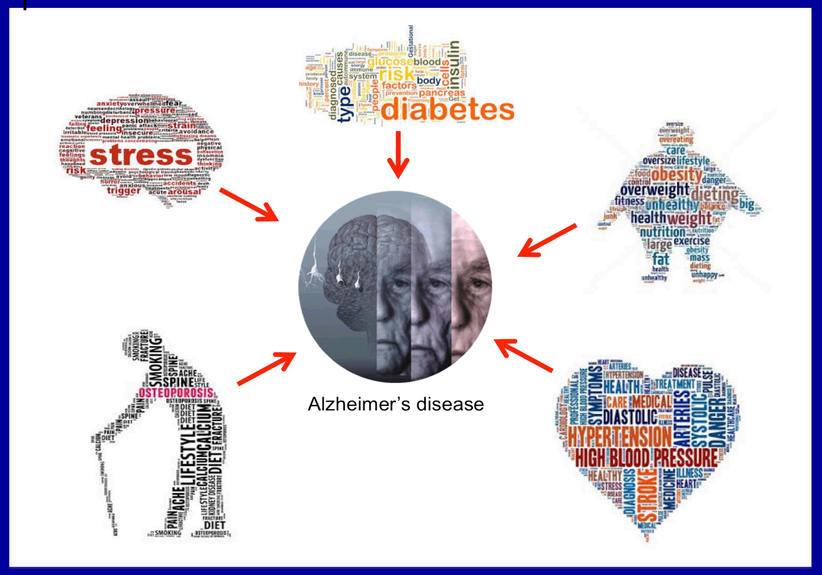
Impact of comorbid conditions in Alzheimer's disease

LaFerla Lab
Department of Neurobiology and Behavior
Institute for Memory Impairments and Neurological Disorders, University of California, Irvine (UCI MIND)

Comorbid conditions and AD

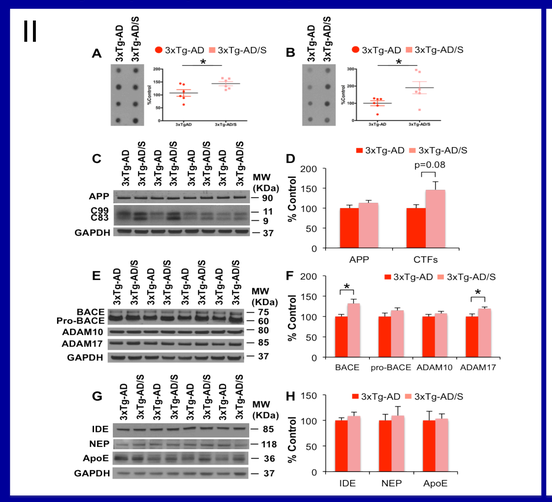
Alzheimer's disease (AD) is an incurable neurodegenerative disease that mainly affects the elderly and causes progressive deficits in memory, language, and other cognitive abilities as well as mood and personality. AD is the most common form of dementia, and is the sixth leading cause of death in the US. From a public health perspective, AD imposes a severe financial and social burden that is expected to grow in the ensuing decades. Alzheimer's Disease International (ADI) estimates that AD affects 5.4 million Americans and 35.6 million people worldwide, a number expected to double in the next 20 years. As the number of individuals with AD increases exponentially each year, the need for efficacious therapeutics is becoming more urgent. The etiology underlying sporadic AD, which represents more than 98% of AD cases, is complex and multi-factorial. Additionally, elderly individuals with AD suffer from a variety of co-morbidities, including diabetes mellitus (DM), stroke (ischemia), stress, seizures, osteoporosis, cancer, and renal disease. The molecular interactions between co-morbid disorders and Alzheimer's is of critical significance but, to date, has largely remained an unexplored area of investigation. My laboratory has a high interest in determining the impact of two of the most prominent comorbid conditions (stress and diabetes) in AD.



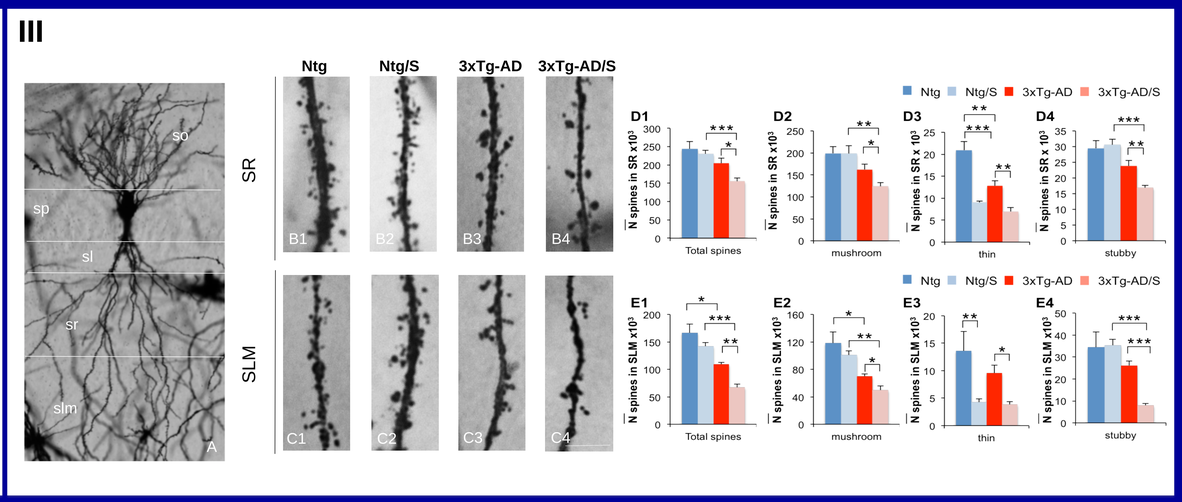
I. Comorbidities and Alzheimer's disease. Schematic representation of the most common comorbid conditions affecting elderly individuals with Alzheimer's disease.

Short modern-life like stress exacerbates amyloid pathology and synaptic loss

Epidemiological studies reveal that adverse lifestyle factors, including stress, play a key role in modulating AD progression. Here, we investigate the implications of modern-life stressful experience on the onset and progression of AD pathogenesis and synaptic plasticity.



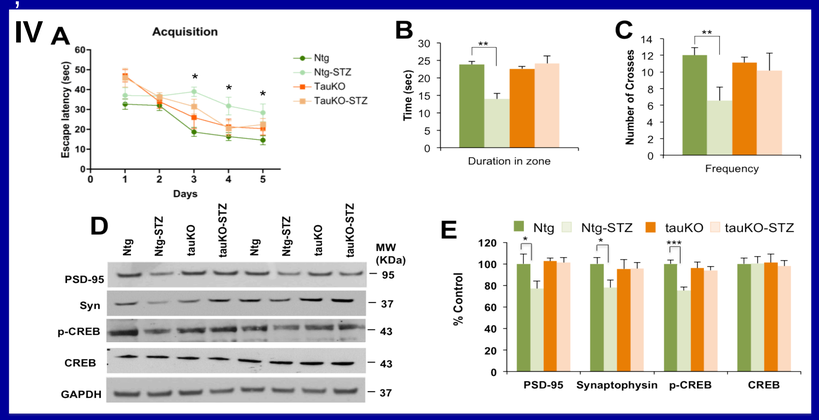
II. **Short modern-lifelike stress increases Aβ pathology in 3xTg-AD mice**. Biochemical analysis showed elevated levels of Aβ oligomers in 3xTg-AD mice exposed to short-term stress compared to non-stressed 3xTg-AD mice (A-B). In addition, short-term stress increased Aβ-oligomers by modulation of APP processing via upregulation of BACE steady state levels (C-F) without altering Aβ degradation (G-H).



III. **Short modern-lifelike stress severely affects dendritic spines in 3xTg-AD.** Dendritic spines are dynamic structures whose plasticity is thought to underlie the learning and memory process. Several lines of evidence revealed that stress is an important factor that impairs the function and stability of dendritic spines. Given that, we analyzed the impact of short modern-lifelike stress on dendritic spines in the 3xTg-AD mice in comparison to Ntg mice. Our study demonstrates that exposure to short-term stress severely decreases the number of dendritic spines in the hippocampus of 3xTg-AD mice. Hence, our findings indicate that modern-lifelike stress severely diminishes dendritic spines in 3xTg-AD mice.

Type 1 diabetes-like diseases induces tau dependent synpatic and cognitive impairments

The incidence and prevalence of age-related neurodegenerative and metabolic disorders are growing because of the increasing life expectancy of the human population in industrialized countries. Diabetes is the most common metabolic disorder and clinical studies show that diabetic patients are at significantly increased risk for developing Alzheimer disease (AD) compared to healthy individuals. Here, we elucidate how diabetes, one of the more prominent co-morbidities, promotes cognitive decline and synaptic dysfunction by alteration of the AD-related protein "tau."



IV. Type 1 diabetes-like diseases induce tau-dependent cognitive and synaptic impairments. To elucidate whether the cognitive decline induced by diabetes is dependent on tau, we administered streptozotocin (STZ) to Ntg and mouse tauKO (tauKO) mice. STZ, a glucosamine-nitrosourea compound, is toxic to the insulin-producing beta cells of the pancreas, and intraperitoneal administration of STZ induces hyperglycemia and insulin deficiency, rendering it a valuable model to study Type 1 diabetes-like diseases. Here, we show for the first time that type 1 diabetes-like diseases impair cognition in Ntg mice, as assessed by performance on the Morris water maze (MWM), compared to tauKO mice which are protected and show no deficit (A-C).

Furthermore, we show that memory and learning impairments observed in the MWM are likely due to alterations in synaptic proteins and memory-related transcriptional factors (D-E). Interestingly, tauKO mice did not show synaptic deficits. Our study indicates that the AD-related protein tau is a key factor for type 1 diabetes-like diseases to induce synaptic and cognitive impairments.

Acknowledgments

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