but may be related to the type of lesion.

In the current study, we explored the relationship between cerebellar degeneration and dystonia in the *leaner* mouse mutant, which carries a mutation in the *Cacan1a* gene, encoding $Ca_V2.1$ (P/Q)-type calcium channels (Doyle et al., 1997). This gene is prominently expressed in cerebellar Purkinje cells and different mutations in humans have been associated with markedly different clinical phenotypes including spinocerebellar ataxia type 6, episodic ataxia type 2, benign torticollis of infancy, focal dystonia in adults, familial hemiplegic migraine and epilepsy (Ophoff et al., 1996; Zhuchenko et al., 1997; Pujana et al., 1999; Giffin et al., 2002; Spacey et al., 2005; Roubertie et al., 2008; Cuenca-Leon et al., 2009; Hu et al., 2013). Different *Cacan1a* mutations in rodent models cause a similarly broad array of disorders, including generalized dystonia or ataxia, paroxysmal dystonia, epilepsy and migraine (Meier and MacPike, 1971; Doyle et al., 1997; van den Maagdenberg et al., 2004; Raike et al., 2005; Tokuda et al., 2007; Shirley et al., 2008). We selected the *leaner* mutant not because of its relationship to a variety of different disorders, but because it is known to have severe

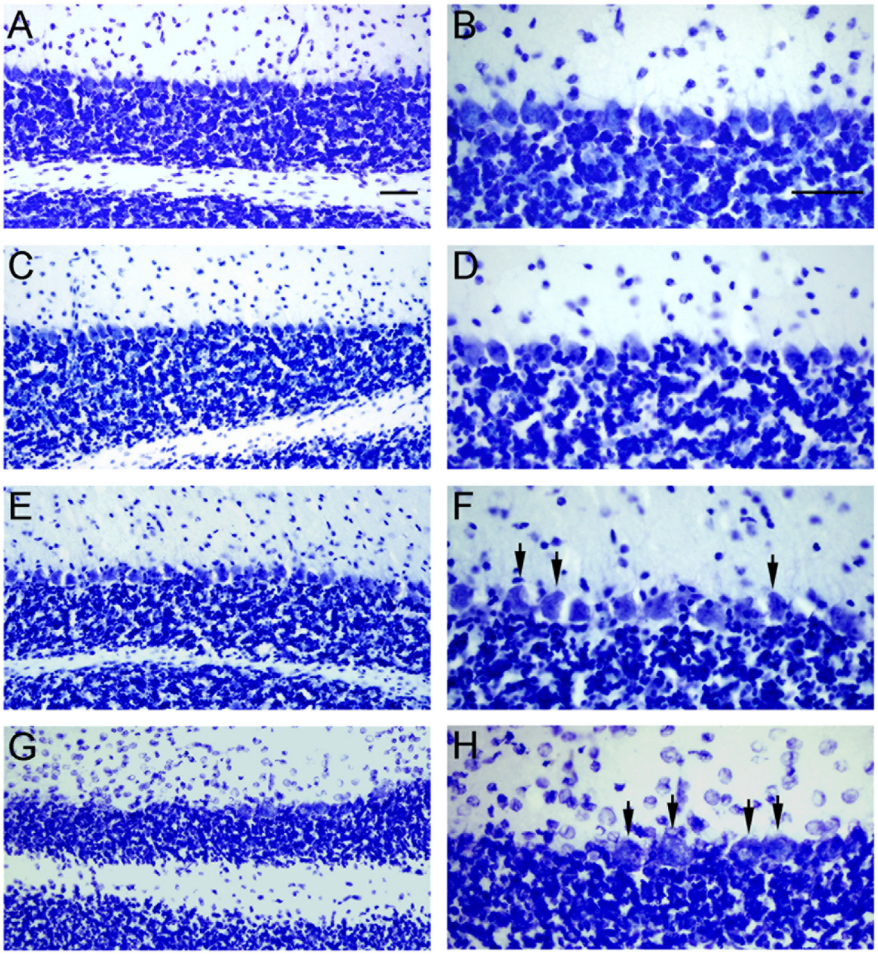

Fig. 1 – Cerebellar tissue sections from young and old control and *leaner* mice. Cerebellar sections from 4 and 32–36 week old normal and *leaner* mice were compared to assess the degeneration of Purkinje cells with age in *leaner* mice. Sections from 4 week-old normal mice (A, B) and from 4 week-old *leaner* mice (E, F) contained similar numbers of Purkinje cells, though the Purkinje cell layer within sections from 4 week-old *leaner* mice appeared disorganized and often contained misshapen Purkinje cells (F, arrows). No obvious abnormalities were observed in sections from 32–36 control mice (C, D), but sections from 32–36 *leaner* mice (G, H) contained many fewer Purkinje cells that often appeared swollen and granular (H, arrows). Scale bars = 100 μm.