Altered Purkinje cell firing contributes to disease onset in a mouse model of ARSACS

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**Abstract:**
The autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is an early onset inherited neurological disease. A major symptom of ARSACS is cerebellar ataxia characterized by progressive loss of Purkinje cells in the anterior vermis of the cerebellum. ARSACS is caused by one of many different mutations in the SACS gene encoding the protein sacsin. A Sacs knockout (Sacs KO) mouse has recently been generated that develops motor deficits and neuronal abnormalities resembling those of ARSACS patients. Sacs KO mice first show cerebellar-related motor abnormalities at postnatal day 40 (P40), before Purkinje cell loss is detected, suggesting that the pathophysiology of disease onset arises from functional changes in Purkinje cells and/or other cells in the cerebellar microcircuit.

To investigate functional changes in Purkinje cells in Sacs KO mice, we recorded spontaneous pacemaker firing activity from Purkinje cells in cerebellar slices in Sacs KO and wildtype (WT) mice. At the age of the first documented motor deficit (P40), we observed a significant decrease in the average firing rate of Purkinje cells from the anterior lobule 3 in Sacs KO mice (WT: 78.2 ± 6.6 Hz, n = 38 cells; Sacs KO: 58.5 Hz ± 3.7, n = 34 cells; p < 0.005), while no significant difference was observed in posterior lobule 9 firing properties (p > 0.05). In contrast to results from several other ataxias, no change in the pacemaker precision of firing was observed in Sacs KO mice (coefficient of variation; WT: 0.24 ± 0.05, n = 24 cells; Sacs KO: 0.27 ± 0.07, n = 34 cells; p > 0.05).

We wondered if changes in synaptic properties of the cerebellar microcircuit were involved in ARSACS, and looked for changes in the excitatory input onto Purkinje cells in Sacs KO mice. We found a significant increase in AMPA mediated miniature excitatory current (mEPSC) amplitude as well as a reduction in the mEPSC frequency in Sacs KO mice (p < 0.05). Purkinje cells make synapses onto large neurons in the Deep Cerebellar Nuclei (DCN). We found no alterations in the density of large DCN neurons (WT: 18 ± 1 cells/100μm³; Sacs KO: 17 ± 3 cells/100μm³; p > 0.05).

We conclude that the pathophysiology underlying disease onset in Sacs KO mice is predominantly arising from changes in Purkinje cell functionality.
Presentation Preference (Complete): Poster Only
Linking Group (Complete): None selected
Nanosymposium Information (Complete):
Theme and Topic (Complete): C.04.d. Ataxias ; D.14.b. Cerebellum: Cortex and nuclei
Keyword (Complete): CEREBELLUM ; ATAXIA ; NEURODEGENERATION
Support (Complete):
  Support: Yes
  Grant/Other Support: Ataxia Charlevoix-Saguenay Foundation
  Grant/Other Support: Canadian Institute of Health Research
  Grant/Other Support: Canadian Foundation for Innovation

Special Requests (Complete):
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