The Study of AD Pathological Events Through Behavioral Testing

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OVERVIEW

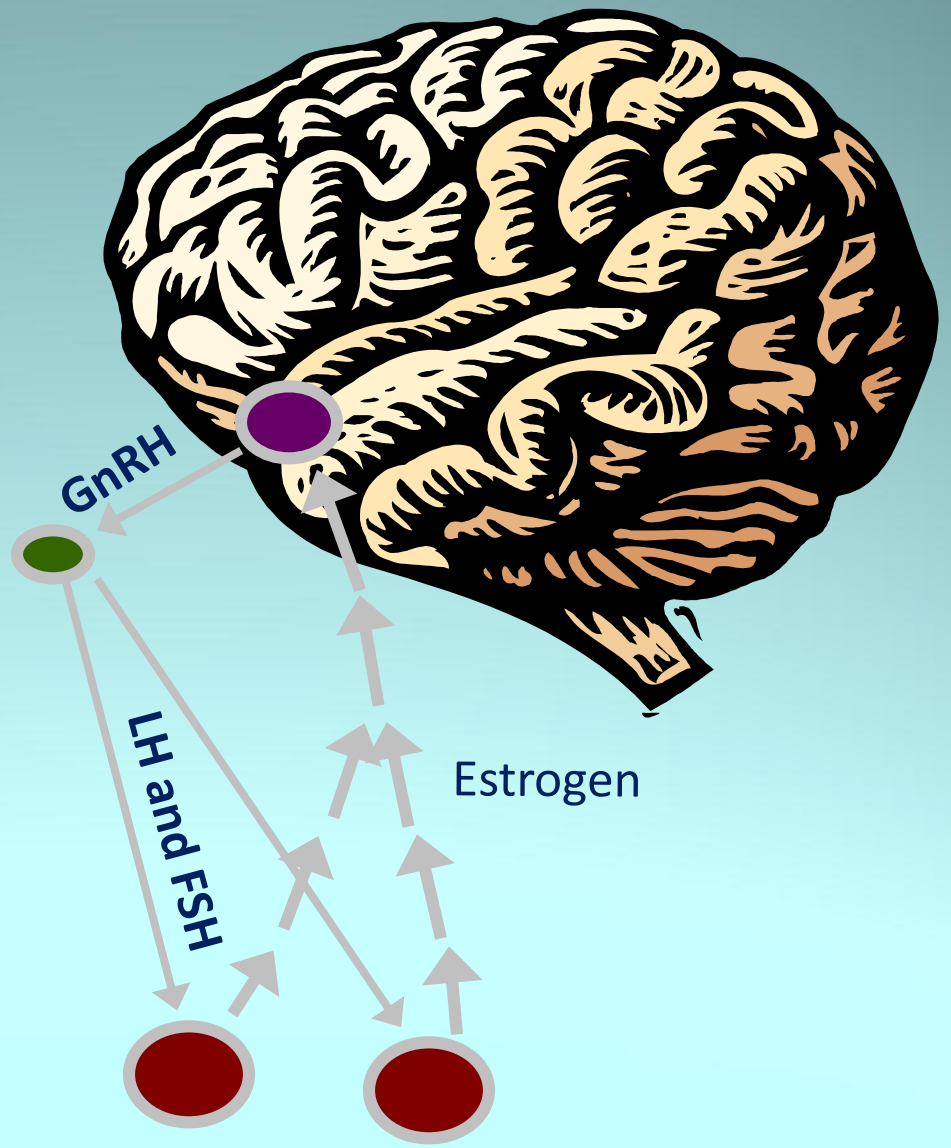
- The role of gonadotropins on cognition
- The study of the SAMP8 mouse as a Model of AD
- Rodent behavior Core

HPG axis during Menopause

Hypothalamus

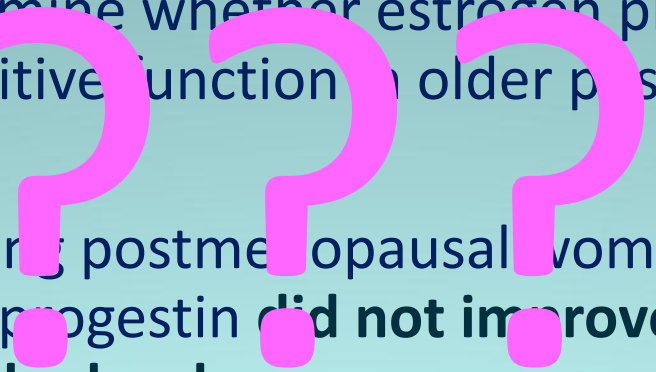
Pituitary

Gonads



Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the WHIMS: a randomized controlled trial

- OBJECTIVE: To determine whether estrogen plus progestin therapy protects global cognitive function in older postmenopausal women.



- CONCLUSIONS: Among postmenopausal women aged 65 years or older, estrogen plus progestin **did not improve cognitive function when compared with placebo**…

- **"Older women taking combination hormone therapy had twice the rate of dementia, including Alzheimer's disease (AD), compared with women who did not take the medication. The study also found that the combination therapy did not protect against the development of Mild Cognitive Impairment (MCI).**

Luteinizing Hormone:
Links to Alzheimer Risk & Disease Factors

LH receptor is present in hippocampus & ICV injection of hCG leads to behavioral changes

RISK FACTORS

- Aging
- Gender (F>M)
- Down's Syndrome (M>F)

LH

Memory/Cognitive DEFICITS
Casadesus et al., 2006

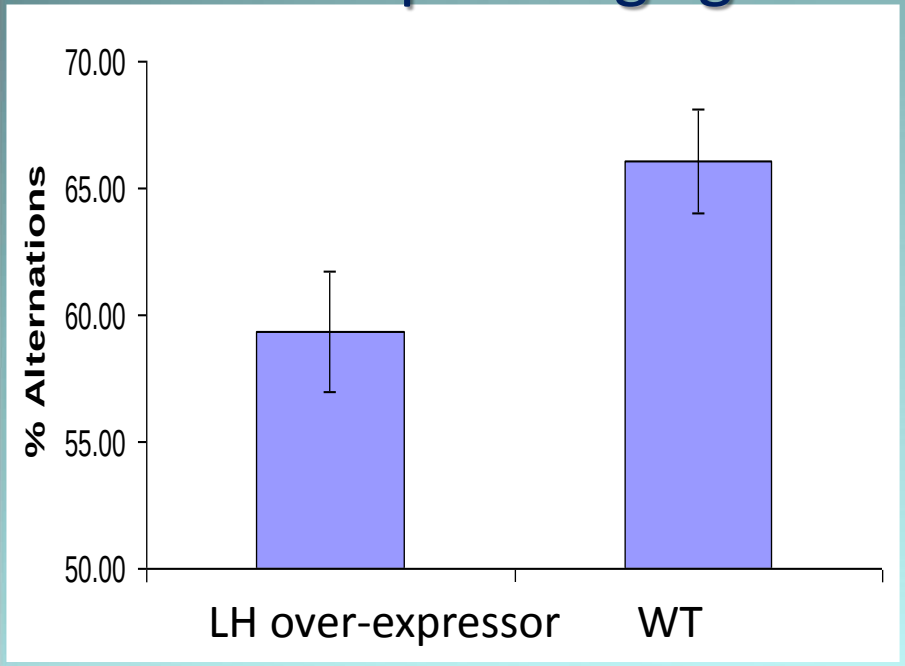
DISEASE FACTORS

- **LH is higher in AD patients** (Short et al., 2001)
- **Selective Neurodegeneration** (Bowen et al., 2002)
- **Amyloid-beta** (Bowen et al. 2004; Casadesus et al., 2006)
- **Tau Phosphorylation** Choi et al., 2008 in prep

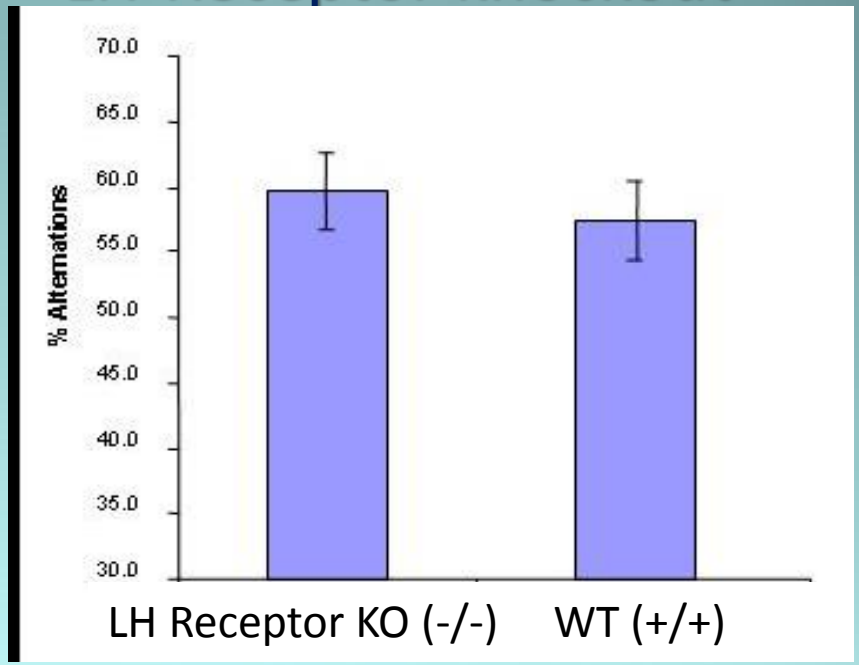
Do Increases in Gonadotropins/GnRH lead to Declines in Cognitive Function in non-AD models?

Does LH mediate cognitive changes?

LH over-expressing Tg



LH-Receptor knockout

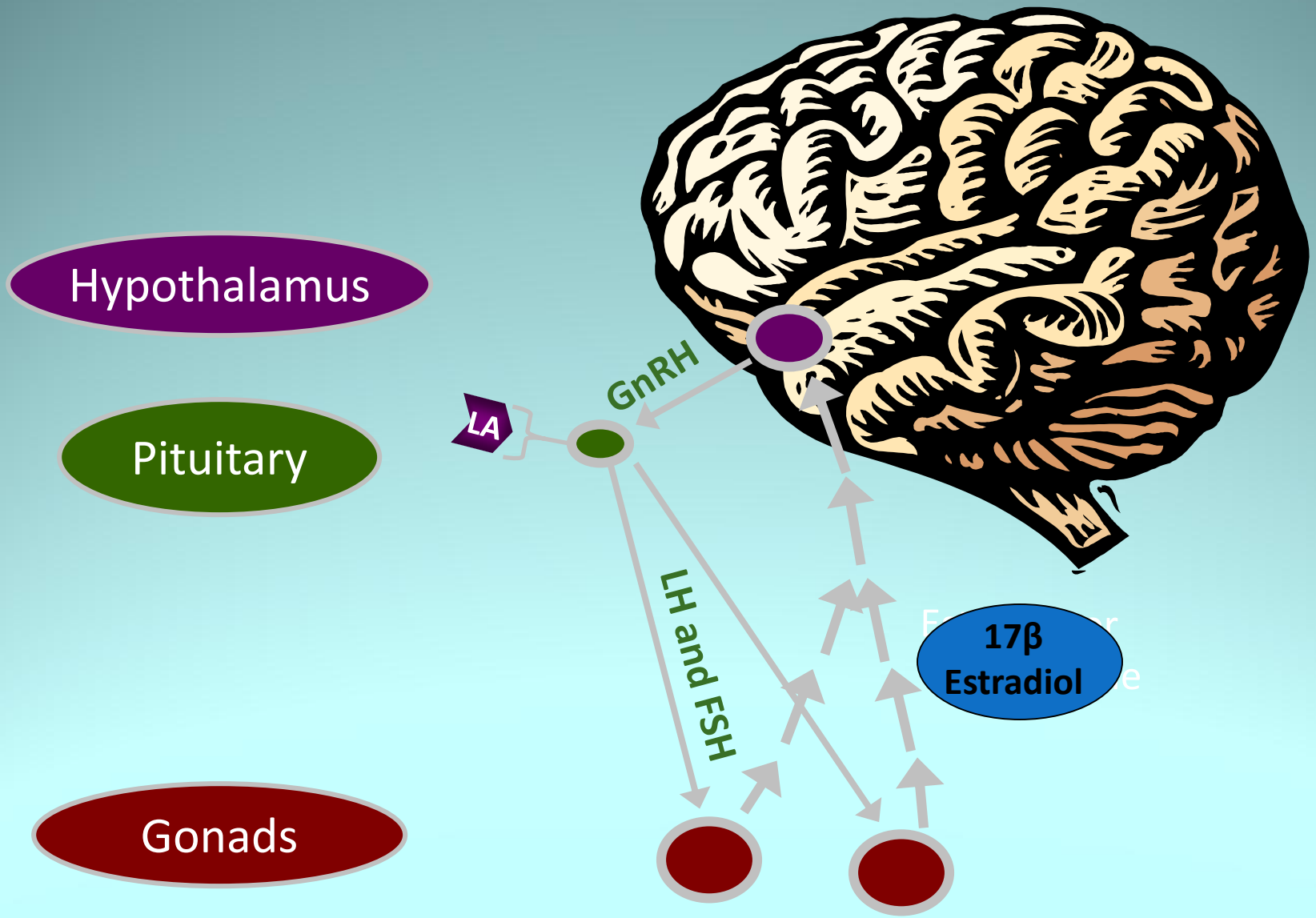


LH: INCREASED
LH-R: INTACT
Estrogen: INCREASED
Cognition: DECREASED

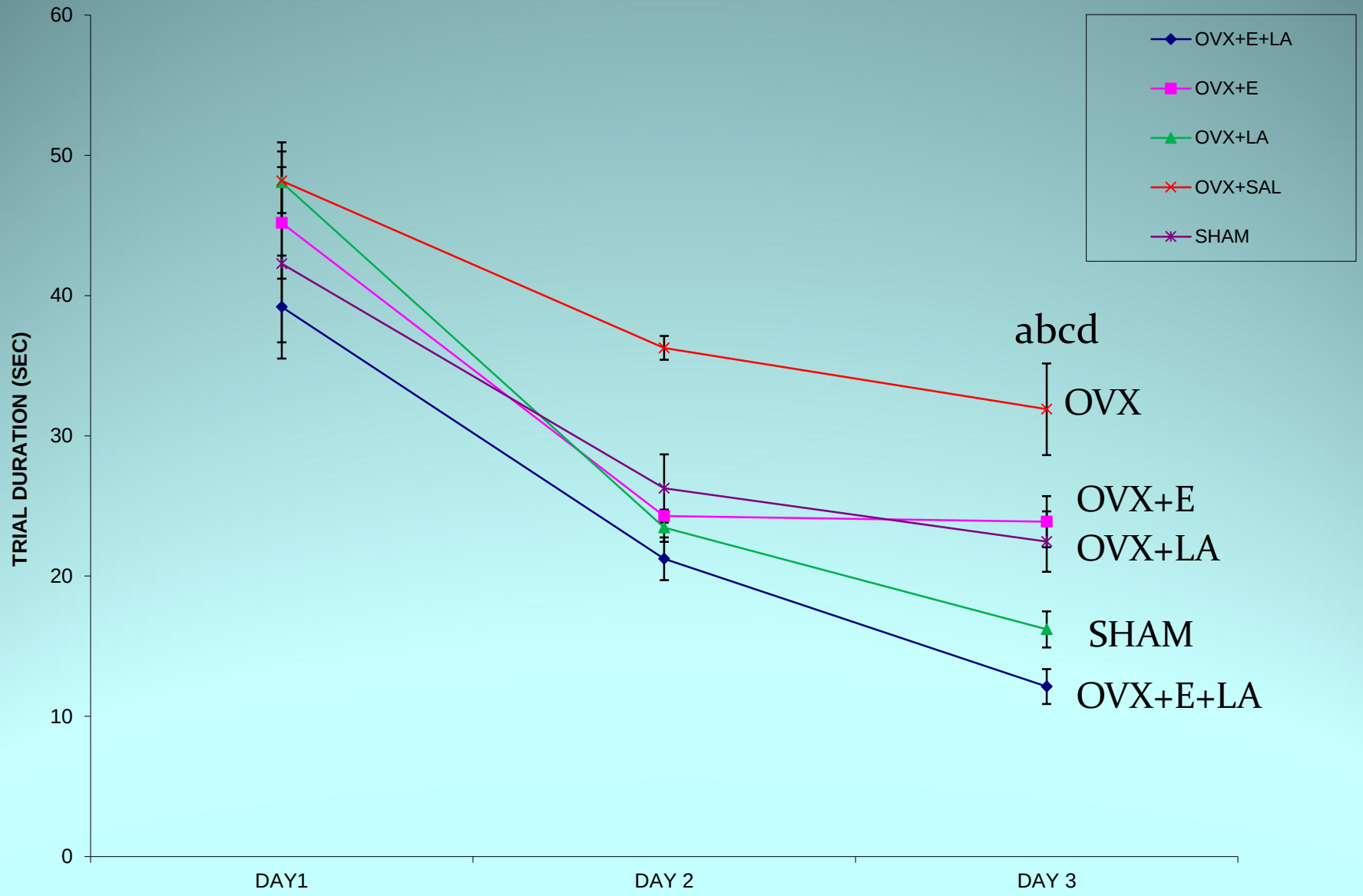
LH: INCREASED
LH-R: DECREASED
Estrogen DECREASED
Cognition: NO CHANGE

Casadesus et al., 2007 (J Neuroendocrinol)

Dissection of Gonadotropins & Estrogen Effects on Cognition Using and OVX Model



MWM performance in OVX mice treated with Leuprolide acetate



GnRH Agonists & Antagonists

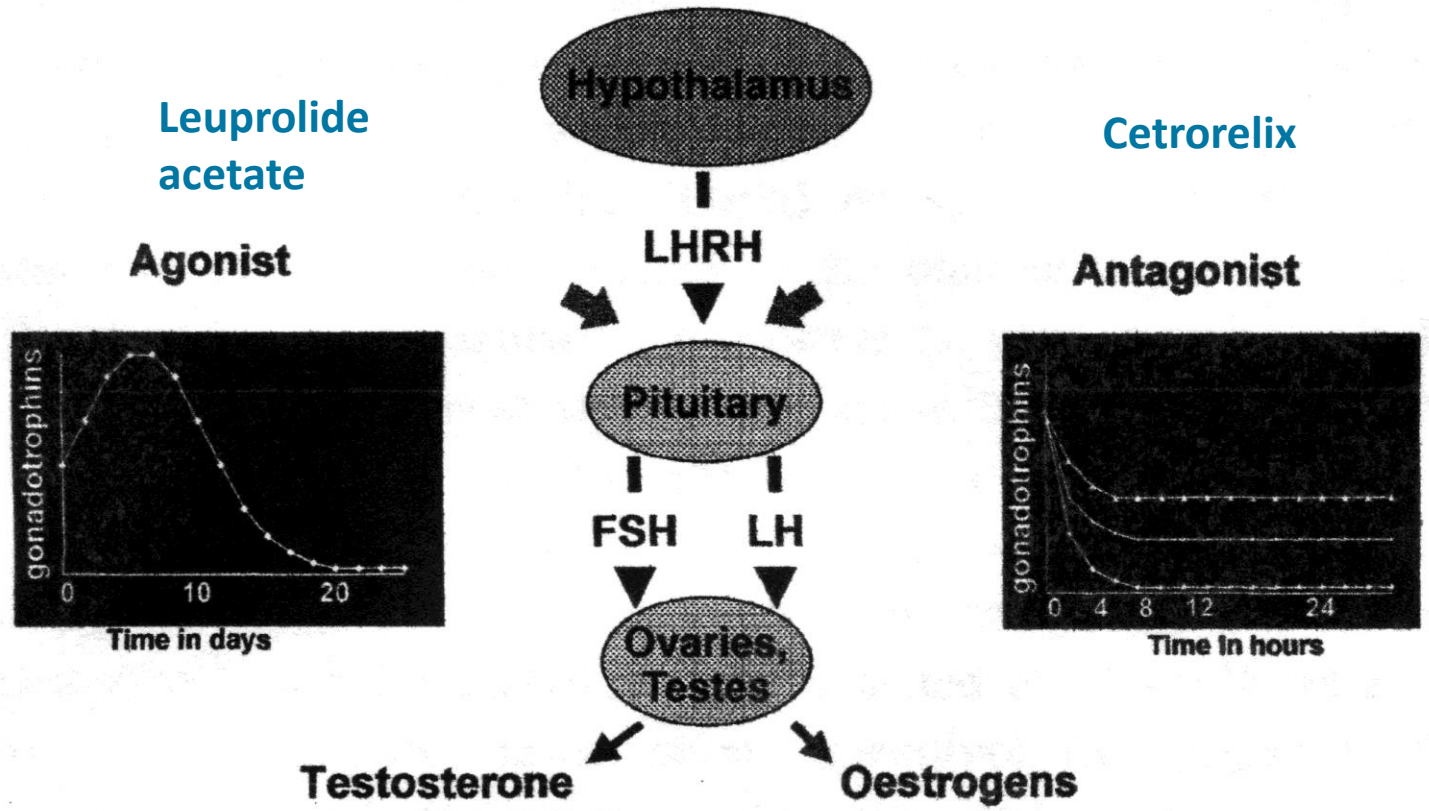
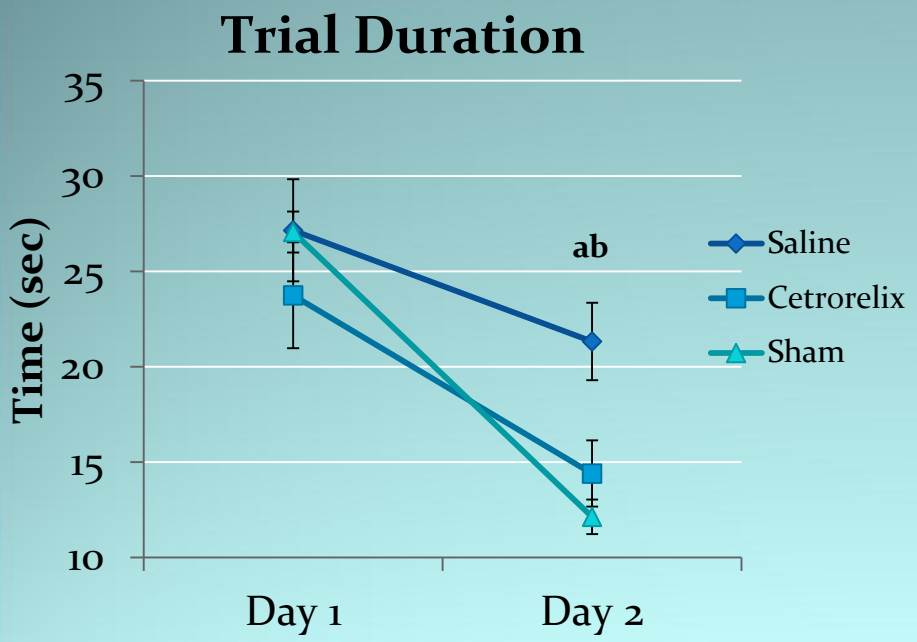
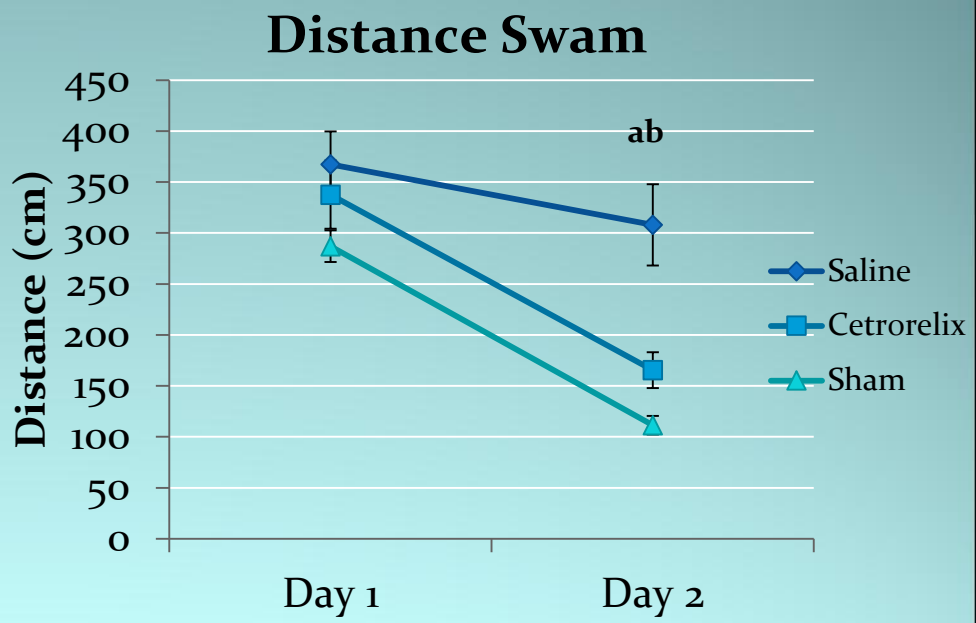


Figure 1. Luteinizing hormone-releasing hormone (LHRH) analogues – mode of action.

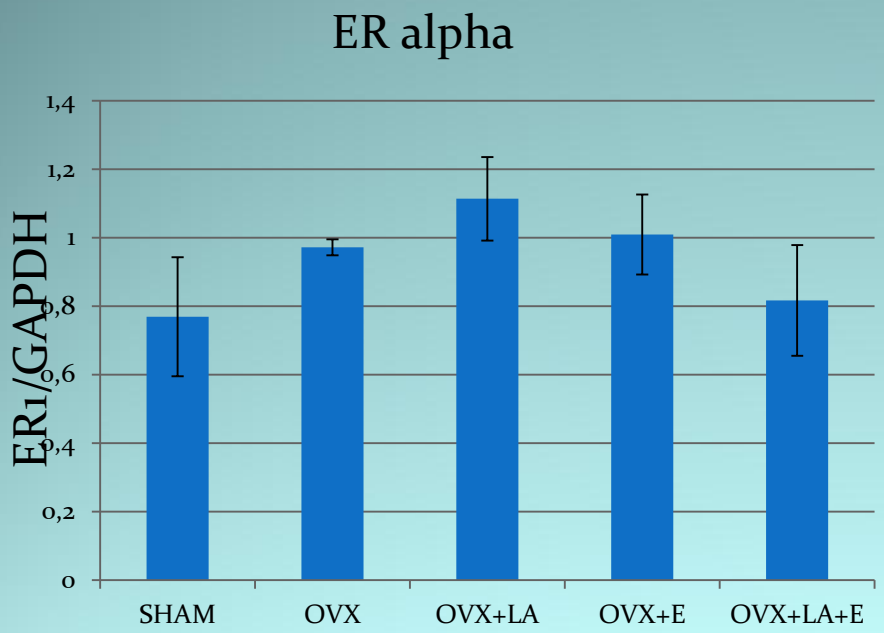
Modulation of Cognition by Cetrorelix

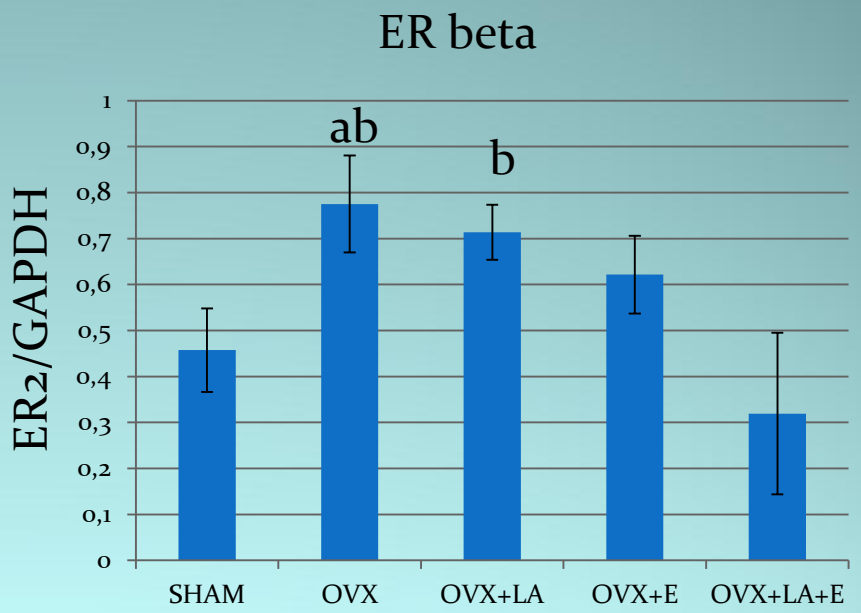




a= Significant difference from cetrorelix
b= Significant difference from SHAM

LA mediated effects on ERα & Erβ mRNA expression





Modulation of synaptophysin by LA

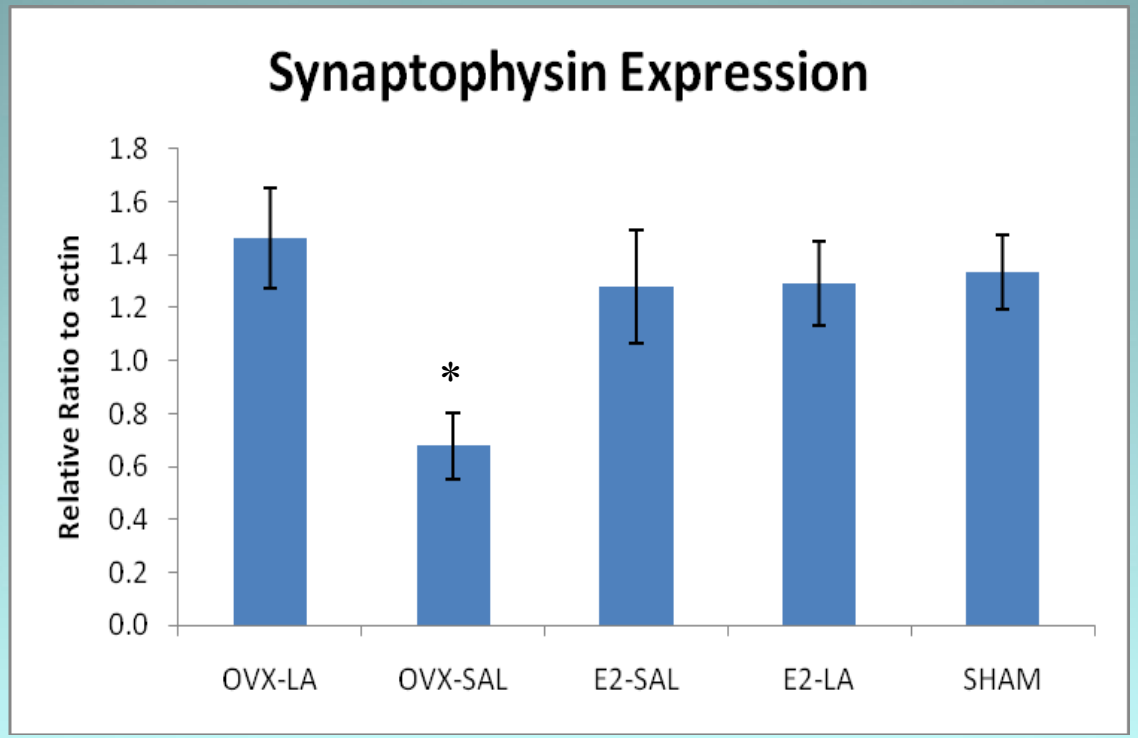
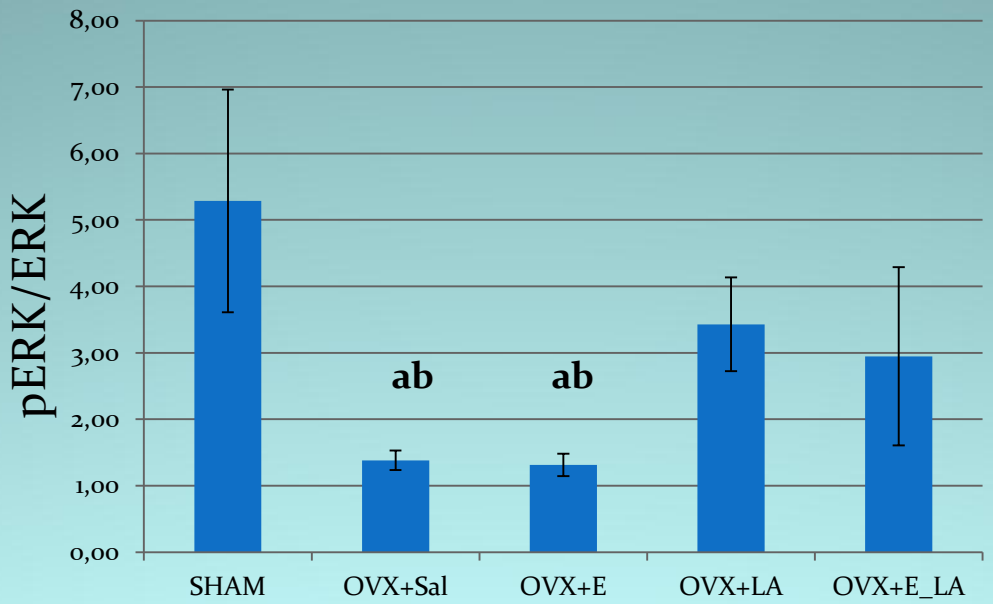
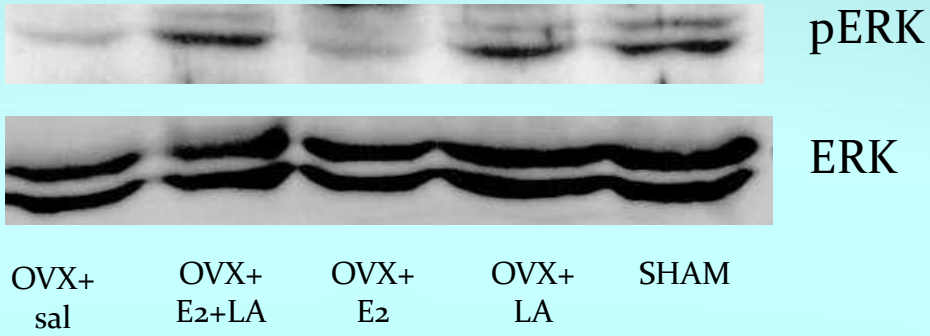
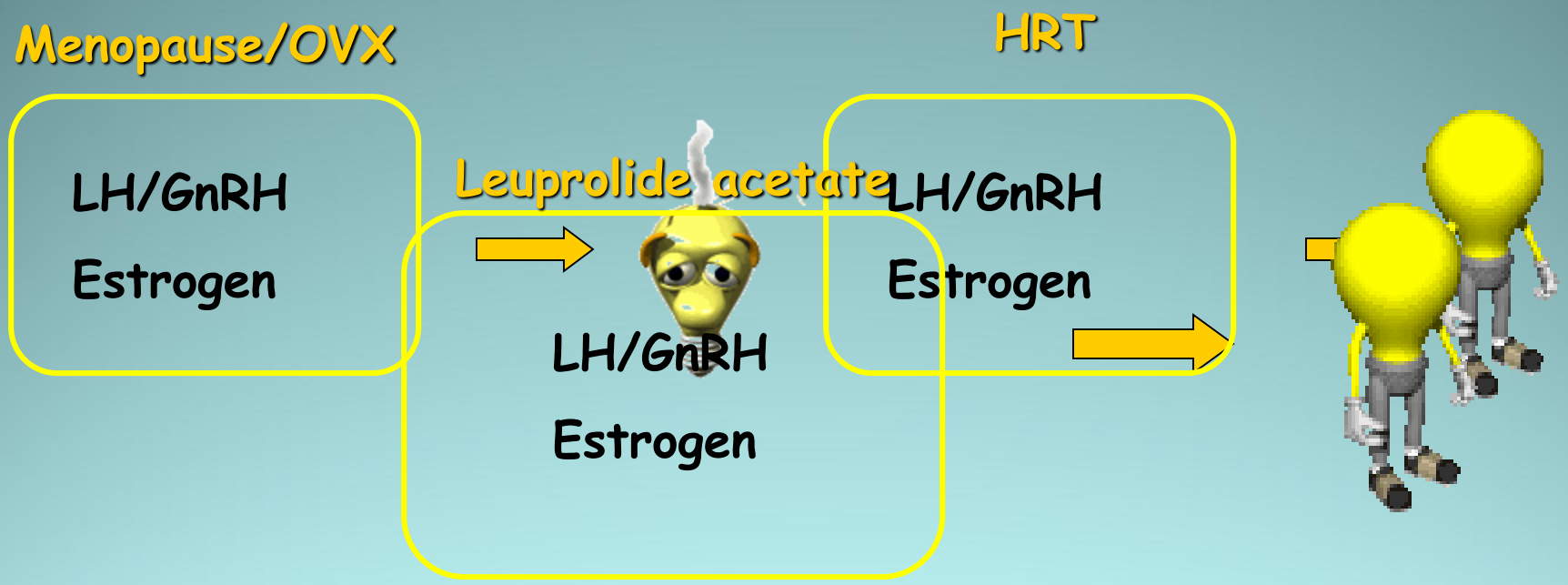


Figure 15 - MEAN and SEM of Relative quantification (ratio to actin) of synaptophysin preotein expression in the hippocampi of OVX animals with or without estrogen replacement (E2) and treated with leuprolide acetate (LA) or saline (SAL) and SHAM operated animals. n=4-7 animals/group. Western blotting was carried out using standard methodology as published in [143] and quantified using Bio-rad density quantification software (Quantity One).

Modulation of pERK expression by LA







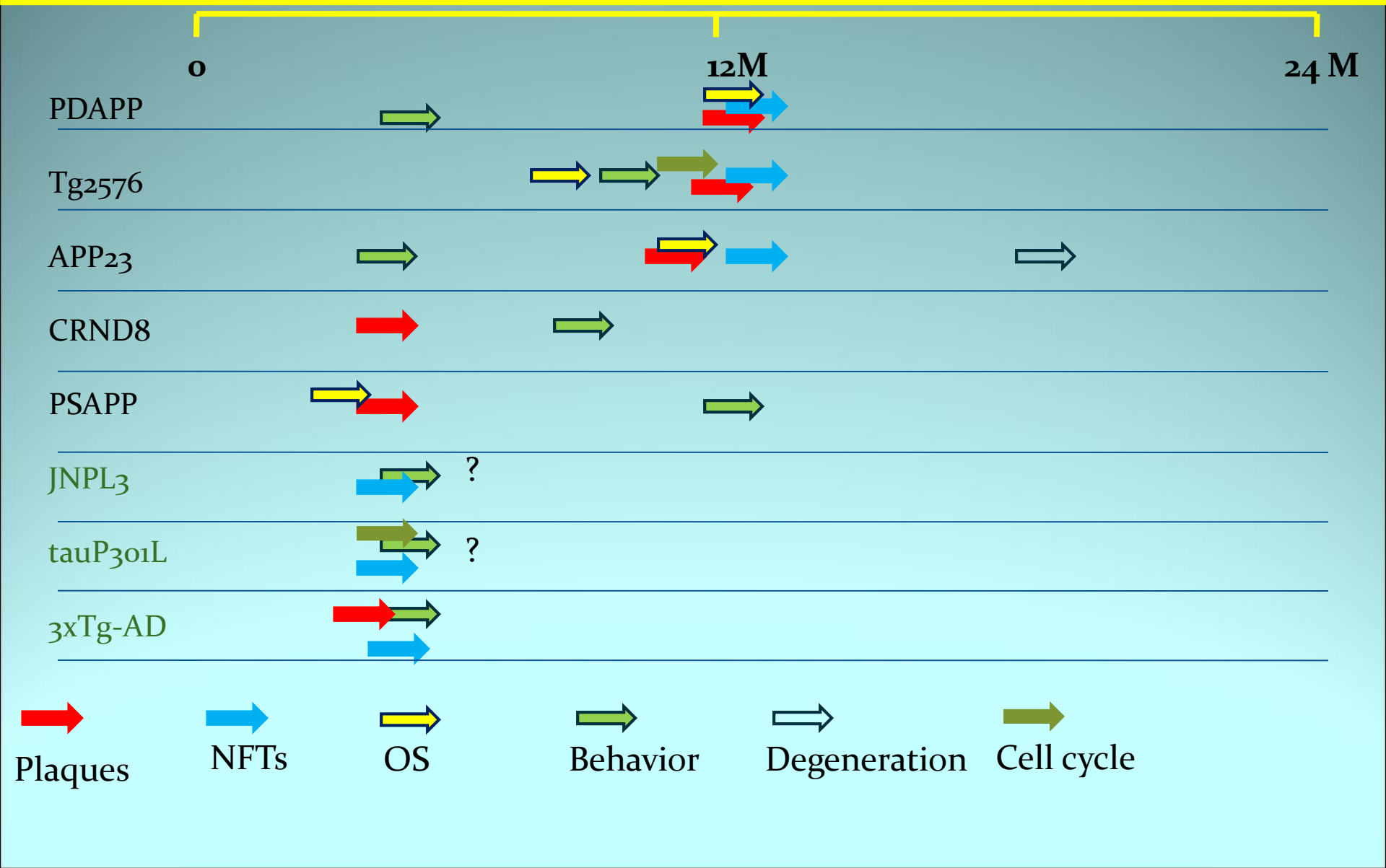
New treatment for cognitive decline and AD???

Age-Accelerated SAMP8 Mouse Model

12 months of age

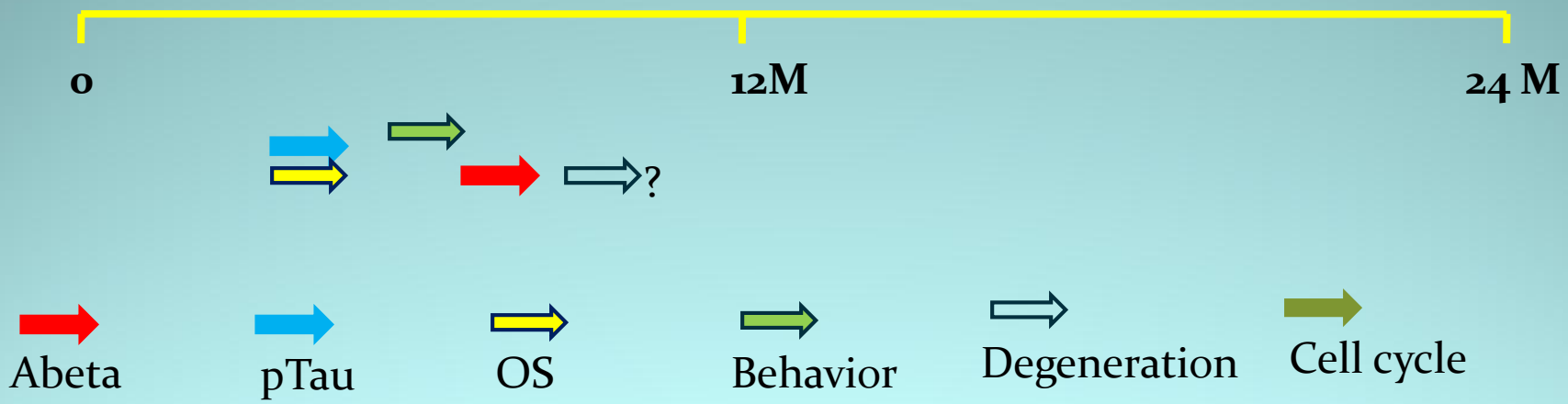
- The SAM strain of mice is derived from AKR/J strain.
- littermates which became senile at an early age in life and had a shorter life span were selected as the progenitors of the SAMP.
- Littermates in which the aging process seemed normal were also selected as the progenitors of SAMR.
- Retrospective pedigree selection and inbreeding were applied based on the degree of senescence, the lifespan and the age-associated pathologic phenotypes.

AD-related Markers in AD-mouse models



AD-related Marker expression in SAMP8

More similar to aged humans



Objectives

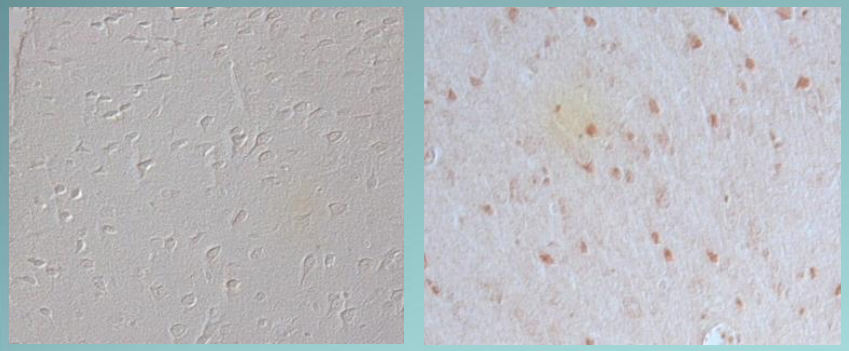
- **Determine the chronology of appearance**
  - Tau hyper-phosphorylation (2M, 5M, 9M)
  - Oxidative stress (2M, 5M, 9M)
  - Cell cycle re-entry (2M, 5M, 9M)

- **Use pharmacological inhibitors to determine the inter-relationship between these pathological markers**
  - LiCl
  - Resveratrol
  - Roscovitine

- **Characterize cognitive function after these treatments to fine-tune the best pharmacological strategy to target the disease at early stages**

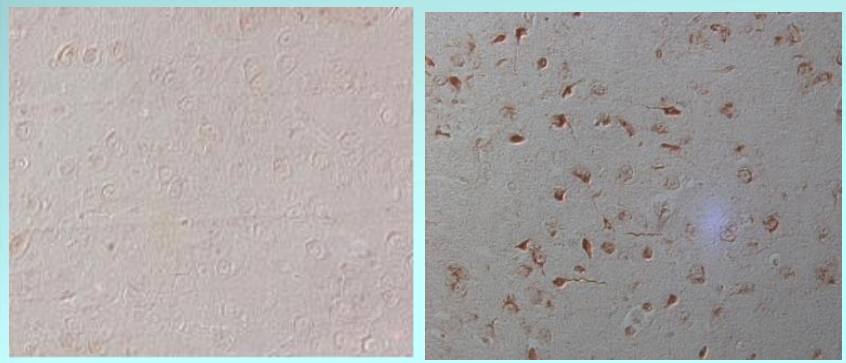
Cell cycle Marker Expression in SAMP8

SAMR1 SAMP8

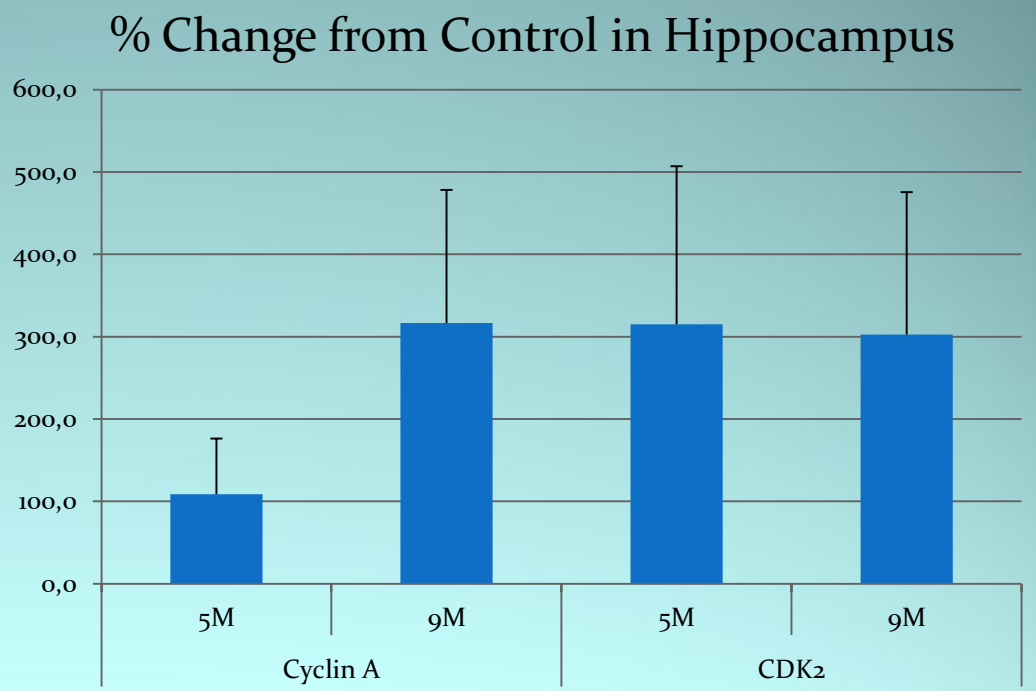


CDK2

SAMR1 SAMP8



Cyclin A



Thanks!

Lab members:

- Katy Bryan, PhD
- Joseph Mudd B.S.
- Natalia Biel B.S.
- Michele Ionno B.S.
- Jennifer Reeves B.S.
- Andrew Law
- Steven Chou
- Jeannie Choi
- Ted Kim

Collaborators:

SAMP8 work

- Merce Pallas (UB, Spain)
- Toni Camins (UB, Spain)
- Jordi Vilapana (UB, Spain)
- Cristina Pelegri(UB, Spain)
- Smith/Perry/Zhu lab

LH Work

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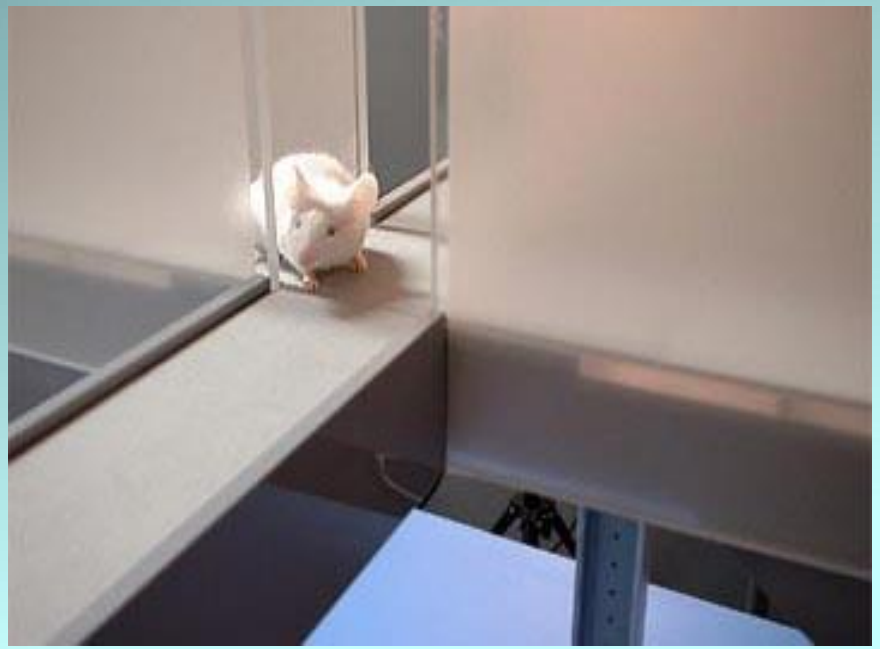
Phenotyping of Complex Behavioral Traits to Assess Nervous System Function and Dysfunction



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Core Objective

- Behavioral testing resource for CWRU and vicinity
- Experimental design
- Statistical analysis
- Interpretation
- Training & use of the facility for some testing