Cerebellar Cortex Development in the *Weaver* Mouse

Bosch Borràs, Èlia. Bachelor's Degree in Biomedical Sciences. *Universitat Autònoma de Barcelona.*

Universitat Autònoma de Barcelona

Introduction

Weaver (*wv*) is a pleiotropic mutation in the *Girk2* gene (chromosome 16) that encodes for a K^+ channel. This leads to a loss of K^+ selectivity, allowing Na^+ and Ca^{2+} to enter cells and causing constitutive channel activation, chronic depolarization, and cell death.

Wv/wv mice present important anatomical deficits in the cerebellum, including cerebellar cortex disorganization and severe depletion of granule cells, Purkinje cells and deep cerebellar nuclei neurons, which are the neurons better studied in the *weaver* cerebellum.

The aim of this study is to propose an experimental design to better understand the development of different neuronal populations in the cerebellar cortex of this model for hereditary cerebellar ataxia.

Methods

- Search of reviews and original articles in databases such as PubMed (NCBI) and Web of Knowledge using the following keywords: cerebellar development, weaver, ataxia, cerebellar neurons, autoradiography, and immunohistochemistry
- Selection of the appropriate papers depending on relevance and date of publication
- Narrowing of the objectives
- Design of the experiments grounded in existing studies of other cerebellar neurons and existing background about the cells of study

Neurons of Study

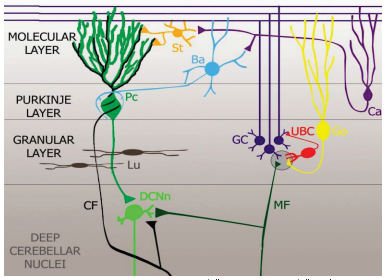


Figure 1. Schematic representation of the neurons in the cerebellar cortex and deep cerebellar nuclei and their connections. Legend can be seen on the right of the picture; the grey circle represents a cerebellar glomerulus. (Own contribution)

PC: Purkinje cell
GC: Granule cell
DCNn: Deep Cerebellar Nuclei neuron

→ Neurogenetic Timetables already studied

St: Stellate cell
Ba: Basket cell
Ca: Candelabrum cell
Lu: Lugaro cell
UBC: Unipolar Brush cell
Go: Golgi cell

→ Neurogenetic Timetables not yet known → Neuronal Populations of Study

CF: Climbing Fibres
MF: Mossy Fibres

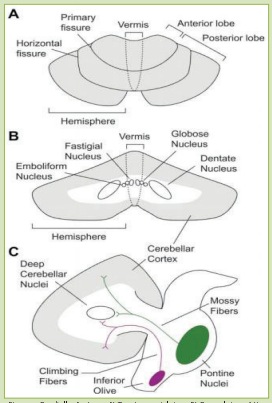
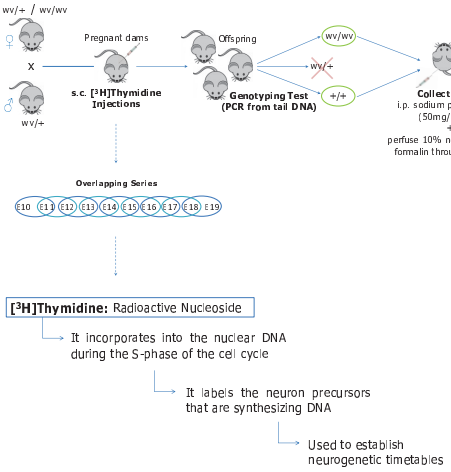


Figure 2. Cerebellar Anatomy. A) Top-down axial view. B) Coronal view of the deep cerebellar nuclei. C) Sagittal view highlighting the major afferent pathways into the cerebellum. Mossy fibres project to granule cells in the cerebellar cortex, and send collaterals to the deep cerebellar nuclei. Climbing fibres extend to Purkinje cells, and also have collateral projections to deep cerebellar nuclei. The axons of the deep cerebellar nuclei form the primary output channels away from the cerebellum, and to the brainstem and cerebral cortex. (Moulton E. A. et al, 2014)

Results: Experimental Design Proposed



Neuronal type	Primary antibodies	Evaluation
Basket/Stellate cells	anti-parvalbumin, anti-calbindin D-28K	Parvalbumin+/Calbindin−
Candelabrum cell	anti-Gly, anti-GABA, anti-GAD	Gly+/GABA+/GAD+
Golgi cell	anti-calretinin, anti-Rat-303	Rat-303+/Calretinin−
Lugaro cell	anti-calretinin, anti-Rat-303	Rat-303+/Calretinin+
Unipolar Brush cell	anti-calretinin, anti-Rat-303	Rat-303−/Calretinin+

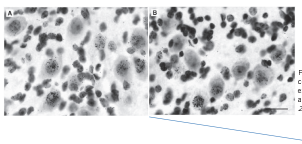


Figure 3. Audiograms of the cerebellar cortex from *wv/wv* mice exposed to [3H]thymidine on E13+4 and surviving to P90. *Scale bar 20μm.* (Marti3. et al, 2007)

Neuronal population	Injection group	% Labelled cells (mean ± SD)	% Cells originating
Basket/Stellate cells	E10-E11	(A)	(A – B)
	E11-E12	(B)	(B – C)
	E12-E13	(C)	(C – D)
	E13-E14	(D)	(D – E)
	E14-E15	(E)	(E – F)
	E15-E16	(F)	(F – G)
	E16-E17	(G)	(G – H)
	E17-E18	(H)	(H – I)
	E18-E19	(I)	
Candelabrum cells	" "	" "	" "
Golgi cells	" "	" "	" "
Lugaro cells	" "	" "	" "
Unipolar Brush cells	" "	" "	" "

NEUROGENETIC TIMETABLES → $(\%TBaSt_{E10-11}) - (\%TBaSt_{E11-12}) = \%BaStG_{E10}$

$TBaSt_{E10-11}$: Labelled Basket/Stellate cells by the E10-11 injection schedule
$TBaSt_{E11-12}$: Labelled Basket/Stellate cells by the E11-12 injection schedule
$BaStG_{E10}$: Proportion of Basket/Stellate cells generated on E10

Conclusions

- Despite recent advancements in the knowledge of cerebellar ataxia, no definitive cure is currently available for this group of disorders.
- The experimental design proposed in this study would be the first to establish the neurogenetic timetables of the neuronal populations of the *weaver* cerebellum for which these are not yet known.
- With this information, more detailed knowledge about cerebellar development in the *weaver* mouse, a good model for hereditary cerebellar ataxia, could be achieved.

References

(1) E. A. Moulton, I. Elman, L. R. Becerra, R. Z. Goldstein, and D. Borsook, "The cerebellum and addiction: insights gained from neuroimaging research.," *Addict. Biol.*, vol. 19, no. 3, pp. 317–31, May 2014.
(2) J. Martí, M. C. Santa-Cruz, S. a. Bayer, B. Ghetti, and J. P. Hervás, "Purkinje cell age-distribution in fissures and in foliar crowns: A comparative study in the weaver cerebellum," *Brain Struct. Funct.*, vol. 212, pp. 347–357, 2007.
(3) J. Martí, K. V. Wills, B. Ghetti, and S. a. Bayer, "A combined immunohistochemical and autoradiographic method to detect midbrain dopaminergic neurons and determine their time of origin," *Brain Res. Protoc.*, vol. 9, no. 3, pp. 197–205, 2002.
(4) D. Marmolino and M. Manto, "Past, present and future therapeutics for cerebellar ataxias.," *Curr. Neuropharmacol.*, vol. 8, no. 1, pp. 41–61, Mar. 2010.