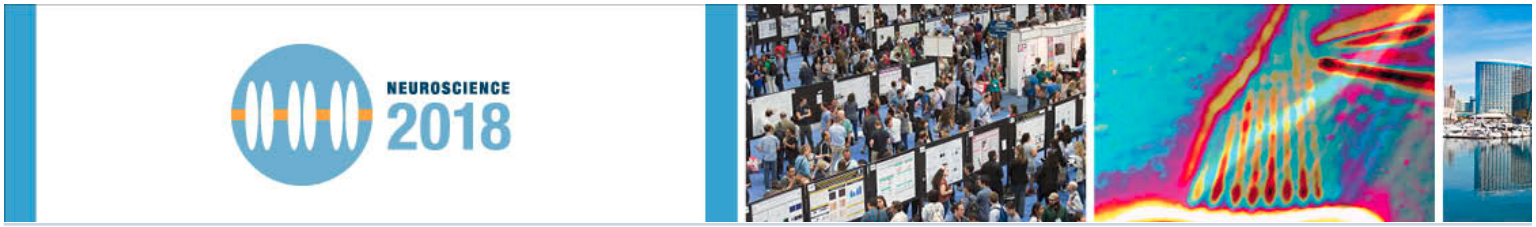

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SATURDAY, NOV. 3, 2018

☆ **Session 053** Neurotoxicity, Inflammation, and Neuroprotection: Preclinical Studies — 1:00 PM - 5:00 PM

SDCC Halls B-H

☆ **Presentation 053.08 / Y6** Secreted amyloid precursor protein alpha activates nf kappa b and increases sod2 expression in cultured peripheral neurons — 4:00 PM - 5:00 PM

*B. AULSTON, G. GLAZNER;
St. Boniface Res. Ctr., Winnipeg, MB, Canada

Abstract
Sensory neuropathy is characterized by peripheral nerve degeneration and is a common complication in patients with diabetes. We have found previously that diabetes may contribute to the development of peripheral neuropathy by reducing the activity of the transcription factor NFκB, and in turn, decreasing the expression of neuroprotective genes such as MnSOD (SOD2), in DRG neurons. MnSOD is a mitochondrial scavenger of ROS and it's hypothesized that insufficient MnSOD antioxidant capacity is a key pathological feature of diabetes and neurodegenerative disorders. Previous reports demonstrate that insulin treatment can reverse MnSOD deficits in diabetic DRG neurons and that MnSOD protects against diabetic peripheral neuropathy. In addition to insulin, the amyloid precursor protein (APP) cleavage product secreted amyloid precursor protein alpha (sAPPα) can induce NFκB activity and activate insulin signaling pathways and therefore may offer an alternative strategy to increase MnSOD expression and reduce oxidative stress that is associated with diabetic neuropathy. With this in mind, we examined the effect of sAPPα on NFκB and MnSOD in DRG neurons cultured from healthy and diabetic rats. We found that sAPPα increased neurite outgrowth in both diabetic and wild-type (Wt) DRG neurons and that DRG neurons had a greater response to sAPPa treatment. Furthermore, we determined that sAPPα increased NFkB activity in diabetic DRG neurons and increased MnSOD expression. In total, these findings suggest that activation of the NFκB-MnSOD axis may underlie the protective effects of sAPPα on DRG neurons. Moreover, our results indicate that the development of sAPPα based therapies as a treatment for diabetic-induced neuropathy is warranted.

SUNDAY, NOV. 4, 2018

☆ **Session 206** Alzheimer's Disease and Other Dementias: Frontotemporal Lobar Degeneration: Vascular Disease — 1:00 PM - 5:00 PM

SDCC Halls B-H

☆ **Presentation 206.17 / I12** Secreted amyloid precursor protein alpha as a therapeutic for diabetic encephalopathy — 1:00 PM - 2:00 PM

*Y. HUANG[1,2], B. D. AULSTON[2], G. L. ODERO[2], G. W. GLAZNER[2,1];
[1]Pharmacol. and Therapeut., Univ. of Manitoba, Winnipeg, MB, Canada; [2]Div. of Neurodegenerative Disorders, Albrechtsen Res. Ctr., Winnipeg, MB, Canada

Abstract
Secreted amyloid precursor protein alpha (sAPPα) is produced by the cleavage of full length amyloid precursor protein (APP). A designated sAPPα receptor has yet to be discovered, but there is evidence that sAPPα protein is an insulin receptor agonist which can modulate the neuronal AKT-mediated neurotrophic insulin pathway. When phosphorylated, AKT protects the call by inhibiting GSK3 kinase and phosphorylation of tau. Hyperphosphorylation of tau causes aggregation, creating neurofibrillary tangles that predisposes the brain to neurodegeneration. The ability for sAPPα to be effective in the absence of insulin (type 1 diabetes) was tested by comparing diabetic transgenic sAPPα overexpressing mice to diabetic wildtype mice. Mice were rendered diabetic via injection of streptozotocin to reduce the beta cells in the pancreas. After 16 weeks post injection, cortical tissue was collected and western blots were completed to observe levels of AKT, GSK3 and pTau. Decreased levels of pAKT, GSK3, and pTau were detected in the transgenic diabetic in comparison to wildtype diabetic animals. This indicates that sAPPα can ameliorate the effects of insulin loss in the brain, and is a potential therapeutic for diseases that involve tau hyperphosphorylation.

MONDAY, NOV. 5, 2018

☆ Session 318 Brain Blood Flow

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 318.25 / VV21 Endothelial NMDA receptors are critical mediators of neurovascular coupling in awake behaving mice

8:00 AM - 9:00 AM

*A. D. HOGAN-CANN[1,2], P. LU[1,2], C. ANDERSON[1,2];
[1]Pharmacol. & Therapeut., Univ. of Manitoba, Winnipeg, MB, Canada; [2]Neurosci. Res. Program, Kleysen Inst. for Advanced Med., Winnipeg, MB, Canada

Abstract
Functional hyperemia (FH) ensures that active brain regions receive proportional delivery of blood flow. FH requires both local effects and coordinated upstream conduction of vasodilatory signals in an endothelium-dependent manner. There is strong literature consensus that this local response is mediated by neuronal N-methyl-D-aspartate (NMDA) receptors and nitric oxide produced by neuronal NO synthase (nNOS), or by inducing release of vasodilatory gliotransmitters from perisynaptic astrocytes with perivascular endfeet processes. However, neither of these mechanisms is endothelium-dependent, leaving neuro-endothelial coupling as a key conceptual deficit in understanding FH. We have observed that isolated middle cerebral artery segments free of neurons dilate in response to NMDA receptor agonists in a manner that requires functional endothelium and endothelial NOS. We also found that two-photon photolysis of caged astrocyte Ca^{2+} in mouse cortical slices led to NMDA receptor and eNOS-dependent vasodilation. The current study was designed to test the possibility that endothelial NMDA receptors participate in neurovascular coupling by measuring the hemodynamic responses in awake, head-fixed mice following sensory stimulation. To distinguish between neuronal and endothelial NMDA receptors we created conditional endothelial NMDA receptor loss of function mice that were characterized by greater than 50% loss of endothelial GluN1 (eGluN1) expression. Laser-Doppler flowmetry revealed that targeted whisker stimulation increased regional cerebral blood flow (CBF) in the somatosensory cortex of wild-type mice. This hyperemic response was dramatically impaired in eGluN1 deficient mice. Using two-photon microscopy, we measured vascular lumen diameter and red blood cell (RBC) velocity to better understand the dynamics of neurovascular coupling at the single vessel level in awake mice. In eGluN1 knockdown mice, the increase in lumen diameter and RBC velocity following whisker simulation was dramatically impaired relative to littermate controls. Spatial and temporal mapping of the vascular responses revealed signals that originated at cortical microvessels and were propagated throughout the vascular network to reach upstream pial arteries. Interestingly, pial vascular responses were unaffected by eGluN1 knockdown. These results suggest that eGluN1 loss of function reduces local vasodilatory effects while the upstream propagation of these signals is spared. Our results identify a novel mechanism of neuro-endothelial coupling by showing that endothelial NMDA receptors mediate activity-dependent, neurovascular signaling.

☆ Presentation 318.27 / WW1 Cerebrovascular morphology and mechanics in rodent models of hypertension and heart failure

10:00 AM - 11:00 AM

*C. ACOSTA, C. M. ANDERSON, H. ANDERSON;
Univ. of Manitoba, Winnipeg, MB, Canada

Abstract
There is growing evidence that heart failure (HF) is a risk factor for dementia and Alzheimer's disease (AD). In fact, HF patients often

exhibit cognitive deficits, although the prevalence of AD in HF is unknown. Hypertension often precedes HF and in itself, is an independent risk factor for dementia. This may be related to the arterial wall remodeling, stiffening, and dysfunction that, by reducing lumen diameter, may compromise blood flow. Indeed, cerebrovascular remodeling leads to inadequate brain perfusion, and arterial stiffening is associated with dementia. We investigated cerebrovascular remodeling and stiffening as putative underlying mechanisms. Morphological and mechanical changes were characterized in middle cerebral arteries (MCAs) and penetrating arterioles (PAs) using genetic animal models of hypertension alone (spontaneously hypertensive rat, SHR) and hypertension associated with risk for HF (spontaneously hypertensive heart failure rat, SHHF). Vascular properties of isolated MCAs and PAs from Wistar Kyoto (WKY) and SHR, as well as, Sprague-Dawley (SD) and SHHF rats were measured by pressure myography. SHHF MCAs exhibited eutrophic remodeling, as evidenced by increased media-lumen ratio (15.9±2 vs. SD 8.9±0.5, ***p<0.05***) and unchanged media cross-sectional area (mCSA). An increasing trend in the latter, however, resulted in a growth index of 44%, suggesting hypertrophic growth was in process. SHHF MCAs also exhibited mechanical changes in terms of stiffening and reduced compliance ***(***vs. SD, ***p<0.01)***. In contrast, smaller, downstream PAs in SHHF exhibited solely eutrophic remodeling (increased media-lumen ratio (***p<0.01***) in the absence of any change (significant or trend) in mCSA. SHHF PAs experienced less arteriolar wall stress (0.003±0.0001 vs. SD 0.004±0.0001, ***p<0.01***) and were less compliant (13.1±0.8 vs. SD 9.3±0.5, ***p<0.01***). SHHF PAs were significantly stiffer (0.07±0.01 vs. SD 0.04±0.002***, p<0.01***) due to greater wall component stiffness (23.9±4 vs. SD 10±0.6, ***p<0.01***). Similar to SHHF, SHR PAs exhibited eutrophic remodeling (***p<0.01***) and were exposed to reduced stress on their arteriolar walls (0.0028±0.0001 vs. WKY 0.004±0.0001, ***p<0.01***). However, in contrast to SHHF, SHR PAs were significantly more compliant (8.2±0.1 vs. WKY 11.2±0.09, ***p<0.01***), less stiff (0.03±0.002 vs. WKY 0.04±0.002, ***p<0.01***), and had unchanged wall component stiffness. This study identified eutrophic remodeling in both SHHF and SHR PAs, as well as, changes in mechanical properties that may be protective against HF and HF-induced dementia in SHR but are absent in SHHF.

☆ Session 367 Axon Growth and Guidance

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 367.08 / B19 Early trigeminal ganglion afferents enter the cerebellum before the purkinje cells are born and target the nuclear transitory zone

4:00 PM - 5:00 PM

*H. MARZBAN[1], M. RAHIMI-BALAEI[2], R. HAWKES[3];
[1]Dept. of Human Anat. and Cell Sci., [2]Human Anat. and Cell Sci., Univ. of Manitoba, Winnipeg, MB, Canada; [3]Cell Biol. and Anat., Univ. of Calgary, Calgary, AB, Canada

Abstract
In the standard model for the development of climbing and mossy afferent pathways to the cerebellum the ingrowing axons target the embryonic Purkinje cell somata (around embryonic ages (E)13-E16 in mice). In this report we describe a novel earlier stage in afferent development. Immunostaining for a neurofilament-associated antigen (NAA) reveals the early axon distributions with remarkable clarity. By using a combination of DiI axon tract tracing, analysis of ***neurogenin1*** null mice, which do not develop trigeminal ganglia, and mouse embryos maintained ***in vitro***, we show that the first axons to innervate the cerebellar primordium as early as E9 are direct projections from the trigeminal ganglia. Therefore, early trigeminal projections are ***in situ*** before the Purkinje cells are born. Double immunostaining for NAA and markers of the different domains in the cerebellar primordium reveal that afferents first target the nuclear transitory zone (E9-E10), and only later (E10-E11) are axons, either collateral projections from the trigeminal ganglia or a new afferent source (e.g., vestibular ganglia), seen in the Purkinje cell plate.

☆ Session 412 Appetitive and Incentive Learning and Memory I

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 412.12 / ZZ6 CRF neurons in the paraventricular thalamus reduce food-seeking behavior

4:00 PM - 5:00 PM

*A. B. TERZIAN[1,2], D. S. ENGELKE[2], M. NAIM-RASHEED[2], S. LI[3], J. J. O'MALLEY[2], R. DASGUPTA[2], J. A. FERNANDEZ-LEON[2], N. J. JUSTICE[4], M. BEIERLEIN[2], G. J. KIROAC[3], F. H. DO-MONTE[2];
[1]Pharmacol., Univ. of São Paulo, Ribeirão Preto, Brazil; [2]Neurobio. and Anat., The Univ. of Texas Hlth. Sci. Ctr., Houston, TX; [3]Dept. of Oral Biol., Univ. of Manitoba, Winnipeg, MB, Canada; [4]Metabolic and Degenerative Dis., Univ. of Texas, Houston, Houston, TX

Abstract
The paraventricular nucleus of the thalamus (PVT) regulates behavioral responses under emotionally arousing conditions. Photoactivation of anterior PVT (aPVT) neurons abolishes sucrose seeking and induces aversive behaviors in rodents. However, the specific aPVT neuronal subpopulation regulating these functions remains unknown. The stress neuropeptide corticotropin-

releasing factor (CRF) has been shown to reduce food intake and induce anxiety-like behavior in different species. Interestingly, a recent neuroanatomical study demonstrated that CRF neurons are present in the aPVT, but their physiological functions have never been explored. To assess the role of aPVT-CRF neurons during sucrose seeking, adult male Long-Evans rats were infused with a mixture of viral vectors (AAV-CRF-Cre and AAV-ChR2-DIO-eYFP) to express channelrhodopsin in aPVT-CRF neurons. Animals were trained in a reward conditioning task, where each bar press during a 30s cue tone delivered a sugar pellet in a nearby dish. High-frequency photoactivation of aPVT CRF neurons (20 Hz, 5ms pulse width, 10 mW) during the cue tone reduced bar presses when compared to the eYFP-Control group (aPVT-CRF-ChR2, presses/min: Laser OFF: 14.5±1.4, Laser ON: 4.2±1.1; eYFP-Control, presses/min: Laser OFF: 17.5±1.1, Laser ON: 18.8±1.2, $p<0.05$). In contrast, 5Hz low-frequency photoactivation of aPVT-CRF neurons had no effect (aPVT-CRF-ChR2, presses/min: Laser OFF: 17.2±0.9, Laser ON: 14.88±1.6, $p=0.20$). Photoactivation of aPVT-CRF neurons also reduced the time spent on the side of the chamber paired with 20Hz laser stimulation in a real-time place preference task, indicating that stimulation of aPVT-CRF neurons is aversive (Laser OFF side: 80.7%, Laser ON side: 19.2%, $p<0.05$). Neuroanatomical investigation of aPVT-CRF efferents revealed dense projections to the nucleus accumbens shell (NAc-shell); moderate projections to the nucleus accumbens core, lateral region of the bed nucleus of the stria terminalis, lateral subnuclei of the central nucleus of the amygdala and suprachiasmatic nucleus; and relatively weak projections to the infralimbic/prelimbic cortex, basolateral nucleus of the amygdala, and medial regions of the hypothalamus. Slice recordings from NAc-shell neurons demonstrated that photoactivation of aPVT-CRF fibers in the NAc-shell elicits large excitatory postsynaptic responses, which are blocked by AMPA and NMDA receptor antagonists. Our results demonstrate the existence of a defined glutamatergic-CRF-expressing subpopulation of neurons in aPVT that is sufficient to mediate anorexigenic and aversive effects in rats.

☆ Session 425 Learning and Memory: Molecular Mechanisms

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 425.20 / III62 Secreted amyloid precursor protein alpha overexpressing neural stem cells increase cognition in healthy mice

4:00 PM - 5:00 PM

*G. W. GLAZNER[1], B. AULSTON[1], G. L. ODERO[2];
[1]Div. Neurodegen Disorders, Winnipeg, MB, Canada; [2]St. Boniface, Winnipeg, MB, Canada

Abstract
Secreted amyloid precursor protein alpha (sAPPα) is a neurotrophic factor that plays a pivotal role in learning and memory acquisition. Numerous studies demonstrate that sAPPα administration in the brain can enhance cognition in multiple species of animals and decreased sAPPα levels are hypothesized to contribute to cognitive impairment associated with Alzheimer's disease. Here, we tested the hypothesis that sAPPα overexpressing neural stem cells (sAPPα-NSCs) could improve cognition in healthy in mice. sAPPα-NSCs and wild-type NSCs (Wt-NSCs) were engrafted into the hippocampi of 7-month old SAMR1 mice and cognition evaluated 6 weeks later using the Morris water maze (MWM). Both types of NSCs survived implantation and differentiated primarily into astrocytes. Strikingly, sAPPα-NSC injected mice performed better in both the acquisition trials and in the probe trial compared to Wt-NSC injected mice and artificial cerebrospinal fluid (ACSF) treated controls. These datum demonstrate that NSCs can be utilized to improve cognition via clinically available methods and warrant additional studies examining the therapeutic potential of sAPPα-NSCs

TUESDAY, NOV. 6, 2018

☆ Session 600 Subcortical Neurocircuitry in Motivated Behaviors

1:00 PM - 5:00 PM

SDCC Halls B-H

☆ Presentation 600.25 / FFF15 Chemogenetic inhibition of neurons in the paraventricular thalamus that project to the nucleus accumbens has no effect on the expression of morphine conditional place preference

1:00 PM - 2:00 PM

*X. DONG[1], S. LI[1], Y. LI[2,3], G. J. KIROUAC[1,4];
[1]Dept. of Oral Biology, Col. of Dent., Univ. of Manitoba, Winnipeg, MB, Canada; [2]Key Lab. of Mental Health, Inst. of Psychology, Chinese Acad. of Sci., Beijing, China; [3]Dept. of Psychology, Univ. of Chinese Acad. of Sci., Beijing, China; [4]Dept. of Psychiatry, Col. of Med., Winnipeg, MB, Canada

Abstract
The paraventricular nucleus of the thalamus (PVT) is anatomically positioned to mediate addiction behaviors because it projects to multiple brain areas involved in appetitive motivation and drug-seeking. Indeed, experimental evidence shows that the PVT

contributes to cocaine- and alcohol-seeking and that a projection from the PVT to the nucleus accumbens (NAc) may be involved in cocaine-seeking. In the present study, we examined the role of PVT-NAc projecting neurons in the expression of morphine conditioned place preference (CPP) in mice. We expressed Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) in the form of the inhibitory hM4Di in PVT neurons that project to the NAc using an intersectional dual-virus approach. This approach involved injections of AAVrg-Syn1-EBFP-Cre bilaterally in NAc and injections of the Cre-dependent AAV8-hSyn-DIO-hM4Di-mCherry or AAV8-hSyn-DIO-mCherry in the PVT. Following a recovery of 2-3 weeks, mice were trained using an unbiased CPP task in which mice received either morphine (10 mg/kg) or saline immediately before a 30-min training session. After four rounds of pairing, mice showed preference to the morphine paired side and clozapine (0.1 mg/kg, i.p.) had no effect on morphine CPP expression in mice expressing hM4Di. In a separate experiment, mice expressing hM4Di that were treated with clozapine showed a lower level of anxiety-like behavior in an open field compared to mice expressing hM4Di treated with saline or in mice expressing mCherry alone treated with clozapine. The number of PVT neurons with both mCherry and c-Fos was reduced specifically in hM4Di-expressing mice treated with clozapine validating that clozapine induced inhibition of neural activity specifically in hM4Di-expressing neurons. In summary, our results do not support a role of the PVT-NAc pathway in the expression of morphine CPP. This study also points to a potential role of the PVT-NAc projection in anxiety-like behavior.

WEDNESDAY, NOV. 7, 2018

☆ Session 639 Genes and Molecules Implicated in Autism Spectrum Disorders

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 639.02 / B30 Investigating the DNA methylation signature of the brain in Rett syndrome patients

9:00 AM - 10:00 AM

*M. RASTEGAR[1], D. KROFT[2], K. SHEIKHOLESLAMI[4], S. AMIRI[2], V. SIU[5], T. PEMBERTON[2], M. DEL BIGIO[3];
[1]Dept. of Biochem. and Med. Genet., [2]Biochem. and Med. Genet., [3]Pathology, Univ. of Manitoba, Winnipeg, MB, Canada; [4]Med., Univ. of Toronto, Toronto, ON, Canada; [5]Biochem., Western Univ., London, ON, Canada

Abstract
Rett Syndrome (RTT) is an X-linked progressive neurodevelopmental disorder that is caused by ***MECP2*** gene mutations. RTT is one of the leading causes of mental disability in young females and has no cure or effective treatment. Individuals with RTT develop normally during their first 6-18 months of life, but then start to exhibit symptoms that include developmental regression, mental disability, seizers, speech problems, anxiety, and autistic characteristics. We have previously shown the expression of MeCP2 isoforms E1 and E2 to vary temporally and regionally during brain development and in the adult mouse brain. Moreover, we found that MeCP2E1 and E2 are differentially controlled by DNA methylation and that specific types of DNA methylation regulate MeCP2 homeostasis. Thus, genome-wide patterns in DNA methylation might be perturbed to varying extents in different regions of RTT brains. Here, we explore genome-wide DNA methylation patterns in human post-mortem RTT brains using genomic DNA extracted from the cortex, hippocampus, amygdala, and cerebellum of RTT patients with confirmed ***MECP2*** gene mutations and age-/sex-matched controls. Global DNA methylation patterns were determined using Illumina's Infinium MethylationEPIC BeadChip, while global levels of different types of DNA methylation were studied by dot blot analysis. Comparative analyses of global 5mC and 5hmC as well as MethylationEPIC data in RTT patients and controls identified clear differences in the methylation patterns of specific gene promoter regions across different brain regions. Additional permutation-based significance tests identified marginally significant ($p < 0.10$) differentially methylated regions between RTT patients and controls in cortex, amygdala, and cerebellum. Our results support existence of a distinctive DNA methylation signature in the human RTT brain, providing important new insights into how molecular abnormalities at the cellular levels may lead to compromised brain function in RTT patients.
Control brain tissues and some RTT brain regions were obtained through NIH NeuroBioBank Program (neurobiobank.nih.gov). Additional RTT brains were donated to the Rastegar lab by patient family members with proper consent for research. Research with human brain tissues was reviewed and approved by the University of Manitoba Bannatyne Campus research ethics board.

☆ Session 666 Peripheral Mechanisms of Neuropathic Pain

8:00 AM - 12:00 PM

SDCC Halls B-H

☆ Presentation 666.23 / EE7 Over-expression of secreted amyloid precursor protein alpha ameliorates pathological hallmarks of type 1 diabetes

10:00 AM - 11:00 AM

*G. L. ODERO[1], B. D. AULSTON[2,3], D. R. SMITH[2], G. W. GLAZNER[2,3];
[1]Pharmacol. & Therapeut., [2]Div. of Neurodegenerative Disorders, Albrechtsen Res. Ctr., Winnipeg, MB, Canada; [3]Pharmacol. & Therapeut., Univ. of Manitoba, Winnipeg, MB, Canada

Abstract
Secreted amyloid precursor protein alpha (sAPPa) has been shown to confer beneficial properties in central nervous system neurons such as increasing neurite outgrowth, enhancing long-term potentiation and acting in a neuroprotective capacity. However, relatively little is known about the function of sAPPa in the peripheral nervous system, specifically, in the context of diabetes. To study its function, we used transgenic mice that over-expressed sAPPa. Expression of the transgene was detected in whole DRG and sciatic nerve as determined by reverse transcript-polymerase chain reaction (RT-PCR). Immunohistochemistry (IHC) in whole dorsal root ganglia (DRG) detected increased expression of APP protein most dramatically in the satellite glial cells. IHC also indicated increased expression of APP protein in sciatic nerve, presumably in Schwann cells. In this study, wild type and transgenic sAPPa over-expressing mice were rendered type 1 diabetic by injection of streptozotocin. After 4 months of uncontrolled diabetes, thermal testing revealed retention of thermal sensation in the transgenic sAPPa mice relative to their wild type controls. Furthermore, histological quantitation of intra-epidermal nerve fibers showed a greater density of nerve fibers in the transgenic sAPPa mice relative to their controls. We also report that demyelination of nerve fibers associated with type 1 diabetes was decreased in the diabetic transgenic sAPPa mice relative to their diabetic controls. Hematoxylin and eosin staining indicated no differences in neuronal morphology or distribution of neuronal cell sizes between the wild type and transgnic mice, nor did it indicate increased number of satellite glial cells/DRG neuron. Collectively, our data suggests that sAPPa may mediate pathways in the development of key neuropathological hallmarks of type 1 diabetes and may represent a novel target for future therapeutic interventions. This data also suggest that the effects observed may be glial-derived.