

influences on functional, physiological and anatomical parameters were assessed. We found significant hypertension, blockage of brain microvessels (2-photon microscopy) and white matter atrophy in HFSS diet animals. As in Experiment 1, profound, specific set-shifting executive dysfunction was noted following both small MD infarcts (0.332 mm³) and the HFSS diet. In summary, these data describe a middle-aged animal model of VCI that includes clinically-relevant metabolic disturbances and small vessel disease and as such may be helpful in developing new cognitive therapies.

ABSTRACT A12

Clinical and neuropathological features of ALS/FTD with *TIA1* mutations

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Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) represent a disease continuum with common genetic causes and molecular pathology. We recently identified mutations in the T-cell restricted intracellular antigen-1 (*TIA1*) protein as a cause of ALS +/- FTD. *TIA1* is an RNA-binding protein containing a low complexity domain (LCD) that promotes the assembly of membrane-less organelles, such as stress granules (SG). Whole exome sequencing of two family members with fALS/FTD revealed a novel missense mutation in the *TIA1* LCD (P362L). Subsequent screening identified five more *TIA1* mutations in six additional ALS patients, but none in controls. All mutation carriers presented with weakness, behavioral abnormalities or language impairments and had a final diagnosis of ALS +/- FTD. Autopsy on five *TIA1* mutation carriers showed widespread neurodegeneration with TDP-43 pathology. Round eosinophilic inclusions in lower motor neurons were a consistent feature. Cellular assays revealed abnormal SG dynamics in the presence of *TIA1* mutations. In summary, missense mutations in the LCD of *TIA1* are a newly recognized cause of ALS/FTD with TDP-43 pathology and strengthen the role of RNA metabolism in the pathogenesis in this disease.

ABSTRACT A13

The Calgary Brain Bank

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With the financial assistance from two donors, we have established a neurodegenerative disease brain bank at the University of Calgary. At autopsy, tissues from anatomically specific regions are frozen in liquid nitrogen vapour and stored in small, bar-coded cryovials. Cases include patients with dementia, movement disorders, demyelinating diseases, and normal

controls. We prepare additional FFPE blocks for diagnosis or banking. Sampling includes all major areas of cortex and most subcortical structures. All brains, including "normal" controls, are characterized with a basic set of stains and major classification schemata are used for Alzheimer and Lewy body diseases. These tissues are available to investigators with IRB-approved research on human tissues

Control tissue is important in the study of age-associated neurodegeneration. We preserve tissues from areas of brain that either are severely or minimally affected by neurodegeneration (e.g. in Alzheimer disease, Brodmann areas 9 and 17, respectively). In our "normal" aging cohort, which includes patients with no described neurodegenerative diseases, we find frequent evidence of low-stage Alzheimer or Lewy body related pathological changes. We also find relatively frequent small vessel disease, which in part relates to our preferential selection of patient's who died suddenly.

In preliminary studies, we have examined amyloid plaque structure with confocal microscopy using beta-sheet sensitive dyes and have studied the distribution of different chaperones in normal brain.

ABSTRACT A14

The role of ATP and P2X purinoreceptor 7 in the pathogenesis of cerebral tau

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The tauopathies are a group of neurodegenerative diseases characterized by abnormal deposition of hyperphosphorylated-tau. The pathogenesis of these changes remains uncertain. In chronic traumatic encephalopathy, tauopathy is hypothesized to occur after repeated mild traumatic brain injury (TBI). Post-traumatic extracellular ATP release and signalling via the P2X purinoreceptor 7 (P2RX7) has been shown to be important in mediating pathological changes in TBI. We hypothesized that ATP-P2RX7 is involved in the development of tauopathy.

We injected ATP analogue bzATP or vehicle intraventricularly into C57BL/6 mice, pre-treated with either intraperitoneal P2RX7 antagonist Brilliant Blue G (BBG) or vehicle. At 2 weeks and 3 months, behavioural change was assessed with the tail suspension test, accelerating rotarod, and fear conditioning; mice were then sacrificed for immunohistochemistry and western blot.

We observed increased immobile time in the tail suspension test for mice treated with bzATP at 3 months. Similarly, for rotarod, mice treated with bzATP showed poorer performance at 3 months. These effects were diminished by BBG pre-treatment. Fear conditioning, however, did not demonstrate a significant difference between groups. Immunohistochemical staining for GFAP showed increased intensity at both 2 weeks and 3 months for bzATP-treated mice compared to those pre-treated with BBG. Levels of phosphorylated tau (AT8) were increased in bzATP-treated mice compared to controls.

In summary, ATP-P2RX7-mediated mechanisms may play a role in the development of behavioural deficits and tauopathy.